

Journal of the
American Osteopathic College
of Dermatology

Journal of the American Osteopathic College of Dermatology

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Letter From The JAOCD Editors



Jay S. Gottlieb, D.O.



Stanley E. Skopit, D.O.



James Q. DelRosso, D.O.

It is with great pride, excitement and anticipation that our dream of launching our College's first journal, the JAOCD, has come to fruition in this inaugural edition. This journal will hopefully serve several functions. The mission of the Journal of the American Osteopathic College of Dermatology serves to better the continuing education needs of the AOCD members, residents and the dermatology community at large. The JAOCD will be a vehicle for our residents throughout the country to have the opportunity for their required papers to be published during their residency program. The Journal will provide our dermatology colleagues, as well, the ability to report on interesting and rare disorders of the integumentary system.

We will cover topics that will be academically challenging. We will include such areas as dermatologic therapeutic modalities, original presentation of research, brief opinions, a review of dermatology affiliated clinical studies, brief individual case reports of unusual interest, basic science as it relates to dermatology, articles emphasizing cutaneous surgery, dermatopathology, cosmetic dermatology, pharmaceutical dermatology, editorials, letters to the editors, and finally Pearls and anecdotes in dermatology.

At this time we must extend our sincere appreciation to our Founding Sponsors. These six companies, without hesitation, stepped up to the plate to back our efforts. We look forward to a long and mutually beneficial relationship with each one. Our deepest thank you goes to Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Novartis Pharmaceuticals Corporation, Medicis-The Dermatology Company and 3M Pharmaceuticals who have made the financial commitment to see that our dream has been fulfilled.



Get information about the JAOCD at www.aocd.org or e-mail us at jaocd@aol.com.

Fraternally yours in Dermatology,

Jay S. Gottlieb, D.O., F.O.C.O.O. (Editor)
Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)
James Q. Del Rosso, D.O., F.A.O.C.D. (Associate Editor)

Letter from the President of the AOCD



Robert F. Schwarze, D.O.

I would like to take this opportunity to congratulate Drs. Gottlieb, Skopit and DeRosso on their fine accomplishment in producing this inaugural issue of the Journal of the American Osteopathic College of Dermatology. This endeavor took initiative, insight and perseverance to bring to fruition. We can be even more proud of our college now that it has such a fine publication. I urge each and every one of our members to contribute to the JA OCD. Program directors need to encourage their residents to present their yearly manuscripts for publication in our journal.

I am proud to be the current president of our college and I want to thank the founding sponsors of the JA OCD that made the financial commitment to this effort. I want to invite input from all of our dermatology colleagues across the country and ask that they also seek to contribute their manuscripts to this fine publication.

This inaugural issue is something that we can all be very proud of. We should also look forward to a future where our distribution, author contribution and publication quality continues to only get better.

And lastly, congratulations to the authors of the published manuscripts in this, the first issue, of the JA OCD. Your accomplishment is to be commended. As your current president, again I am proud of our accomplishment.

Robert F. Schwarze, D.O., F.A.O.C.D.

Patient Assessment in the Treatment of Premenstrual Acne Flare with Vitamin B6 Therapy: A Two-Year Retrospective Study

Bill V. Way, D.O.,* Rick Lin, D.O., M.P.H.,** Dan J. Ladd Jr., D.O.***

Abstract

Premenstrual acne flare (PAF) is a common condition among female acne patients. Vitamin B6 is used by some physicians to treat this condition. This study provides statistical data in support of Vitamin B6 therapy for the treatment of premenstrual acne flare. There are 67 female participants in this study. Among the 57 patients in the 100mg treatment group, 19 patients (33%) perceive no response while 38 patients (66%) experience positive response. Among the 21 patients in the 200mg treatment group, 5 patients (24%) did not experience any improvement of their premenstrual acne flare, while 16 patients (76%) experienced improvement with the treatment. The results of 100 mg treatment group ($p < 0.001$) and 200 mg treatment group ($p < 0.001$) were both statistically significant against the baseline rating. The use of Vitamin B6 in the treatment of premenstrual acne flare provides both clinically and statistically significant results.

Introduction

It is estimated that up to 60-70% of females experience an exacerbation of acne shortly prior to their menses.¹ The use of Vitamin B₆ (pyridoxine) in the treatment of this condition has been used by clinicians for more than 25 years. Very few studies regarding this treatment have been published during this period of time.^{2,3}

The possible physiologic mechanism of premenstrual acne flare (PAF) is that prior to menses, progesterone exerts its influence and leads to such phenomenon.⁴ This explanation is consistent with research performed with Vitamin B₆ (pyridoxine) and its role in the expression of steroid hormones, such as progesterone.⁵ The biologically active form of vitamin B₆ can modulate and decrease the transcriptional response to progesterone.⁵ This blunts the effect progesterone has on the body, and theoretically alleviates the symptoms of premenstrual acne flare.

It should be noted that the role of progesterone in PAF is not conclusive. There is research in the literature that conflicts with the progesterone effect theory. Some researchers found that sub-physiologic daily doses ranging from 5-25 mg of progesterone did not worsen PAF. On the contrary, it improved the patient's condition.^{6,7} In contrast to these observa-

tions, other researchers found that progesterone administration exacerbated the PAF.⁸

While the use of Vitamin B6 (pyridoxine) for the treatment of PAF may not be conclusively supported by the scientific literature, it has been used by clinicians since the 1970s.³ The only reported clinical result of this therapy was done in 1974 by Snider and Dietsman in the form of a letter to the editor of Archives of Dermatology.³ This letter has been referenced by many consumer health books, alternative medicine publications, and internet websites as the scientific basis for Vitamin B₆ (pyridoxine) therapy in the treatment of PAF.

The purpose of this study is to evaluate the efficacy of Vitamin B₆ (pyridoxine) treatment for the condition of PAF. The results of this study will provide additional data for this therapy.

Methods

Treatment Protocol

The Duncanville Dermatology Clinic has incorporated a standardized research treatment protocol for PAF for the past 2 years. When a patient presents for treatment of acne, she will be routinely screened for PAF. If she presents with the symptoms of PAF, she would be put on Vitamin B₆ (pyridoxine) 100mg daily for 3 months. If premenstrual acne flaring symptoms decrease, the patient will be advised to maintain the current dose. If PAF shows no improvement, the patient will be asked to increase the daily Vitamin B₆ (pyridoxine) dose to 200 mg. If the patient still shows no improvement after 3

months of taking the increased dose, the treatment is declared ineffective for this patient and other treatment options are explored at that time, such as oral contraceptive pills.

The treatment protocol is also summarized in FIGURE 1.

Criteria for Inclusion

This is a retrospective chart study conducted among all female patients diagnosed with PAF between the 2 years period of June 1, 1998 to June 1, 2000. In order to be included in the study, the patient will need to have at least one (1) follow-up visit after the initial diagnosis and treatment of PAF. If the symptoms are not completely controlled at the first follow-up visit, one (1) additional follow-up visit will be required to collect the data subsequent to the Vitamin B₆ (pyridoxine) dosage increase.

Another reason for exclusion will be incomplete or inconclusive patient subjective data in the chart. Also for patients who initiate the treatment but failed to have adequate follow-up data, their charts will not be included in this study.

Collection of Data and Definition of Treatment Response

The clinical severity of the patient's PAF will be assigned a numerical rating of 1 (none to minimal), 2 (moderate), 3 (severe). The assignment of this numerical value will be based on the subjective descriptions of the patient in the chart following appropriate visits. Duncanville Dermatology Clinic uses a set of standardized subjective evaluation as part of

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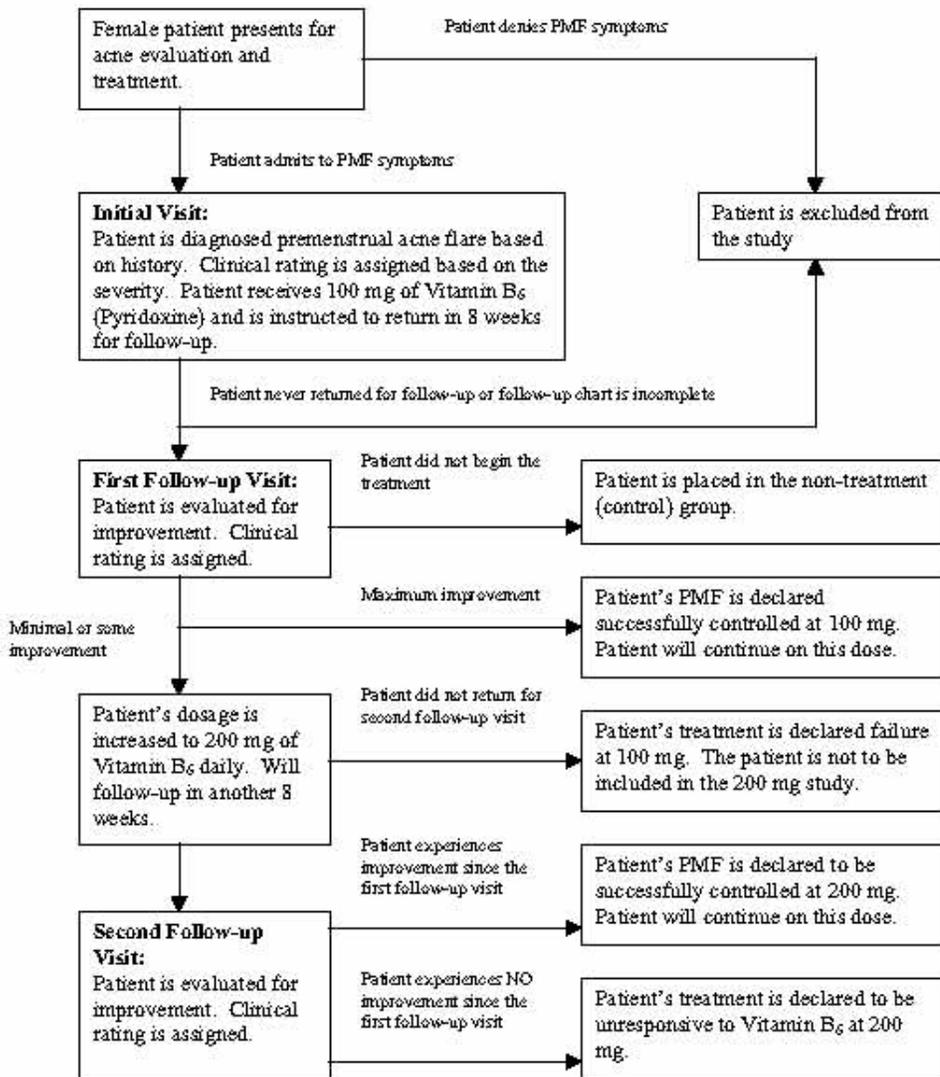


FIGURE 1: Duncanville Dermatology Clinic Vitamin B₆ Treatment Protocol

TABLE 1: Clinical evaluation rating assignment based on the qualifying phrase used in the description of premenstrual acne flare

Clinical Evaluation Rating (3) severe
"No Improvement."
"Does flare more with menstrual cycle."
"She does have cycle flares."
"Flares with her menses."
"She still has cycle flares"
"Her acne flares prior to her menstrual cycle."
Clinical Evaluation Rating (2) moderate
"Condition has been improving but not completely."
"Some improvement but she continues to breakout especially with menstrual cycle."
"History of occasional premenstrual acne."
Clinical Evaluation Rating (1) minimal
"Completely cleared."
"Patient states she has minimal flare with menstrual cycles."
"Has no menstrual cycle flares at this time."
"Premenstrual acne has decreased when taking Vitamin B6."
"Patient not having problems with present program."
"Had no flare ups since last visit."

their dictation system. The numerical rating of severity is assigned based on this system as summarized in TABLE 1. When one of the descriptors is used in the chart for patients visiting for PAF, the appropriate clinical rating is assigned to that patient for that visit.

The evaluation of the patient at the initial treatment will be collected as the baseline in which to be used in comparison with the results of the treatment. At the first follow-up visit following the 100 mg of Vitamin B₆ (pyridoxine) treatment, the results from patients who are compliant with the treatment will be used as the experimental group. For the other group who did not start the treatment as instructed, their evaluation will be used as the result of the control (non-treatment) group. If the clinical rating of 1 (minimal symptoms) is not achieved at this follow-up visit, the treatment of 100 mg of Vitamin B₆ (pyridoxine) is declared a failure.

Patients who failed the 100 mg Vitamin B₆ (pyridoxine) treatment, their dosage of Vitamin B₆ (pyridoxine) would be increased to 200 mg at the first follow-up visit. If a patient did not return for the second follow-up visit after the dose increase, this patient will be excluded from the 200 mg treatment group. However, the response from 100 mg treatment will still be used as part of the 100 mg treatment results.

On the second follow-up visit, their subjective evaluation will once again be assessed a numerical rating. The clinical rating of this patient in response to the 200 mg Vitamin B₆ (pyridoxine) treatment will be compared to her 100 mg response in order to determine whether there is an improvement of her condition from the dose increase.

Statistical Analysis

Clinical ratings of the patients are summarized as means-Standard Deviations. Differences between group means and the baseline rating were assessed with the two-tailed paired t-test; the null hypothesis of no difference is tested. Analysis of Variance (ANOVA) is used to compare the group means of control, 100 mg, and 200 mg treatment groups.

Association between treatment and non-treatment groups was evaluated with Chi-square analysis and Fisher Exact Test. Both 100 mg and 200 mg Vitamin B₆ (pyridoxine) treatment groups are tested against expected value of the control (non-treatment) group.

The data is analyzed using Microsoft Excel. Statistical significance is indicated by P value of less than 0.05. All reported

TABLE 2: Patients' subjective response to Non-treatment, Vitamin B₆ 100 mg treatment, and Vitamin B₆ 200 mg treatment.

	No Improvement	Improvement	Total
Non-treatment	9 (90%)	1(10%)	10
100 mg Treatment	30(53%)	27(47%)	57
200 mg Treatment	5(24%)	16(76%)	21

P values are two-tailed. All reports will include aggregated data only.

Results

This study is derived from a population of patients at Duncanville Dermatology Clinic who had the diagnosis of PAF. There are a total of 67 patients participating in the study. These patients' ages range from 13 to 50 years old. All of them are pre-menopausal. The average age is 26.19 years old with a standard deviation of 11.91. The ethnicity of this sample breaks down into 48 Whites, 12 B l a c k s , 6 Hispanics, and 1 Asian.

All patients in the study are receiving Vitamin B6 (pyridoxine) treatment for the first time. The initial clinical ratings of 1 (severe), 2 (moderate), 3 (minimal) were averaged for all 67 patients to use as the baseline evaluation. The baseline mean is 1.09 with standard deviation of 0.28.

The 10 patients in the non-treatment group have the mean clinical rating of 1.1 with standard deviation of 0.32.

Among the 57 patients in the 100 mg treatment group, 19 patients (33%) perceive no response (Clinical rating:1) while 38 patients (66%) experience positive response. Among the 38 positive responders, 11 patients (30%) experience some improvement and received clinical rating of 2 (moderate symptoms). 27 patients (47%) are satisfied with the treatment and experience minimal or no PAF. They receive the clinical rating of 3 (minimal symptoms). The mean clinical rating of 100 mg treatment group is 2.14 with a standard of deviation of 0.92.

Among the 49 patients in the 200 mg

treatment group, 4 patients (8%) failed treatment (Clinical rating:1) and 3 patients (6%) did not achieve complete resolution of the symptoms (Clinical rating:2). The other 42 patients (86%) are satisfied with the treatment (Clinical rating:3). The mean clinical rating of the 200 mg treatment group is 2.78 with stand deviation of 0.56

Overall, total of 42 out of 57 patients (74%) experience near-complete control of PAF from either 100 mg or 200 mg Vitamin B₆ (Pyridoxine) treatment after 3 to 6 months of initiation of the therapy.

In order to compare the means of the control group, 100 mg treatment group, and 200 mg treatment group, Student's t-test was performed separately. The result of the non-treatment group was not statistically significant from the baseline clinical rating prior to the treatment. (p=0.95) The confidence interval of the difference between means of control group and the baseline is (-0.21) to (0.19). The results of the 100 mg treatment group yield a p-value of less than 0.001, and are thus statistically significant. Confidence interval of the difference between the baseline and 100 mg treatment group rating is (0.82) to (1.28). The 200 mg treatment group has a statistically significant p-value of less than 0.001 when compared to the baseline. Confidence interval of the difference is (1.53) to (1.85).

Repeat Measure Analysis of Variance is also performed to compare the control group, 100 mg treatment group, and 200 mg treatment group. Results show significant differences among 3 groups (p<0.001).

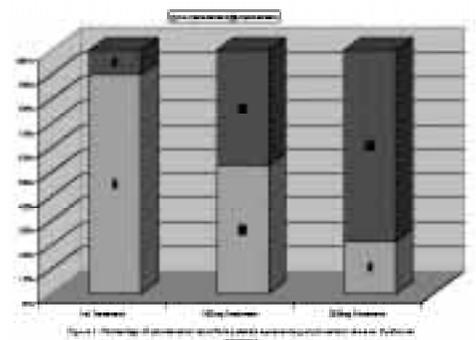
TABLE 3: Statistical analysis of the clinical ratings among different groups

	Baseline	Non-Treatment	100 mg Treatment	200mg Treatment
Sample size (n)	67	10	57	21
Rating 1	0	0	27	14
Rating 2	5	1	11	3
Rating 3	62	9	19	4
Mean Rating	2.93	2.9	1.86	1.52
Standard Deviation	0.26	0.32	0.91	0.81

Two-tailed Fisher Exact Test shows positive association with treatment in both the 100 mg treatment group versus the non-treatment group (p=0.001). And for 200 mg treatment group and non-treatment group, the Fisher Exact Test also shows the positive association with treatment (p<0.001)

Discussion

The results of this study demonstrate that Vitamin B₆ (Pyridoxine) therapy decreases the acneiform lesions on patients who suffer PAF. Up to 74% of the patients who are treated experienced complete control of PAF symptoms within 6 months after treatment with 100mg or 200mg daily. This study is similar to the design of Snider and Dieteman in 1974.³ In their study, the patients were put on 50mg of Vitamin B₆ daily and the improvement is based on a standardized patient questionnaire.(3) Their study was not followed by any additional studies in the use of Vitamin B₆ in the treatment of PAF. It was our intention in this study to provide more data for the Vitamin B6 (Pyridoxine)



therapy on PAF.

The US recommended daily allowance (RDA) of Vitamin B₆ is 1.6-2.0 mg per day.⁹ Taking high doses of more than 500mg of Vitamin B₆ daily can lead to toxicity, which manifests in the form of peripheral neuropathy. Typical symptoms are tingling (pins and needles), clumsiness and numbness. These signs are reversible when the high dose intake of Vitamin B₆ is stopped. The US's Institute of Medicine has concluded that 500 mg/day represents the lowest-observed-adverse-effect-level (LOAEL) for Vitamin B6 intake. This report also arrives at a no-observed-adverse-effect-level (NOAEL) of 200 mg/day.¹⁰ In our study, all patients on Vitamin B₆ treatment, be it 100 mg or 200 mg, were all monitored for signs of toxicity. In the two year period included in this study, no signs of peripheral neuropathy were reported. The treatment protocol of the Duncanville Dermatology Clinic includes that if any patients were to complain of the signs of Vitamin B6 toxicity during this treatment, the treatment would stop immediately.

The results of this study support the efficacy of Vitamin B₆ in controlling patient's PAF. As with all studies, there are intrinsic biases in the study that cannot be eliminated. Due to the nature of the retrospective chart study design, we were unable to collect data on placebo effect. Consequently, we are unable to account for the placebo effect in this treatment study.

Another difficulty of this study is the fact that the non-treatment (control) group is derived from a relatively smaller group of patients than the other treatment group. This is also inevitable because of the retrospective nature of this study. A relatively small number of the patients did not start the Vitamin B₆ (Pyridoxine) treatment as compared to the patients who did initiate the therapy. However, part of the analysis of the data was done by repeat measure analysis of variance. This eliminated the use of the control group in the analysis and does not provide a statistical significance in this study.

In addition to the use of Vitamin B₆ sub-physiologic doses of prednisone (5 mg) have been recommended by another

author to alleviate the symptoms of PAF.³ No study on the use of prednisone for the treatment of PAF has been published. It may be worthwhile to compare prednisone therapy with Vitamin B₆ therapy in a prospective double blind clinical study in the future.

Another possible future study would be to explore the unanswered role of Vitamin B₆ in the control of PAF. We suspect that there may be relationship between Vitamin B₆ and progesterone level. The future study design can measure the progesterone levels in groups of patients that are on¹ no treatment,² placebo, and ³ Vitamin B₆. This will allow a clearer demonstration of the relationship between Vitamin B₆ intake and progesterone levels in the blood stream.

Although our study provides statistically and clinically significant results in the use of Vitamin B₆ for the treatment of PAF, repeated clinical trial study is warranted. The lack of placebo control and the relatively small study sample can be overcome by a prospective study design. It can also be used as part of future meta-analysis to confer a more definitive result.

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Squamous Cell Carcinoma of the Lip

Jay S. Gottlieb, D.O., F.O.C.O.O.*

With approximately 4,300 cases of lip cancer resulting in 100-150 deaths per year in the United States, the topic of lip cancer is timely. The lip is the most frequent site for cancer of the oral cavity. If treated early, the prognosis is excellent. Prognostic indicators which may herald an aggressive disease and a poor outcome will be discussed.

The incidence of lip cancer in the United States is 1.8 per 100,000. Patients typically present in their 7th or 8th decade. All reported series demonstrate that the disease occurs more frequently in males. There is a male to female ratio that approaches 79:1 for cancer of the lower lip and 5:1 for the upper lip.

Many factors have been implicated in lip cancer. Sunlight is a major contributor to the development of lip cancer. The lip is prone to sun damage because it lacks a pigmented layer for protection. Cigarette and pipe smoking also play a role. A positive serology to syphilis was implicated in some early studies, with the incidence nearing 20%. More recent papers report not more than a 3% association. Poor oral hygiene results in persistent irritation and possibly lip cancer. The use of alcohol has been associated with the development of carcinoma of the lip as well as other sites in the oral cavity. Mouthwashes that contain alcohol have also been implicated. The lower lip is the most frequent location of lip cancer and is found between 90 and 96%. The upper lip is involved between 1.3 and 7.7% of the time and the commissure is involved in 1 to 2%.

The incidence of squamous cell carcinoma of the lip approaches 95%. They are most frequently of the well-differentiated variety. Basal cell carcinoma may extend onto the labial surface. Basal cell carcinoma is twice as common on the upper lip and is the most frequent neoplasm in that location. Salivary gland tumors of the lip have been reported. Of these, about 20% were malignant. The

majority of these occurred on the upper lip. Melanoma infrequently involves the lips.

Squamous cell carcinoma of the lip is typically a crusted ulceration, which bleeds easily. Occasionally the patient has been treated with antibiotics and may even report having had some improvement. The lesion only later develops into a palpable mass. Actinic changes are usually visible on the lip and on other exposed area of the head and neck. Leukoplakia of the lip may be seen. Enlarged palpable lymph nodes, if present, are most likely inflammatory in nature rather than suggesting metastatic disease. An enlarged lymph node must always be addressed. Hypesthesia of the lip must make the physician consider the possibility of perineural invasion.

When treating cancer of the lip the primary goal is eradication of the cancer. Consideration is also given to preserving oral competence and an adequate buccal sulcus, minimizing the surgical deformity, and restoration of a cosmesis. Primary surgical excision offers the advantage of eradication of disease, pathological survey of margins and reconstruction of the defect in a single stage.

A T1 or small T2 lesion of the lip can be excised with a 6-10mm margin and result in a defect less than 1/2 the length of the lip and can be closed primarily. The resulting defect from excising the middle of the upper lip may require excision of perialar skin.

Lip augmentation is generally required when 1/2 to 2/3 of the length of the lip is resected. The Abbe flap can be used. It is a full thickness flap from the opposite lip which is pedicled at the vermillion border and may be used to reconstruct defect of either the upper or lower lip not involving the commissure. If the commissure is involved then the Estlander flap from the opposite lip can be used to reconstruct the defect. The myocutaneous innervated flap may also be used.

If more than 2/3 of either the upper or the lower lip is resected an adjacent cheek tissue flap is required. Several cheek advancement flaps have been

utilized. The use of nasolabial flaps can be considered and used unilaterally or bilaterally for reconstruction of the entire length of the lip. Resection of large lip cancers can require total lip reconstruction.

Infiltrating squamous cell carcinoma of the lip may require resection of bone and adjacent soft tissue. If cheek tissue is inadequate for closure then regional flaps are preferable to distal flaps. Since large lip cancers will require the adjuvant use of radiation therapy, reconstruction should be directed toward closing the defect and covering exposed bone. This will help achieve early wound healing. The forehead flap has also been used to accomplish lip reconstruction. Both bipedicated and unilaterally based flaps can be used. The visor flap has been utilized for near total lip reconstruction. Other flaps available for reconstruction of the anterior oral cavity include the trapezius myocutaneous flap, the pectoralis myocutaneous flap, the deltopectoral flap as well as the latissimus dorsi flap.

About 10% of patients with lip cancer will present with local metastasis. An additional 15% will subsequently develop local node metastasis. If local node metastasis is confirmed the five year survival approaches 50%. The survival rate for treatment of the initial neck metastasis by elective neck dissection and for salvage for the subsequent development of neck nodes is essentially the same. Since less than 10% of patients with T1 or T2 lip cancers develop neck metastasis, most authors do not feel that a neck dissection is empirically indicated. In the clinically negative neck, when the tumor size approaches T3 and T4, then sentinel node sampling procedure should be performed for biopsy.

If the patient presents with lip carcinoma and has positive unilateral neck nodes, a radical neck dissection is indicated. If the patient presents with a large midline tumor or a large tumor that approaches the midline, consideration should be given to performing a contralateral node sampling procedure. If the patient has a confirmed regional metastasis

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sis, it should be treated postoperatively with radiotherapy.

The extent of disease at the time of presentation determines the patient's prognosis. The five-year cure rate for T1 and T2 lesions without cervical metastasis approaches 90%. This excellent cure rate can be achieved with either surgery or irradiation. The five-year survival falls to 60% for T3 lip cancers and to 40% for T4 lip cancers. If metastatic disease is present in the neck, the five-year survival rate falls to 50%.

There are several prognostic indicators for squamous carcinoma of the lip. The prognosis of carcinoma of the upper lip and commissure is worse than the prognosis for the lower lip. The five-year survival is 10 to 20% lower than for the lower lip. Cervical metastasis, especially when large, bilateral or fixed indicate a poor prognosis as does the presence of distant metastasis.

A worse prognosis is seen with poorly differentiated squamous cell carcinoma as well as with melanoma. Recurrent squamous cell carcinoma at the site of the initial resection carries a worse prognosis and suggests an aggressive tumor. The presence of bony mandibular involvement has a five-year survival rate of 29%.

Case Presentation

A 65 year old white male presented to the dermatology clinic with a three-month history of a progressively enlarging lower lip mass. He reported a nonhealing, painless ulceration in that location where he had some dental procedure performed 3 years prior. He admitted to smoking three packs of cigarettes per day for the past 39 years and consumed alcohol regularly. Past medical history was otherwise unremarkable.

On exam he was found to be a thin white male with a large amount of diffuse actinic skin damage in the head and neck area. Examination revealed a firm, nontender 1cm mass in his right lower lip which extended to the midline. There was no cervical adenopathy. His laboratory values were normal.

A punch biopsy was performed which revealed invasive well differentiated squamous cell carcinoma. Subsequently he underwent a full thickness resection of 35% of his lower lip. Surgical margins were free of tumor. Reconstruction was carried out employing a W-Plasty. His postoperative course was unremarkable. (FIGURES 1,2,3.) The final pathology reported invasive well differentiated squamous cell carcinoma with all surgical margins clear. There was, however,

perineural invasion of the right mental nerve. For this reason he is to undergo radiotherapy postoperatively.

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Figure 1

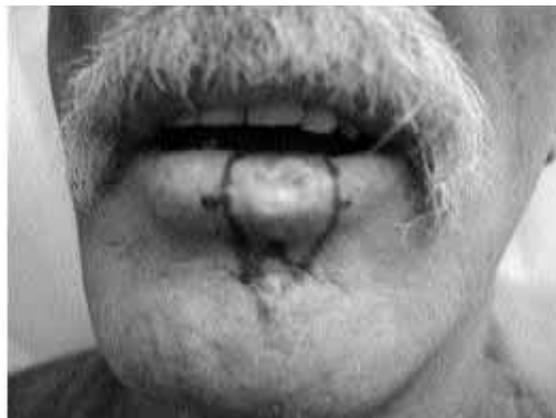


Figure 2



Figure 3



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Phakomatoses

Kellie Mosley, DO*, Stanley E. Skopit, D.O., F.A.O.C.D.**

Phakomatoses

The phakomatoses are neurocutaneous diseases. They are a group of hereditary disorders which occur spontaneously, which lesions involve the nervous system and the skin.¹ Phakomatosis is derived from the Greek word phakos which means "mother spot". The mother spots will be malformative and dysplastic lesions found most often in the brain, the skin and the viscera of the patient. The masses or tumors which develop from the mother spots are termed phakomas. These included a spectrum of proliferative activity, which were benign and other malignant neoplasms. Phakomatosis include tuberous sclerosis, von Recklinghausen's disease (neurofibromatosis), von Hippel-Lindau's disease (angiomas retinae), ataxia telangiectasia, basal cell nevus syndrome, nevus sebaceous, and Sturge-Weber syndrome.²

This paper will review four of the more common neurocutaneous diseases, including neurofibromatosis, tuberous sclerosis, von Hippel-Lindau's disease and Sturge-Weber disease.

Neurofibromatosis

There are two forms of neurofibromatosis which have been described including neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2).

Neurofibromatosis or von Recklinghausen's disease is inherited autosomal dominantly and encompasses developmental changes in the skin and in the nervous system. Type 1 neurofibromatosis encompasses approximately 85% of the cases and is termed classic neurofibromatosis. Cutaneous manifestations of neurofibromatosis includes neurofibromas which measure a few millimeters to a few centimeters in diameter. These are widely distributed.

The patients also have multiple café au lait spots. Also, approximately one-fourth of the patients under 6-years-old have Lisch nodules which are found in the irises. These nodules are also found in 94% of older patients.³

The hallmark of the neurofibromatosis is the café au lait macule. It is a uniformly pigmented, light brown macule, round or oval with irregular or uneven borders. The macules are most often present at birth or by the time the patient reaches his/her first birthday. The diagnostic marker for Type 1 neurofibromatosis is the finding of six (6) or more café au lait macules of at least 1.5-cm in diameter.⁴

Axillary freckling or Crowe's sign may often occur usually on the neck, but may also involve the inguinal region extending to the peritoneal area. There may also be marked hyperpigmentation of the skin present along with xanthogranulomas.

Many organ systems may also be involved in neurofibromatosis. Endocrine disorders occur such as acromegaly, cretinism, hyperparathyroidism, myxedema and pheochromocytoma. Patients with neurofibromatosis Type 1 are four times more likely to develop malignancies than the general population. Malignant peripheral nerve sheath tumors develop in approximately 5% of patients with NF1, which usually occurs after 10-years of age. However, it has been noted that younger children are also affected. Osteocytomas are the most common intracranial tumor involving the optic nerves, the hypothalamus, brain stem and the cerebellum.

Seizures, dementia and mental retardation, along with a variety of intracranial malignancies may also occur. Melanoma, however, does not appear to be a true association.

In neurofibromatosis, approximately 40% of patients have abnormalities of the bone. These skeletal abnormalities vary from asymptomatic, erosive-type changes resulting from pressure from adjacent neurofibromas to painful pathologic fractures. The most common skeletal manifestation is kyphoscoliosis.^{5,6} Additional radiographic findings include

segmental hypertrophy, cystic lesions in cancellous bones, cortical bones or pedunculated from the bone and scalloping of the posterior vertebral body. The exact cause of these changes is not known, however, segmental hypertrophy from increased vascular supply has been implemented.

Generalized osteomalacia has also been described in patients with AF. Absence of the greater or lesser wing of the sphenoid bone and congenital bowing of the bones of the leg and pseudoarthrosis are classic, but unusual skeletal findings in neurofibromatosis.⁷

Histologically, neurofibromas are found to have faintly eosinophilic, thin, wavy-type spindle cells which have a spindle-shaped nucleus. Mast cells are greatly increased in the background matrix.⁸

While laboratory tests are helpful in identifying the complications of neurofibromatosis, there are no specific laboratory tests for the disorder. The diagnosis of neurofibromatosis is made in patients when two or more of the following criteria are present:

- 1) Six or more café au lait macules with greatest diameter greater than 5-mm in pre-puberty patients and greater than 15 in post-puberty patients.
- 2) Two or more neurofibromas of any type or one plexiform neurofibroma.
- 3) Freckling in the axillary or inguinal region.
- 4) A distinctive osseous lesion including sphenoid dysplasia or thinning of the longbone cortex with or without pseudoarthrosis.
- 5) Optic leioma.
- 6) Two or more Lisch nodules.
- 7) A parent, sibling or offspring with neurofibromatosis Type 1 on the basis of the above criteria.⁹

There is no treatment available for neurofibromatosis except for excision of the neurofibromas. There have been deaths reported from intracranial meningiomas and gliomas, peripheral nerve scar sarcomas and other malignancies. The disease is exacerbated during pregnancy and treatment resistant hypertension also occurs. The

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literature suggests obtaining a baseline MRI of the brain and spinal cord, along with a baseline ophthalmologic examination. The prognosis favors a shortened life span secondary to neurofibrosarcoma, pheochromocytoma or vascular or CNS tumor complications. There is a noted great variation in severity of this disease.¹⁰

Neurofibromatosis 2

(Bilateral Acoustic Neurofibromatosis)

This is also inherited autosomal dominantly. The incidence is 1 in 35,000 with males equaling females and is seen in all races. The symptoms frequently appear at 15 to 25 years of age. The genetic and phenotypic characteristics of NF2 are distinct from those of NF1, with the NF2 gene being located on chromosome 22.¹⁰ The characteristic feature of NF2 is bilateral vestibular schwannoma. Also, café au lait spots and cutaneous neurofibromas are less common in NF2 than are in NF1. Plexiform neurofibromas and Lisch nodules are also rarely seen in NF2. Schwannoma is a central nervous system tumor, usually of low grade malignancy and occurring with increased frequency in NF2. Pre-senile cataracts or lens opacity develop in approximately 50% of NF2 patients. The tumors may be complicated by deafness, tinnitus, poor balance, headache, muscular wasting and underwater disorientation.¹¹ Neurofibromatosis 2 can be diagnosed when the following characteristics are present:

- 1) Bilateral cranial nerve mass visualized with either CT or MRI.
- 2) A first-degree relative with NF2.
- 3) And either a unilateral nerve mass or any two of the following: neurofibroma, glioma, meningioma, schwannoma (osteo or capsular) cataract or lens opacity at a young age.

Management includes referral to a neurologist or neurosurgeon with surgical debulking of the tumors or referral to other specialists as warranted along with examination of a first-degree relative. Prognosis includes progressive deterioration with loss of hearing, ambulation and sight. Death is usually due to tumors in the CNS which occur approximately 20 years after onset of symptomatology.¹²

Tuberous Sclerosis

Tuberous sclerosis is an autosomal dominant disorder. The diagnosis is based on clinical, radiological and pathological findings. It presents classically with a triad of mental retardation, epilepsy and adenoma sebaceum. It has a low

penetrance and a spontaneous mutation rate of approximately 60%. This is due to a deletion on chromosome 9.13,14 The presenting features usually are monogenic seizures seen in infancy with mental retardation developing in approximately 50-80%. The earliest characteristic finding is the ash-leaf or hyperpigmented macule that is polygonal in shape, and this usually develops before the adenoma sebaceum. Adenoma sebaceum is a nodular rash seen on the face, particularly in the nasolabial folds, which develops between one and five-years-of-age. Other skin manifestations include angiofibromas, which occur in the trunk, the gingiva and periungual region. Shagreen patches, which are connective tissue nevi, also occur along with retinal nodular hamartomas.¹⁵

The pathognomonic central nervous system lesions of tuberous sclerosis include hamartomas and astrocytic tumors which involve the cerebral cortex and the ventricular borders. The cortical lesions which are termed tubers are made of astrocytes, neurons and dysplastic cells with astrocytic and neuronal features. The four main intracranial manifestations of tuberous sclerosis are cortical tubers, subependymal nodules, subependymal giant cell astrocytomas and white matter abnormalities. The common histological finding in all of these lesions is the presence of giant cell which show a spectrum of varying differentiations into a neuronal or astrocytic element. Cortical tumors are firm lesions and involve the gray matter and underlying white matter. The cortex is iso intense with gray matter but there is high signal on T-2 weighted images, and there are underlying white matter due to gliosis or edema.¹⁶ Another common finding in adults is sclerosis of the bones of the skull. Bony sclerosis has also been identified in the lumbosacral spine and pelvis, the phalanges of the hands and feet, and rarely the ribs.¹⁷ The incidence of intracranial calcification increases from approximately 15% in infants to 60% in children age 10 to 14-years-old.¹⁸ The classic radiographic features of tuberous sclerosis often times are completely asymptomatic. Mental development does not correlate well with the presence or absence of intracranial lesions.¹⁹

Laboratory evaluation includes wood's light examination, transfontanelle ultrasound, CT/MRI of the brain, EEG, fundoscopic exam, renal ultrasound and echocardiogram in infancy. Management would include referral to an appropriate specialist such as a neurosurgeon/neurologist for removal of brain tumors, or referral to a laser specialist for CO2 laser excision of facial angiofi-

bromas. The prognosis for tuberous sclerosis is good except for a rare incidence of premature death due to status epilepticus or a malignant brain tumor. Differential diagnosis would include nevus depigmentosus, nevus anemicus, vitiligo, idiopathic guttate hypomelanosis or hypomelanosis of Ito.²⁰

Sturge-Weber Syndrome

Sturge-Weber syndrome or encephalofacial angiomatosis includes nevus flammeus of the face which is present at birth and ipsilateral meningeal angiomatosis which involves the posterior parietal, temporal and occipital lobes.²¹ This usually occurs unilateral, but may also be bilateral in up to 25-30% of people. Additional clinical features include seizures, mental retardation, hemiparesis, and ipsilateral glaucoma.²² Sturge-Weber syndrome has been hypothesized to be due to a cerebral vascular abnormality which occurs between 4-8 weeks of gestation. Seizures will occur clinically in approximately 90% of the cases.

The cutaneous lesion is a simple capillary angioma of the dermis. This usually involves the upper eyelid or supra-orbital region and is localized to the region of the cutaneous distribution of the ophthalmic division of the trigeminal nerve. This is present at birth.²³

Angiomatosis of the choroid of the eye is usually seen in approximately 35-50% of the cases. This may lead to increased intraocular pressure which results in buphthalmos.

The leptomenigeal angiomatosis usually lies over the ipsilateral occipital lobe with varying degrees of extension over the parietal or temporal lobes. This involves the thin-walled vessels which are confined to the pia. There is a loss of normal superficial cortical veins which results in shunting to the deep venous system. Contrast CT or MRI demonstrates extensive leptomenigeal angiomatosis.²⁴ The pathnomonic radiographic feature is the presence of opaque double-contoured sinusoidal lines that follow the convolutions of the brain. This radiographic feature represents calcium deposits in the outer layers of the cerebral cortex in the region of the meningeal angiomatosis. They are usually seen only after the age of 2-years-old.²⁵ Other radiologic findings which have been reported include a thickened cranium, an elevated petrous bone with ipsilateral enlargement of the human cranium.²⁶ Differential diagnosis would include periorbital hemangioma and salmon patch. Laboratory evaluation would include MRI with gadolinium and EEG if MRI is positive. Management would be a referral to a dermatologist for

a pulsed dye laser treatment and also a referral to an ophthalmologist and neurologist if seizures are present. The course of the disease is dependent on the severity and extent of the cerebral and ocular lesions present. Prognosis is a reflection of the difficulty in controlling the seizures. This could be reflected in an increased frequency of mental retardation over time.²⁷

Von Hippel-Lindau Syndrome

VHL, also known as, CNS angiomatosis is an autosomal dominant disease with incomplete penetrance. Approximately 1 in 40,000 of the general population are affected, and it is due to a defect in chromosome 3.²⁸ Clinical presentation is usually by the fourth decade of life. The pathogenesis is unknown. Retinal hemangioblastomas with secondary visual impairment and blindness if untreated, is the characteristic lesion. Other lesions seen include a renal cyst, renal cell carcinoma in approximately 25-40% of the patients, pheochromocytoma seen in approximately 10% of the patients and pancreatic cysts.²⁹ The criteria proposed by Melmon and Rosen, frequently used for the diagnosis of Von Hippel-Lindau disease: two or more central nervous system hemangioblastomas or a single central nervous system hemangioblastoma in association with the visceral manifestation of the disease. With a family history of retinal or central nervous system hemangioblastoma, only one hemangioblastoma visceral lesion is required for the diagnosis. There is cutaneous involvement seen in approximately 5% of the cases, which would involve

capillary malformations of the head and neck including capillary angiomas. Approximately 10-20% of cerebellar hemangioblastomas produce erythropoietin which are accompanied by a secondary polycythemia.³⁰ Diagnosis would include cerebellar tumors. Laboratory evaluation would include a CT or MRI scan of the brain and spinal cord, abdominal CT, MRI scan, a VMA level, serum catecholamine level and a complete blood cell count. Management would include referral to ophthalmology, neurosurgeon and neurologist, along with urologist. The prognosis is grim with this being a progressively fatal disease with death occurring by the fourth decade. Hematuria is usually the common presenting sign. Premature death is secondary to the progressive growth of CNS hemangioblastomas or metastatic renal cell carcinoma.^{31,32}

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Mid-dermal Elastolysis: A Case Report and Literature Review

Matthew B. Doppelt, D.O.*, Stanley E. Skopit, D.O.,F.A.O.C.D.**

A 37 year-old female presented to the office distressed over subtle wrinkling of her abdominal skin. A punch biopsy was performed to aid in the diagnosis. Microscopically, elastic tissue stains revealed a well-defined mid-dermal absence of elastic tissue. The diagnosis of idiopathic mid-dermal elastolysis was made. This disease is rarely reported in the literature and what follows is a case report and review of the other documented cases.

Case Report

History

A 37 year-old female presented to the office complaining of a subtle wrinkling on her abdomen that had been slowly progressing over the course of a year. As an actress she was quite distraught with anticipation that this rash might continue to evolve causing further "disfigurement." She denied any prior rash in the areas affected and her past medical history was completely non-contributory. She also denied any history of cosmetic surgery such as breast augmentation or liposuction. There were no altered sensations such as pruritus, burning, or numbness at the affected sites. She had sought treatment from a naturopathic physician who prescribed various herbal remedies; none of which helped the condition. She had also applied an over-the-counter steroid cream for one month without benefit.

Physical Examination

In general, the patient was well-nourished, well-hydrated and somewhat anxious. Initial superficial inspection failed to reveal any rash. However, when the lines of skin tension were relaxed, large, poorly defined patches of fine skin wrinkling and yellowish papules could be observed on the abdomen and to a lesser extent the lower back, forearms, and medial thighs (Fig. 1 & 2). Mild hyperelasticity of the skin on the neck and the bilateral antecubital fossa was noted.

Investigations

A three-millimeter punch biopsy was taken from a representative area of the abdomen. H&E staining revealed disorganized collagen bundles in the mid-retic-



Fig.1. Fine wrinkles on abdomen characteristic of MDE.



Fig. 2. Magnified view of MDE wrinkles

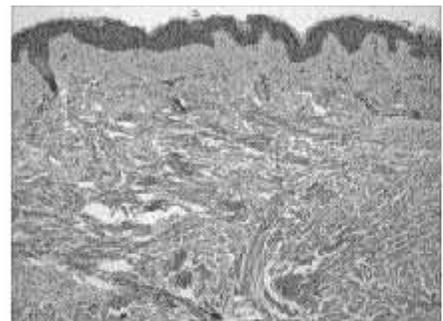


Fig. 3 Three-millimeter punch biopsy specimens from a lesion in figure 1. Disorganized collagen bundles identified in the mid-reticular dermis (H & E).

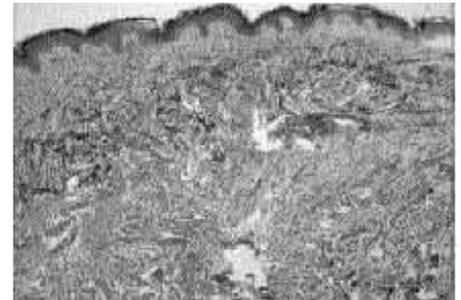


Fig. 4. Elastic stain (EVG) demonstrates absence of elastic outlined to the mid-dermis.

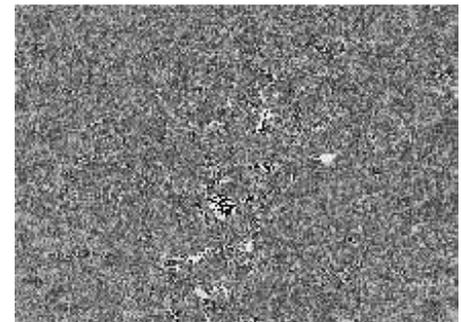


Fig 5. High power magnification (EVG) demonstrates the absence of inflammatory cells or granuloma formation.

diagnosis of mid-dermal elastolysis was made.

The CBC, CMP and UA were all within normal limits. Autoimmune blood work was performed. The only positive was an ANA 1:160 in the speckled pattern. The anti-smooth muscle, antimitochondrial, anti-SS-A/-SS-B, RNP, anti-SM, antihistone, antichromatin, anti-DSDNA antibodies were all negative. The rheumatoid factor was also negative and the sedimentation rate and complement levels were normal.

After the patient was given the diagnosis she utilized the Internet to learn more about this disease. Even though she denied any history of tick bites or charac-

ular dermis (Fig. 3). Elastic van Gieson stain demonstrated loss of elastic fibers in the mid-reticular dermis (Fig. 4 & 5). A

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teristic rash, she had a Lyme titer performed. Interestingly, this was "positive

DISCUSSION

At 32 weeks of age elastic fibers are well-developed. They are thickest in the dermis and become thinner as they approach the epidermis. Elastic fibers of the dermis consist of two components: microfibrils (15%, electron-dense) and the matrix elastin (85%, electron-lucent). Microfibrils are aggregated at the periphery of the elastic fiber, and are also present within the elastin as strands. Elastic fibers are significantly changed during maturation and exposure to UV light. The microfibrils, which confer elasticity, are slowly lost as they mature. Additionally, the physiologic turnover of elastic tissue is markedly decreased in mature tissues.¹² Elastin degradation may be markedly increased in various disease states. Polymorphonuclear elastases are among the most powerful elastolytic enzymes and probably play a role in post-inflammatory elastolysis.¹³

Demographics

Shelley and Wood first described mid-dermal elastolysis (MDE) in 1977.¹⁸ It is described as a rare, acquired disorder characterized histologically by a band-like absence of elastic tissue confined exclusively to the mid-dermis. A Medline search ranging from 1977 until the present day utilizing the identifiers "mid-dermal" and "elastolysis" was performed. After reviewing the articles a total of thirty-two cases have been reported with this being the thirty-third.¹⁻²² Only four of the cases reported were males. The average age at presentation was thirty-nine with the vast majority of cases ranging between thirty and fifty. The oldest patient was seventy-nine and the youngest patient was fifteen.

Clinical Presentations: Clinically, MDE is characterized by diffuse fine wrinkling of the skin with a predilection for the trunk and upper extremities. Yellow to white papules and plaques as well as perifollicular papules have also been described. Shelley and Wood's case was that of a 42 year-old female with fine wrinkles on the trunk and arms.¹⁸ In their case, there was an urticarial event that lasted for more than a year and preceded the wrinkling by seven years. They believed MDE represented a post-inflammatory event related to the antecedent urticarial event. The youngest case, a 15 year-old female developed MDE in areas clinically diagnosed five years previously with granuloma annulare.²² In 2001, Boyd and King described MDE in two patients with lupus erythematosus.³ Our patient has a positive ANA and Lyme titer, but no other

diagnostic criteria for SLE and never had the characteristic rash of Lyme's disease. Kirsner and Flanaga reported two female patients with MDE who also had positive ANAs and false-positive Lyme titers.¹⁰ One of their cases was attributed to silicone mammoplasty. In one case reported in the European literature, Hashimoto's thyroiditis was associated with the development of MDE.⁷ Others^{9,19,21} have implicated the role of UV light as the wrinkling tends to occur in photodistributed areas, including Bannister² who reported two males with widespread persistent reticulate erythema concentrated within chronically sun damaged skin. However, only six of the thirty-four described cases have known previous inflammatory conditions.

Pathogenesis

Several pathogenic mechanisms of MDE have been postulated. These include decreased elastic fiber production (UV light playing a considerable role), an autoimmune process causing destruction of elastic fibers,¹⁰ and an inflammatory process.

Shelley and Wood¹⁸ hypothesized that the cause of the disorder in their patient was immune elastolysis. Autoimmune diseases have been associated with MDE including rheumatoid arthritis,¹⁷ Hashimoto's thyroiditis,⁷ and lupus.³ This coupled with reports of positive ANAs and "false-positive" Lyme titers lends support to an immune mediated mechanism of MDE.

Snider, et al., opined that MDE appears to fall in a spectrum of elastolytic disorders that also includes cutis laxa, anetoderma, perifollicular elastolysis, and actinic granuloma.¹⁹ Although MDE was originally described as a non-inflammatory condition, multiple reports have demonstrated the presence of inflammatory infiltrates and elastic fiber phagocytosis supporting an inflammatory hypothesis of MDE pathogenesis.^{3,9,18} Neri, et al.,¹³ have performed the most in depth investigation as to a potential inflammatory pathogenesis of MDE. They undertook a pathological and ultrastructural study of five cases of MDE. A lymphocytic perivascular infiltrate was present in all five patients with three of five showing histiocytes among collagen bundles. Additionally, all five cases revealed mononuclear cells often showing phagocytized elastic fibers. Subsequently, the authors surmised that the elastolysis in MDE is most likely a post-inflammatory phenomenon.

None of the theories that have been advanced specifically addresses why, or how the elastolytic process remains confined to the mid-dermis.

Diagnosis, Prognosis, and Treatment

The astute dermatologist should suspect MDE based upon the unique clinical presentation of fine wrinkling and/or follicular protrusions of skin primarily overlying the abdomen and arms. A punch biopsy with microscopic examination utilizing elastic tissue staining should be performed. Histologically a distinct band of elastolysis confined exclusively to the mid dermis will confirm the diagnosis. Additionally, it may prove beneficial to perform screening tests for autoimmune, collagen-vascular, endocrine, and hematological diseases to identify otherwise subclinical disease states. While MDE tends to be progressive, no internal organ involvement has been reported. The specific pathophysiologic process has yet to be clearly elucidated and as such, there is no known effective treatment. However, because of the predominant photodistribution of the wrinkling, it is logical to encourage patients to adopt protective measures against UV radiation. Additionally, the use of colchicine and retinoic acid have been recommended but have shown little benefit.¹²⁰ Oral and topical steroids have proven ineffective.¹⁶

Conclusion

We have presented a case of a rarely reported disease known as MDE in a 39 year-old Caucasian female. This disease is characterized clinically by slowly progressive, very fine wrinkling of the skin and/or follicular protrusions usually over the abdomen and arms. Histologically, it is characterized by the destruction and loss of elastic fibers confined exclusively to the mid-dermis. While several pathogenic mechanisms of MDE have been postulated, the specific histogenesis of this disease is still poorly understood. At present, there are no known effective treatments. Hopefully, through further reports, a common unifying theme may become apparent that will explain its pathogenesis. Once this is known, perhaps we will have more effective treatment options.

Acknowledgments

The author thanks Drs. Evangelos Poulos and Andrew Hanly at Global Pathology for their expertise in dermatopathology, and their assistance in providing the histopathologic images contained within this report.

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††Data from moderate patients in a 6-month study conducted in adults to determine the safety and efficacy of ELIDEL in the long-term management of atopic dermatitis (N=192).

Reference: 1. Data on file, Novartis Pharmaceuticals Corporation.

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A Rare Case of Bleomycin Induced Flagellate Hyperpigmentation Presenting Histopathologically as an Urticarial Drug Hypersensitivity Reaction

Risa Gorin, D.O.*, Charles Gropper, M.D*, Cindy Hoffman, D.O.** , Damian DiCostanzo, M.D.***

Abstract

A case of flagellate hyperpigmentation after administration of bleomycin in a patient with Hodgkin's Lymphoma is described. Clinically and histologically, the eruption was consistent with an urticarial drug hypersensitivity reaction. This is the second reported case in which bleomycin-induced flagellate hyperpigmentation was found to have these histological findings. A review of the literature was performed, and the various clinical and histopathological features for this distinctive eruption is discussed.

Case Report

A 27 year-old Hispanic male was referred to the dermatology clinic by his hematologist for evaluation of a pruritic eruption of 3 months duration. The patient's past medical history was significant for Stage IIb Hodgkin's Lymphoma that was diagnosed 4 months prior to presentation by a biopsy of a mediastinal mass. Prior to this, the patient was otherwise healthy, took no medications on a daily basis, and reported no drug allergies. One month after diagnosis, he was started on a chemotherapeutic regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) every 2 weeks. He stated that the eruption began within 24 hours of his first treatment with ABVD, was progressively worse after subsequent treatments, and never fully resolved. The pruritic eruption was recalcitrant to oral prednisone and antihistamines.

At the time of presentation to the dermatology clinic, a comprehensive cutaneous examination revealed multiple linear hyperpigmented streaks coalescing into patches on his trunk and upper extremities, erythematous, edematous urticarial papules and plaques on his trunk and proximal interphalangeal joints bilaterally, mild edema distally in his upper extremities and hands, and diffuse non-scarring alopecia. There were no oral lesions.

Our differential diagnosis at that time was post-inflammatory hyperpigmentation, primary cutaneous lymphoma, metastatic disease, urticarial drug reaction, and bleomycin-induced hyperpigmentation. A clinical diagnosis of bleomycin-induced flagellate hyperpigmentation was made. The patient was advised to complete his course of oral prednisone and antihistamines and was given fluocinonide 0.05% ointment for additional symptomatic relief. In addition, a 3-mm punch biopsy was performed from one of the hyperpigmented streaks on his trunk. Microscopic analysis revealed a superficial perivascular and interstitial mixed cell infiltrate with numerous eosinophils and slight epidermal spongiosis consistent with an urticarial drug hypersensitivity reaction. Also noted was an increased number of melanophages in the dermis.

In support of a diagnosis of urticarial drug hypersensitivity reaction was the finding of a significant blood eosinophilia. The blood eosinophils were 1.6% (reference range, 0 to 7.0%) after his first treatment but then ranged from 8.5% to 14.3% during his next 5 treatments.

On follow-up examination 3 weeks later, the hyperpigmented streaks and erythematous nodules and papules persisted but his upper extremity joint edema had improved. He reported a burning sensation from the fluocinonide 0.05% ointment and discontinued its use. His pruritus persisted, and therefore, he was maintained on antihistamines for symptomatic relief. One week prior to his follow-up visit, the ABVD was discontinued as he experienced clearing of his mediastinal mass and adenopathy.

Comment

Bleomycin is a cytostatic, sulfur-con-

taining antineoplastic antibiotic derived from the soil fungus *Streptomyces verticillus*.¹⁻⁵ It has antitumor, anti-bacterial, and antiviral properties. It works by inhibiting incorporation of thymidine into DNA resulting in single and double stranded breaks and subsequent DNA degradation.

Bleomycin was initially isolated in 1965 in Japan by Umezawa.^{1, 2, 4, 6} Today, it is a commonly used systemic chemotherapeutic agent used in the treatment of various neoplasms' including non-Hodgkin's lymphoma, Squamous Cell Carcinoma (head, neck, skin, mucosa, cervix, vulva, penis, and larynx), Testicular Carcinoma, and Hodgkin's disease. It is widely distributed throughout the body and is degraded by a hydrolase enzyme present in tissues. However, the skin and lungs do not possess this hydrolase enzyme allowing accumulation of the drug in these locations.^{1, 3, 5, 6} This is considered to be the reason why the majority of side effects occur in the lungs and skin in the form of pulmonary fibrosis and hyperpigmentation, respectively.¹

Like many other chemotherapeutic agents, bleomycin has been reported to cause a variety of mucocutaneous reactions including alopecia, mucositis, hypersensitivity reactions, onychodystrophy, onycholysis, Beau's lines, radiation enhancement, radiation recall, neutrophilic eccrine hidradenitis, eccrine squamous syringometaplasia, and sclerodermatous changes.⁷⁻⁹ Aside from the mucocutaneous reactions, bleomycin is cardiac and pulmonary toxic. However, there is virtually no gonadal toxicity or risk for myeloid malignancies associated with its use.⁹ Local reactions caused by extravasation of the drug into adjacent soft tissue or veins during infusion include

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chemical cellulites and ulceration.⁷

A distinctive “flagellate” hyperpigmentation frequently occurs and is unique to bleomycin. Bleomycin induced flagellate hyperpigmentation occurs in 8 to 38% of patients and was first reported in 1971 by Moulin et al.^{1, 5, 6, 11} Guillet and Guillet reported an occurrence of cutaneous hyperpigmentation in 66% of patients studied in their series.¹² Hyperpigmentation has been reported after intramuscular,¹³ intravenous,^{6,14} intraperitoneal,¹⁵ and intrapleural^{1,3} administration of the bleomycin. Onset of the eruption varies from 24 hours to 9 weeks after administration and after cumulative doses ranging from 60 mg to 285 mg, but has been observed to occur after as little as 15 mg.^{2, 5, 6}

A review of the literature demonstrates a variety of clinical and histopathologic presentations. The eruption typically occurs on the upper trunk, limbs, and face and is extremely pruritic. Clinically,



Figure 1. Multiple linear hyperpigmented streaks coalescing into patches with erythematous edematous urticarial papules and plaques on the right upper extremity.

A Rare Case of Bleomycin Induced Flagellate Hyperpigmentation Presenting Histopathological Urticarial Drug Hypersensitivity Reaction

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Figure 2. Multiple hyperpigmented linear streaks coalescing into patches on the knee.

lesions include linear microvesicular bands,¹² urticarial papules and plaques,¹² erythematoviolaceous macules evolving into papules,¹⁵ and patchy pigmentation in pressure areas and palmar creases.⁹ Less common clinical presentations



Figure 3A. Superficial perivascular and interstitial mixed cell infiltrate with numerous eosinophils and slight epidermal spongiosis (H&E, original magnification x 40).

include dermatomyositis,¹¹ painful inflammatory nodules on the extremities, warty hyperkeratotic plaques on the fingers, erythema multiforme, digital gangrene, Raynauds phenomenon and blisters.⁵⁻⁸

The precise mechanism for bleomycin-induced hyperpigmentation is unknown. The hyperpigmentation is reversible when the drug is discontinued, but may persist up to six months or more,^{4, 9, 16} and may recur on re-challenge.⁶ No treatment is necessary only symptomatic care.¹ Some authors theorize that the hyperpigmented lesions arise as a result of local trauma from scratching or pressure allowing the drug to leak out of dilated blood vessels.¹¹ However, many authors have been unsuccessful in reproducing the lesions by these means.^{3,8,13} Several other theories have been proposed and include inflammatory oncotaxis,⁵ direct or indirect cytotoxic effects on keratinocytes and eccrine epithelium,^{4,12} increased melanocyte stimulating hormone secretion, and stimulation of melanocytes by adrenocorticotrophic hormone.⁶ Also implicated in the pathogenesis of hyperpigmentation is the increased transfer of melanin. In support of this, electron microscopy has revealed decreased epidermal turnover and a prolonged contact between melanocytes and keratinocytes.¹⁴ While the number of melanocytes was not increased, an increase in the number of melanosomes present in keratinocytes was seen.^{1,18} A variety of histopathological

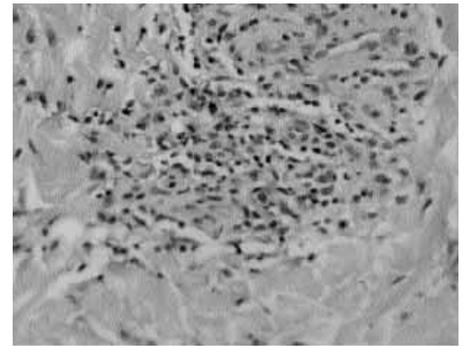


Figure 3B. Superficial perivascular and interstitial mixed cell infiltrate with numerous eosinophils and slight epidermal spongiosis (H&E, original magnification x 100).

reaction patterns have been reported in biopsy specimens of previously reported cases. Epidermal changes have included focal vacuolar degeneration of the basal layer,^{1,11} dyskeratosis and necrosis of epidermal keratinocytes and eccrine epithelium,^{1,4} melanin distribution in the upper horny layers,¹² irregular acanthosis and spongiosis,⁵ and full thickness epidermal acantholysis.¹³ Dermal changes reported include perivascular pigmentary incontinence and extravasation of erythrocytes,¹³ lymphocytic vasculitis,³ moderate papillary dermal edema^{1,11} and a fixed-drug type reaction pattern.¹ Yamamoto et al. reported thickened collagen bundles and a deposition of amorphous homogenous material in the upper dermis consistent with sclerodermatous changes suggesting that bleomycin influences dermal fibroblasts as well.¹⁴ Lastly, in 1999 Rubeiz, et al reported the first case of an urticarial allergic drug reaction histologically.² My patient demonstrates similar clinical and histological findings.

Bleomycin-induced flagellate hyperpigmentation is a unique and distinctive occurrence. Although varying clinical and histological findings have been reported, one of the rarest histopathological findings is that of an urticarial hypersensitivity reaction. Our patients' clinical and histopathological presentation was consistent with this rare variant. Corresponding with the histologic findings, his laboratory data revealed a significant blood eosinophilia consistent with an urticarial drug hypersensitivity reaction.

Further case reports of this rare histological presentation of bleomycin induced flagellate hyperpigmentation are needed to better elucidate the exact mechanism for this unique cutaneous finding.

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Cutaneous Manifestations of Sarcoidosis

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Abstract

Sarcoidosis is a multisystem disorder of unknown cause that is characterized by its pathologic hallmark, the noncaseating granuloma. Since its first recognition as a clinical entity, sarcoidosis has been known to induce secondary derangement of normal tissue as well as organ anatomy and function with prominent cutaneous involvement. The cutaneous manifestations of sarcoidosis often enable the dermatologist to be the first physician to make the diagnosis.

This paper reviews the pathogenesis, cutaneous polymorphisms, systemic involvement, diagnosis, and treatment for cutaneous sarcoidosis to further enhance the dermatologist's understanding of this complex condition.

Introduction

Sarcoidosis is a multisystem disorder of unknown cause that is characterized by its pathologic hallmark, the noncaseating granuloma. Since its first recognition as a clinical entity, sarcoidosis has been known to induce secondary derangement of normal tissue as well as organ anatomy and function with prominent cutaneous involvement. The cutaneous manifestations of sarcoidosis often enable the dermatologist to be the first physician to make the diagnosis.

This paper reviews the pathogenesis, cutaneous polymorphisms, systemic involvement, diagnosis, and treatment for cutaneous sarcoidosis to further enhance the dermatologist's understanding of this complex condition.

Epidemiology

Sarcoidosis occurs worldwide, affecting people of all races, both sexes, and all ages. It has a bimodal peak, first between the ages of 25 to 35 and then in women aged 45 to 65 years.^{1,32} Interestingly, cases of sarcoidosis present most commonly in the winter and early spring months.^{2,32} Worldwide incidence of sarcoidosis ranges from 1 case to 64 cases per 100,000 population with the higher annual incidence reported among African Americans, the Irish, and Scandinavians.^{3,32} African American women between the ages of 30 and 39 years were found to have the highest annual incidence of 107/100,000.^{4,32}

Perhaps more important than variations in incidence are the differences in

severity of disease according to race and ethnic background. A number of studies indicate that cases affecting African Americans have a tendency to be more acute and severe than in other races. Cases affecting Caucasians tend to be asymptomatic and chronic, with a more favorable prognosis.^{5,32}

Pathogenesis

The cause of sarcoidosis remains obscure for a number of reasons, including the heterogeneity of manifestations of the disease, overlap with other diseases, and insensitive and nonspecific diagnostic tests that lead to misclassification of the disease.⁶ There are many postulations as to the origin of sarcoidosis, including immunologic, genetic, infectious, and environmental.

The development of noncaseating granulomas is thought to be the result of local presentation of an antigen by macrophages to CD4 T lymphocytes.^{7,32} The T-cells then act in a twofold manner: in antigen recognition and in amplification of the local cellular immune response.^{7,32} The production of CD4 T-cell derived cytokines enhance lymphocyte proliferation to induce granuloma formation.^{8,32} Thus, a highly focused antigen-driven, overexuberant cellular immune response occurs within the target organ.^{9,32} In addition, the recruitment of CD4 T-cells from the peripheral blood causes the development of anergy.^{10,32} There is also a resultant hypergammaglobulinemia from a nonspecific induction of polyclonal B-cell immunoglobulin.¹¹

A genetic origin is supported by the presence of familial clusters of sarcoidosis.^{12,32} In the United States this occurs more commonly among African Americans. Associations through serologic studies have shown patients with certain class I and II HLA alleles found on chromosome 6, may have

increased susceptibility to sarcoidosis.^{13,32} Further genetic studies through the use of polymerase chain reaction (PCR) restriction fragment polymorphism have pinpointed the HLA-DRB1 locus to determine susceptibility to sarcoidosis.^{14,32}

Definitive identification and proof of an infectious agent are still lacking. The association of tuberculosis and sarcoidosis remains controversial. Popper et al^{15,32} found that 11 out of 35 cases of sarcoidosis lung tissue had mycobacterial DNA sequences. Kon and duBois^{16,32} found acid-fast forms of bacteria grew from the blood of 19 of 20 patients with sarcoidosis. However, Richter et al,^{17,32} by coding for 16S ribosomal RNA, present in all mycobacterial species, found none detectable in 23 lung tissue samples from patients with sarcoidosis. Therefore, studies for the detection of mycobacteria have been shown to be inconclusive. A multicenter study supported by the National Institutes of Health, named ACCESS (A Case-Controlled Etiologic Study of Sarcoidosis), is currently underway to search for possible infectious agents as the cause of sarcoidosis.^{18,32}

Suggestions of environmental triggers for the origin of sarcoidosis include inorganic antigens including clay, talc, pine, pollen, oxalosis, and beryllium.^{16,19,32} Occupational associations have been health care workers,^{20,32} firemen,^{21,32} and navy personnel on aircraft carriers.^{22,32} Interestingly, sarcoidosis is found to be more common in nonsmokers than smokers.^{23,32}

Cutaneous Manifestations

The first case of sarcoidosis was reported by Hutchinson more than a century ago. This first description corresponded to a patient with lupus pernio, and for a long time it was believed

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that the disease was limited to the skin. On average, 25% of sarcoidosis cases have cutaneous involvement that can occur at any stage, however, most often cutaneous involvement occurs at onset of the disease.⁶ For this reason the dermatologist will often be the first to consider a diagnosis of sarcoidosis.

Cutaneous lesions are classified as specific, when histologic examination shows the typical sarcoid granulomas, or nonspecific. Common specific sarcoidosis skin lesions manifest as maculopapules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio.²⁴ Maculopapular lesions are the most common cutaneous manifestations of sarcoidosis. The most important nonspecific skin lesion is erythema nodosum (EN), and its association with hilar lymphadenopathy, also called Lofgren syndrome, the most characteristic form of sarcoidosis.²⁵

Specific Cutaneous Manifestations:

Maculopapular Sarcoidosis. This is the most common form of cutaneous sarcoidosis. They are usually red-brown to purple papules and measure less than 1 cm.²⁵ They are commonly found on the face, lips, nape of the neck, upper back and shoulders.²⁴ In time the lesions involute to faint macules.

Annular Sarcoidosis. Papular lesions may coalesce or be arranged in annular patterns. Central clearing with hypopigmentation, atrophy, and scarring may occur. These lesions favor the head and neck and are usually associated with chronic sarcoidosis.²⁶

Hypopigmented Sarcoidosis. Hypopigmentation may be the earliest sign of sarcoidosis. Favoring the extremities, these lesions vary from a few millimeters to more than a centimeter in diameter. Often, a palpable dermal component is at the center of the lesion.²⁶

Lupus Pernio. This is the most characteristic skin lesion of sarcoidosis. It is most common in African American women and is the hallmark of fibrotic disease.^{27,32} Lesions are typically violaceous, and smooth with shiny plaques on the head and neck, especially the nose, cheeks, lips, forehead, and ears. Lesions may be disfiguring and involve underlying bone. Lupus pernio coexists with chronic fibrotic sarcoidosis of the upper respiratory tract, with nasal, pharyngeal, and laryngeal involvement, pulmonary fibrosis, chronic uveitis, and bone cysts.^{25,27,32}

Ulcerative Sarcoidosis. Affecting primarily young African American women, this type is very rare. Lesions favor the lower extremities. The clinical

appearance is not specific, but skin biopsies are diagnostic.²⁶

Subcutaneous Sarcoidosis. Also known as Darier-Roussy sarcoid, it consists of a few 1 to 3 deep-seated, painless, firm, mobile nodules on the trunk and extremities without epidermal involvement.²⁵

Scar Sarcoidosis. Sarcoid lesions may develop in old scars. Previously flat scars may raise up and develop a red or purple hue resembling keloids. The pathogenesis is unknown.^{28,32}

Plaques. Flat-surfaced and slightly elevated plaques appear with greatest frequency on the cheeks, limbs, and trunk symmetrically. Involvement of the scalp may lead to alopecia.²⁶

Ichthyosiform Sarcoidosis. This form resembles ichthyosis vulgaris with fine scaling on the distal extremities.²⁶

Alopecia. Alopecia due to sarcoidosis is seen in two settings. Plaques may involve the scalp leading to a scarring hair loss. More rarely, circular lesions appear on the scalp resembling alopecia areata.²⁶

Morpheaform Sarcoidosis. Very rarely, lesions present as generalized plaques, but may be localized and be accompanied by dermal fibrosis resembling morphea. Skin biopsies will demonstrate noncaseating granulomas.²⁶

Mucosal Sarcoidosis. Lesions in the mouth are characterized by pinhead-sized papules that may be grouped or fused together to form a flat plaque.²⁶

Nonspecific Cutaneous Manifestations:

Erythema Nodosum in Sarcoidosis. EN is the most common nonspecific cutaneous finding and considered the hallmark of acute sarcoidosis. When associated with bilateral hilar adenopathy, migratory polyarthritis, fever, and iritis, it is called Lofgren's syndrome.^{29,32} EN is associated with a good prognosis, with the sarcoidosis involuting within 2 years of onset in 83% of cases.^{30,32}

Other nonspecific changes seen with sarcoidosis are calcifications, prurigo, and erythema multiforme.

Systemic Involvement

In patients with sarcoidosis one third can present with nonspecific constitutional complaints including fever, fatigue, and weight loss. Sarcoidosis should be included in the differential of a fever of unknown origin. Other symptoms can be associated with the specific organ system affected.

Lung manifestations occur in nearly all cases of sarcoid.^{27,32} Lung disease is mainly granulomatous involvement of interstitial areas, affecting alveoli, blood vessels, and bronchioles. In 10% to 15% of patients there is irreversible fibrosis and severe disability.¹¹

Intrathoracic and peripheral lymphatic adenopathy is common. Up to 90% of patients present with hilar and/or paratracheal adenopathy.¹¹

Hematologic changes are seen in up to 40% of cases, manifesting as leukopenia, lymphocytopenia, and an elevated sedimentation rate.^{31,32}

The liver and spleen are involved between 50% and 80% of the time. Hepatic granulomas may cause jaundice, and splenomegaly is associated with a poor outcome because of its association with extensive fibrotic changes in other organs.³²

Musculoskeletal involvement has been reported to occur in up to 39% of patients, including bone cysts, osteolytic lesions, chronic myopathy and arthritis.³²

Ocular manifestations are present in 30% to 50% of cases. Sarcoidosis classically presents as acute anterior uveitis. Other lesions include lacrimal gland enlargement, iritis, conjunctival nodules, and scleral plaques. There is a definite threat of blindness and all patients need eye examinations.³²

Involvement of the upper respiratory tract is found in 5% to 20% of cases and can present as lupus pernio. There can be granulomatous invasion of nasal and oral mucosa, larynx and pharynx, salivary glands, tonsils, and tongue. Parotid gland enlargement is found in 6% of cases.³²

Cardiac manifestations occur in 5% of cases and may have serious sequelae such as sudden cardiac death, heart block, cardiomyopathy, or pericarditis.⁶

Neurologic manifestations occur in 5% to 10% of cases. The most common is a self-limited cranial nerve VII palsy, but all cranial nerves can be affected. Other problems include aseptic meningitis, seizures, space-occupying masses, peripheral neuropathy, stroke, and myasthenia gravis. Neurologic manifestations are associated with a higher mortality rate.^{32,33}

Endocrine manifestations such as hypercalcemia occur in up to 17% of cases. Diabetes insipidus can result from pituitary involvement, while hyperthyroidism can result from thyroid involvement.³²

Renal involvement can result in diffuse

interstitial nephritis which may lead to renal insufficiency.^{18,32}

Gastrointestinal involvement is rare, however, it most commonly presents in the stomach as an ulcer or mass.³²

Because of the many different presentations of sarcoidosis, several syndromes have been discovered. Lofgren's syndrome, frequent among Irish, Scandinavian, and Puerto Rican female patients consists of acute sarcoidosis, EN, migratory polyarthritis, fever, and iritis. Darier-Roussy sarcoidosis is the presence of subcutaneous nodules of the trunk and extremities. Waldenstrom syndrome is the combination of fever, parotid enlargement, anterior uveitis, and facial nerve palsy. Mikulicz's syndrome is bilateral sarcoidosis of the parotid, submandibular, and lacrimal glands.¹¹

Diagnostic Evaluation

There are no definitive diagnostic blood, skin, or radiologic imaging tests specific for sarcoidosis, hence it is a diagnosis of exclusion.^{13,32} The diagnosis of sarcoidosis is based on the presence of compatible clinical, radiological, and pathological information. At baseline the examination should include a complete history with emphasis on occupational and environmental exposure. The emphasis during physical examination should be placed on the skin, lungs, eyes, nerves, liver, and heart.

When sarcoidosis is suspected, a biopsy of the involved organ system is indicated, such as the skin, lung, or salivary glands, to obtain histologic confirmation of noncaseating granulomas, and tissue culture to rule out bacterial, mycobacterial, and fungal origin.

Histologic examination shows well-demarcated islands of epithelioid cells with occasional giant cell formation and no necrosis. There is a sparse lymphocytic infiltrate concentrated peripherally around the noncaseating epithelioid granulomas. Giant cells are more common in older lesions and often contain Schaumann bodies (altered lysosomes) or stellate asteroid bodies (entrapped collagen). Neither are specific for sarcoidosis, as they have been observed in other granulomas, such as tuberculosis, leprosy, and berylliosis.^{32,34}

Radiographic diagnosis is initiated by chest radiography. Gallium-67 scans may contribute by demonstrating gallium uptake by granulomas in the parotid and lacrimal glands, called the panda sign, or uptake by the bilateral hilar lymph nodes, called the lambda sign.^{32,35} However, gallium scanning adds little true diagnostic value because of their lack of

specificity.^{13,32}

Laboratory evaluation of a suspected patient with sarcoidosis includes liver and renal function tests, complete blood count, erythrocyte sedimentation rate, serum calcium and angiotensin-converting-enzyme (ACE) levels. However, elevated ACE levels are no longer considered specific for the diagnosis of sarcoidosis.^{13,32}

Additional clinical evaluation should include pulmonary function tests, electrocardiography, slit-lamp eye examination, and tuberculin/anergy testing.^{13,32}

Patients found to have sarcoidosis should be monitored for resolution or progression of the disease and for new organ involvement, since all patients are at risk for clinical deterioration in their condition.

Differential Diagnosis

The clinical and histopathologic differential diagnosis for specific cutaneous sarcoidosis consists of lupus vulgaris, leprosy, atypical mycobacterial infections, syphilis, localized foreign body reactions, tattoo-induced granulomatous reactions, necrobiosis lipoidica, granuloma annulare, granulomatous rosacea, metastatic Crohn's disease, deep fungal infection, and lupus miliaris disseminatus faciei.³⁶

Treatment

The heterogeneity of the manifestations of sarcoidosis, its uncertain clinical course, and the potential side effects of treatment compound the challenge of clinical management. There are few firm guidelines regarding whether or when to initiate treatment. As a general rule, oral-corticosteroids are indicated as the first line treatment for severe ocular, neurologic, cardiac, or pulmonary sarcoidosis.^{13,32}

Corticosteroids remain the mainstay of therapy despite the lack of well controlled clinical trials to show that these agents improve patients' long-term outcome. The correct dose, the value of daily as opposed to alternate-day therapy, and the appropriate duration of therapy are unknown. Current protocols suggest the use of 30 to 40 mg of prednisone daily for 8 to 12 weeks, with gradual tapering of the dose to 10 to 20 mg every other day over a period of 6 to 12 months.^(13, 32) However, severe systemic involvement requires a dose of 1 mg/kg per day for 4 to 6 weeks followed by a slow taper over 2 to 3 months.¹¹

In chronic disease nonsteroidal immunosuppressive agents are used to

avoid long-term corticosteroid-induced side effects. The agents most often used are antimalarials, methotrexate, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine.^{27,32} The data on immunosuppressive agents are largely anecdotal from case reports and have not been proven to be efficacious by randomized controlled studies.⁶ This is also true for therapies for specific cutaneous sarcoidosis.

The indication for treating cutaneous sarcoidosis is disfigurement.^{18,32} Chronic cutaneous lesions, particularly lupus pernio and plaques, which may cause scarring, may require oral steroid treatment. Alternative oral therapies that have been reported to be successful with cutaneous sarcoidosis include hydroxychloroquine (200-400 mg/day), chloroquine (250-500 mg/day), methotrexate (15 mg/week in 3 divided doses at 12 hour intervals), allopurinol (100-300 mg/day for several months), thalidomide (300 mg/day for 4 months), isotretinoin (1 mg/kg/day), minocycline (200 mg/day for 12 months), PUVA, and melatonin (50 mg/day).³²

Non-oral therapies for limited cutaneous sarcoidosis have included superpotent topical corticosteroids, topical steroid with hydrocolloid occlusive dressing, intralesional triamcinolone (5-10 mg/ml repeated monthly), intralesional chloroquine (50 mg/ml monthly), and carbon dioxide or pulsed dye laser. Surgical approaches have consisted of dermabrasion, grafting, and plastic surgery for lupus pernio.³²

Prognosis

The prognosis of patients with cutaneous sarcoidosis depends mainly on the extension and severity of systemic involvement. Up to 60% of patients with sarcoidosis experience spontaneous resolution, and an additional 10% to 20% of patients have resolution with corticosteroid use.^{32,37} Some types of specific cutaneous lesions, particularly plaques and lupus pernio, are more persistent, and are associated with more severe pulmonary and extrathoracic involvement. Nevertheless, the presence of specific cutaneous lesions taken as a whole does not have prognostic significance. However, the presence of EN is the best independent predictive factor of a good prognosis of sarcoidosis.²⁵

Relapses as treatment is withdrawn are frequent, especially in African American patients, who tend to have more severe and prolonged symptoms.^{18,32} The disease is chronic in 10% to 20% of patients, but only 1% to 5% will eventually die of the disease.^{27,32} Up to 10% of

patients with cardiac and neurologic disease will die of their illness. Death from sarcoidosis is mostly due to failure of vital organs, specifically the lungs and heart.⁶

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Therapeutic Perspectives in Dermatology #1

Focus on Reviews from Current Literature related to Pharmacotherapy

James Q. Del Rosso, D.O., F.A.O.C.P.

This feature provides reviews of selected references related to the pharmacologic treatment of dermatologic disorders. Emphasis is placed on discussion of specific disease state indications, drug actions, reactions and interactions. The overall goal of this feature is to provide clinically useful information that will be of valued assistance to the practitioner. The review in this issue focuses on treatment of common dermatoses.

The Role of Topical Sulfacetamide 10%/Sulfur 5% in the Treatment of Rosacea.

Clinical studies have evaluated the anti-inflammatory benefit of topical sulfacetamide 10%/sulfur 5% for the treatment of rosacea.¹⁻³ In one multicenter open-label study (n = 54), twice daily application of sulfacetamide 10%/sulfur 5% lotion used over a period of 8 weeks demonstrated a 43% mean reduction in erythema and an 81% mean reduction in inflammatory lesion counts when compared to baseline evaluations.² An 8 week double-blinded trial (n = 94) compared sulfacetamide 10%/sulfur 5% lotion versus placebo vehicle. The active treatment group exhibited a 65% decrease in counts of inflammatory lesions by week 4 and 78% by week 8, as compared to 44% by week 4 and 36% by week 8 in the placebo vehicle group. A significant decrease in facial erythema was also noted in the actively treated study arm; erythema reduction was reported as 66% at week 4 and 83% at week 8, compared to 33% at week 4 and 31% at week 8 in vehicle-treated patients.¹ An investigator-blinded comparative trial of sulfacetamide 10%/sulfur 5% lotion (n = 31) and metronidazole 0.75% gel (n = 32) demonstrated similar efficacy rates based on investigator evaluations and patient assessments of improvement after 8 weeks of therapy.³ Local tolerability of both medications was comparable and significant systemic adverse reactions were noted.

In an 8 week trial of patients with moderate rosacea, sulfacetamide 10%/sulfur 5% cleanser (n = 15) was used twice daily, alone or in combination with metronidazole 0.75% gel (n = 15)

twice daily.⁴ Both treatment groups exhibited statistically significant reduction in papule counts and erythema at all follow-up points. A significant reduction in overall rosacea severity was observed at week 8. Although the sulfacetamide 10%/sulfur 5% cleanser alone demonstrated efficacy as monotherapy, combined use with metronidazole 0.75% gel provided maximum benefit. Treatment was well tolerated in both study groups. A separate investigator-blinded patient preference study compared the tolerability and acceptance of sulfacetamide 10%/sulfur 5% cleanser (n = 25) versus an established commercially available, non-lipid facial cleanser (n = 25). Comparable results were demonstrated in all tested categories which included tolerability, irritation and product aesthetics.⁵

The Role of Benzoyl Peroxide Cleansers in the Treatment of Acne Vulgaris.

Topical benzoyl peroxide continues to be a "workhorse" of acne therapy due to its ability to reduce inflammatory lesions, potentiate the effect of antibiotic therapy and reduce emergence of antibiotic-resistant *Propionibacterium acnes* strains.⁶⁻⁹ *P. acnes* organisms resistant to benzoyl peroxide have not been identified. Informal surveys completed by the author suggest that although dermatologists accept the clinical benefits of benzoyl peroxide "leave on" formulations such as gels, the clinical efficacy and *P. acnes* suppression achieved with some benzoyl peroxide cleanser formulations have not been fully appreciated. The ability of topical benzoyl peroxide gel and cleanser formulations to suppress *P. acnes* organisms and reduce inflammatory acne lesions has been evaluated and confirmed.^{6,9-15} In a vehicle-controlled, double blind study evaluating the impact of benzoyl peroxide 5% wash (n = 75) used twice daily over a period of 12 weeks, a statistically significant reduction

in inflammatory lesions counts was noticed in the active treatment group; the patients treated with benzoyl peroxide 5% wash as monotherapy demonstrated a 39% reduction in inflammatory lesions as compared to < 10% lesion reduction in the placebo vehicle group.¹² Microbiologic assessment of treated patients (n = 16) demonstrated a 46% reduction in *P. acnes* organism counts after 2 weeks of treatment with benzoyl peroxide wash alone.¹²

A 12-week, controlled, investigator-blinded study of male (n = 22) and female (n = 34) adult patients with moderate facial inflammatory acne evaluated the clinical impact and tolerability of combining a benzoyl peroxide cleanser and topical retinoid therapy.¹⁰ The combination of benzoyl peroxide 6% cleanser used in the morning and tretinoin 0.1% microsphere gel in the evening (n = 30) was compared to application of tretinoin 0.1% microsphere gel alone in the evening (n = 26). Both groups were given a gentle non-lipid facial cleanser to be used in morning and evening, except during the morning in those patients using the benzoyl peroxide 6% cleanser. Evaluation parameters included inflammatory (papules, pustules) and non-inflammatory (comedonal) lesion counts, acne severity, severity of acne-associated erythema and conventional indices of irritation (ie. dryness, scaling, erythema, peeling).

By endpoint at week 12, patients using the combination protocol of benzoyl peroxide 6% gel and tretinoin 0.1% microsphere gel demonstrated 58.5% reduction in inflammatory lesions, 44.1% reduction in non-inflammatory lesions, 54.5% reduction in overall acne severity based on lesion counts and 47.5% reduction in acne-associated erythema. The group treated with tretinoin 0.1% microsphere gel alone exhibited 29.8%

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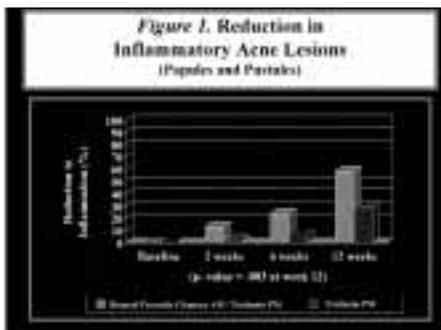


Figure 1: Comparative % reduction in inflammatory acne lesions: benzoyl peroxide 6% cleanser/tretinoin 0.1% microsphere combination versus tretinoin 0.1% microsphere alone.

reduction in inflammatory lesions, 48.9% reduction in non-inflammatory lesions, 30.7% reduction in overall acne severity and 18.2% reduction in acne-associated erythema (see Figure 1). Other than reduction in non-inflammatory lesions, which was comparable in both treatment arms, the combination treatment regimen proved to be statistically superior to tretinoin 0.1% microsphere gel alone. The number of patients experiencing significant irritation was minimal and comparable in both treatment groups. No dropouts occurred in either study arm due to adverse events related to drug usage. This study demonstrates that benzoyl peroxide 6% cleanser provides an additive benefit when used in combination with topical retinoid therapy by reducing inflammatory acne lesions and decreasing acne-related erythema. The use of the benzoyl peroxide cleanser did not interfere with the activity or efficacy of the topical retinoid and was not associated with a significant increase in irritation.

Infliximab Therapy and Pustular Psoriasis.

Several new therapies are under evaluation for the treatment of psoriasis vulgaris. The “big 4 biologic agents” that have currently emerged from this general class of compounds includes etanercept, efalizumab, infliximab and alefacept.¹⁶ These agents have been studied predominantly for patients affected with diffuse, moderate to severe psoriasis vulgaris (chronic plaque psoriasis). A recent report discusses the successful use of infliximab therapy in a patient with severe pustular psoriasis.¹⁷ A 39 year-old Caucasian male with chronic severe psoriasis demonstrating limited control with intramuscular methotrexate, acitretin and corticosteroid therapy (oral prednisone, topical triamcinolone acetonide 0.1%) presented with severe, generalized pustular psoriasis. Treatment was initiated with

intravenous infliximab 5mg/kg at presentation, after 2 weeks and again at 6 weeks. Just prior to the second infusion, persistent erythematous patches with complete absence of pustules were noted. Continued improvement resulted in reduction in the dosages of methotrexate, acitretin and prednisone at the point in time when the third infusion was administered (4 weeks after the second infusion). At follow-up 4 weeks after the third infusion (10 weeks after starting therapy), complete clearance of psoriasis was observed. At follow-up 6 weeks later (10 weeks after the third infusion), complete remission persisted and all other systemic and topical therapies were discontinued by this time point. Marked improvement of unguis dystrophy was also noted with significant new growth of disease-free fingernails observed within the first 10 weeks of initiating therapy. No adverse reaction were observed.

Corticosteroid Foam Formulations and Treatment of Psoriasis Involving Non-Scalp Regions.

The efficacy of both the betamethasone valerate 0.12 % and clobetasol propionate 0.05 % foam formulations have been confirmed in double-blind, placebo-controlled clinical studies of adult patients treated for moderate to severe scalp psoriasis.^{18,19} Betamethasone valerate 0.12 % foam used for the treatment of adult patients (n = 37) with psoriasis involving the trunk and extremities was shown to be effective, with statistically significant improvement in composite psoriasis severity scores demonstrated in a 12 week, split-body, placebo-comparison study.²⁰ Statistically significant superiority in efficacy has also been confirmed with clobetasol propionate 0.05 % foam as compared to placebo foam vehicle for the treatment of adult patients with mild to moderate non-scalp psoriasis (n = 81).²¹

In a double-blind, placebo controlled study of adult patients (n = 279) with non-scalp plaque psoriasis affecting up to 20 % body surface area, clobetasol propionate 0.05 % foam proved to be highly effective.²² Patients were treated for 2 weeks, with the final follow-up evaluation completed at week 4 (2 weeks after completion of therapy). After 2 weeks of therapy, 71 % in the clobetasol propionate 0.05 % foam group and 22 % in the placebo foam group demonstrated complete or almost complete disease clearance by physician global evaluation. At follow-up 2 weeks after completion of therapy, efficacy was sustained in 57 % of patients undergoing active treatment compared to 17% in the placebo-treated arm (see Figures 2A, 2B, 2C). Patient assessment of response proved to be



Figure 2A: Diffuse plaque psoriasis involving the lateral trunk (pre-treatment)



Figure 2B: Close-up of Figure 2A



Figure 2C: Marked clearance of psoriasis after 2 weeks of treatment with clobetasol propionate 0.05% foam applied twice daily (follow-up one week after completion of therapy)

comparable to the evaluations completed by the study investigators. No significant local or systemic reactions were noted in patients involved in either study arm.

Oral Antifungal Therapy and Tinea Versicolor.

Tinea versicolor is a common superficial fungal infection caused by certain commensal yeast species from the genus *Malassezia*. A double-blind study evaluated the comparative efficacy of oral ketoconazole and oral fluconazole

for the treatment of tinea versicolor in adult patients (n = 100).²⁵ Patients greater than 15 years of age were included if tinea versicolor affected at least 25% of the trunk region, with diagnosis based on clinical examination, direct microscopy (potassium hydroxide preparation) and Wood's light evaluation. Study patients were randomized to receive either single dose fluconazole 300 mg (2 x 150 mg capsules) repeated once in 7 days or single dose ketoconazole 400 mg (2 x 200 mg tablets) repeated once in 7 days. Follow-up evaluations were completed over a duration of 12 weeks from the initiation of therapy, with efficacy evaluated by clinical and mycologic assessment. Cure rates were statistically comparable at all follow-up points (week 2, 4, 8 and 12) and were optimal at week 8, with cure observed in 90% of the patients treated with fluconazole and 88% of those treated with ketoconazole. At week 12, mycologic cure rates declined slightly; potassium hydroxide preparation negativity was 82% in fluconazole-treated patients and 78% in patients treated with ketoconazole. An attempt to correlate the resolution of "reversed" skin color (hypo- or hyperpigmentation) with mycologic cure at post-treatment follow up revealed no correlation at week 2, with correlation present during follow-up visits completed during weeks 4 through 12. The treatment regimens were safe and well tolerated in 95% of study patients with few mild adverse effects observed. Fatigue was reported in 2 patients treated with ketoconazole and 1 patient treated with fluconazole, headache and "rash" were noted in 2 patients treated with ketoconazole and diarrhea was reported in 1 patient treated with fluconazole. The relationship of these reported adverse events to the specific study drug are not entirely clear. No severe adverse reactions or significant changes in laboratory profiles completed at week 2 (complete blood cell count, liver profile, renal parameters) were reported during the study.

Topical Imiquimod and Actinic Keratosis Therapy.

Several effective options are available for the treatment of actinic keratoses, including liquid nitrogen cryotherapy, topical 5-fluorouracil, topical diclofenac 5% gel, topical retinoid therapy, photodynamic therapy and various surgical and ablative options.²⁶⁻³⁰ Treatment selection is dependent on many variables, including physician experience and perceptions of efficacy, number and location of lesions, anticipated reactions and patient preferences.^{26,31} An additional therapy under evaluation proven to be effective in the management of actinic keratosis is

topical imiquimod 5% cream.³²⁻³⁶ Currently approved by the Food and Drug Administration for the treatment of external genital verrucae cause by human papillomavirus, imiquimod has been shown to facilitate immunologic disease recognition and natural response.³⁷⁻⁴¹ Studies evaluating imiquimod have demonstrated (a) an increase in Th-1 cytokine response with local induction of the synthesis and release of multiple cytokines including interferon-alpha, tumor necrosis factor-alpha, multiple interleukins (IL-1, IL-6, IL-8, IL-10, IL-12), macrophage inflammatory proteins and macrophage chemotactic protein (b) enhancement of Langerhans cell migration to regional lymph nodes promoting the activation and recruitment of targeted T lymphocytes and (c) indirect effects including stimulation of the release of interferon-gamma and downregulation of Th-2 cytokine response with inhibited production of interleukins -4 (IL-4) and -5 (IL-5).³⁷⁻⁴¹ Studies have demonstrated the presence of cytokine release and activated T-lymphocytes infiltrating tumor in both naturally regressing and interferon-treated basal cell carcinoma and squamous cell carcinoma in situ, findings that are likely to relate at least partially to the mode of action of imiquimod when used to treat epithelial malignancies, including actinic keratoses.⁴⁰⁻⁴³

A preliminary report of 6 male patients presenting with up to 10 actinic keratoses affecting the scalp demonstrated complete clearance with imiquimod 5% cream applied 3 times per week for a duration of 6 – 8 weeks.³² The frequency of application was reduced to twice a week upon the development of significant local inflammation at treatment sites. The cases were described as recurrent after prior treatment with other modalities (ie. cryotherapy, topical 5-fluorouracil). Follow-up examinations ranging over time periods of 2 – 12 months confirmed clinical and histologic remission of the treated lesions. Mild, reversible erythema and pruritus were noted and were interpreted as an anticipated reaction during the course of therapy.

A vehicle-controlled, blinded trial examined the treatment of actinic keratoses using imiquimod 5% cream applied 3 times per week (n = 36).³³⁻³⁵ The endpoint of the study was defined as the time point where clearance of lesions was observed, with a maximum duration of 12 weeks. In approximately half of the actively treated patients, the application frequency was reduced to once or twice a week upon the appearance of application site-related inflammatory reactions, which included erythema and superficial ero-

sions. Clinical and histologic clearance of actinic keratoses was achieved in 80% of patients treated with topical imiquimod.

Based on currently available studies and clinical experience with the use of topical imiquimod for treatment of epithelial malignancy (actinic keratoses, basal cell carcinoma, squamous cell carcinoma in situ), it is important to allow for reduction in application frequency or short rest periods off of therapy in order to reduce associated inflammation.^{33,44} It has been suggested that imiquimod differs from topical 5-fluorouracil in that induction of severe inflammation is not required with imiquimod therapy in order to achieve clearance of actinic keratosis lesions.^{44,45} This is likely due to differences in mechanism of action.

A pilot evaluation of topical imiquimod "cycle therapy" has been completed in patients (n = 25) presenting with 5 – 20 AKs in designated anatomic regions.^{33,36} A "cycle" consisted of the application of imiquimod 5% cream 3 times per week for 4 weeks followed by 4 weeks off of therapy. If persistent actinic keratoses were noted at follow-up, a maximum of 3 treatment cycles were utilized in this initial study. Evaluation at 4 weeks post-therapy after a single cycle demonstrated clearance in approximately 50% of patients. A second treatment cycle demonstrated clearance in an additional one-third of patients. Case reports of patients treated long-term with topical imiquimod for actinic keratoses affecting the forehead and dorsum of the hands noted continued improvement and maintenance of lesion clearance with twice weekly application over a period of 9 months.⁴⁴

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Necrobiotic Xanthogranuloma: A Case Report and Literature Review

by Robin I. Shecter, D.O., Brad P. Glick, D.O., M.P.H., David Tenzel, M.D.,
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Background:

Necrobiotic xanthogranuloma (NXG) is a rare disease which predominantly affects the periorbital region and is frequently associated with a paraproteinemia and lymphoproliferative diseases. To date, only approximately seventy-six cases have been described in the literature.

An 84-year old female presented to the ophthalmologist with a three month history of two orange/yellow plaques on the right periorbital area with similar lesions on the chest and back. An incisional biopsy was performed on the right upper eyelid lesion and was consistent with the diagnosis of necrobiotic xanthogranuloma. Subsequently, a similar lesion appeared on the left periorbital area a few months later. This article will discuss this patient's case in detail. Additionally, a review of the literature will be discussed including the laboratory abnormalities and systemic disorders associated with NXG. Histopathologic findings will be depicted along with the current treatment modalities. The course and prognosis of the disease will also be reviewed.

Case Presentation:

An 84-year old white female presented to the ophthalmologist in August, 2002 with a three month history of two firm, nontender, non-pruritic orange/yellow plaques on the right upper and lower eyelids. The patient also had similar non-pruritic nodules and plaques involving the chest and back. The lesions on the right periorbital area gradually increased in number and size, which caused the patient to seek medical attention. The patient would only reveal the periorbital lesions at the ophthalmology office. The patient's past medical history was consistent with hypertension, hyperlipidemia, and breast cancer, which was diagnosed several years ago. The past surgical history and family history are noncontributory to this case.

The patient had a complete visual examination on the first visit which revealed a visual acuity of 20/30 OD and 20/25 OS. Orange/yellow "xanthelasma-like deposits" were present on the right upper eyelid and also on the right lower eyelid. There were no orbital masses. There was no conjunctival involvement,

keratitis, scleritis, episcleritis, or anterior uveitis. Motility was intact and there was no diplopia. An incisional biopsy was taken from one of the lesions on the right upper eyelid. Histologic examination revealed a granulomatous process consisting of many foamy histiocytes, multinucleated giant cells (touton and foreign body type) and associated with necrobiotic collagen and cholesterol clefts. Acid fast and PAS stains, did not demonstrate organisms. Control stains were performed. The lesions on the right upper and lower eyelids were then surgically excised with tumor margins free.

The physical examination performed at the patient's primary care physician was within normal limits except for the cutaneous abnormalities described previously. In particular, there were no associated cardiac abnormalities nor hepatosplenomegaly noted on the examination.

Approximately three months later on October 31, 2002, the patient developed another lesion, a yellow /orange papule, on the left upper lid (Figure 1a), which was surgically removed with tumor margins free. There was no evidence of recurrent lesions on the right periorbital area at this visit. The visual examination remained without significant abnormalities.

Laboratory findings included the following values: hemoglobin 16.3 g/dL, hematocrit 46.0%, WBCs 4,200 ul, fasting

glucose 105 mg/dL, cholesterol 153 mg/dL, triglycerides 495 mg/dL, total protein 5.7 g/dL, with 3.4 g/dL of albumin. The serum electrophoresis demonstrated a paraprotein spike in the alpha globulin region; immunoelectrophoresis showed this to be a monoclonal IgG K-type with probable polyclonal IgG, as well. The patient refused to have a bone marrow biopsy or a metastatic bone marrow survey to check for multiple myeloma and other lymphoproliferative disorders.

Discussion:

Necrobiotic xanthogranuloma (NXG) was first recognized as a separate entity by Kossard and Winkelmann in 1980.³ NXG is a rare disease. As mentioned previously only approximately seventy-six cases have been reported in the literature.¹ The age of onset of NXG ranges from seventeen to eighty-five years and the disease does not have a sex predilection.⁴

NXG is a histiocytic disorder often associated with immunoglobulin G (IgG) paraproteinemia and various other systemic laboratory findings.⁴ It is an inflammatory histiocytomatosis involving the dermis and subcutaneous tissue primarily of the face and often the eyelids and less frequently of the trunk and extremities.³ The distinctive cutaneous lesions show some similarities of both xanthomatous and necrobiotic processes.⁴ The orange/yellow color of NXG lesions is similar to the color of classic xanthoma, while the atrophy and telangiectasia seen in NXG give the lesions an appearance that is somewhat

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similar to that of necrobiosis lipoidica.⁵ The differential diagnosis of NXG also includes: granuloma annulare, multicentric reticulohistiocytosis, lipid proteinosis, primary localized amyloidosis, juvenile xanthogranuloma and Erdheim-Chester disease which can present with “xanthoma-like” lesions of the eyelids.^{3,11} Before NXG was recognized as a distinct disease entity, histologic examination often labeled NXG lesions as “atypical necrobiosis lipoidica”.⁶

Clinically, the lesions appear either as firm superficial, waxy yellow/orange papules or plaques with prominent telangiectasia, as deep violaceous plaques, or as flesh-colored nodules. The lesions may ulcerate and undergo some degree of scarring and even hemorrhagic necrosis.² The periorbital region is the most frequently involved area, followed by the trunk, the other areas of the face and extremities.⁷ A case of NXG with involvement of the lacrimal gland and episclera only, without skin lesions has been documented.⁴ The oral mucosa is occasionally involved.³ In addition hepatosplenomegaly is observed in approximately twenty percent of patients.³

When the lesions are periorbital, they are often bilaterally symmetric and can produce a wide range of symptoms, such as pain and blurred vision.⁴ Ulceration is not an uncommon feature of NXG lesions. The incidence of ulceration has been reported as high as forty-three percent.⁴

There have been many laboratory abnormalities reported in patients with NXG. The most characteristic finding is a paraproteinemia, usually of the IgG type.^{8,9} This was present in our patient. IgA paraproteinemia has been reported as well but much less frequently. A serum protein electrophoresis is therefore mandatory in the search for a paraprotein spike in patients with NXG.² Other frequently reported laboratory abnormalities include elevated ESR, decreased CH50, decreased C3 and C4 levels, anemia and leukopenia. Cryoglobulinemia has been found in forty percent of cases.³ Elevated serum lipid and glucose levels have been noted occasionally.⁹ Although it may not help differentiate these patients from those displaying necrobiosis lipoidica, a clinical and laboratory examination to rule out diabetes mellitus is indicated.²

Patients with NXG should be investigated for malignancies of the hematologic or lymphoproliferative type, in particular multiple myeloma. Plasmocytosis of the bone marrow is frequent in patients with NXG but the occurrence of multiple myeloma is still a relatively rare finding.⁴ Other disorders reported less commonly



Figure 1a An orange yellow papule of necrobiotic xanthogranuloma on the left upper eyelid of this 84-year old female patient.

in patients with NXG include chronic lymphocytic leukemia and amyloidosis of the liver.⁴ Involvement of the internal organs with NXG lesions has been reported occasionally but is probably under-reported. There has been no reported association of breast cancer and NXG in the literature. It has also been recommended that a search for cardiac involvement be undertaken in NXG patients.¹⁰ Echocardiography and dynamic cardiac imaging are recommended.¹⁰ Finally, other associated diseases include arthropathy, hypertension, neuropathy, primary biliary cirrhosis, and Graves' disease.³

Histopathologic findings in NXG show a granulomatous infiltrate involving the whole dermis and the subcutis. The mixed infiltrate is composed of lymphocytes, epithelioid cells, foamy cells and numerous bizarre giant cells of either the touton or foreign body type. Cholesterol clefts occur in the necrobiotic areas in one-third of biopsies and one-half of biopsies show lymphoid nodules, usually found around the areas that have numerous plasma cells (Figures 1b,1c,1d). Leukocytoclasia has been reported rarely.² It has been found that NXG cases that are poor in lipid and giant cells are analogous histologically to the early presentation of juvenile xanthogranuloma in which touton giant cells and xanthomatization are absent.¹

Immunohistochemical studies of NXG shows that infiltrates are CD15 and CD4 positive and CD1a and S-100 negative.³ Ultrastructurally, cells are rich in lipid droplets.

Cholesterol clefts and myeloid bodies are similar to those observed in juvenile xanthogranuloma.¹

Therapy:

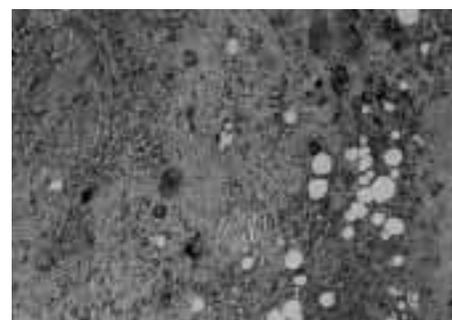


Figure 1b Hematoxylin and Eosin stain (H & E stain) at 100x magnification. Histologic findings shows a diffuse granulomatous infiltrate with cholesterol clefts and touton giant cells.



Figure 1c (H&E stain) at 200x magnification. Histologic findings of necrobiotic xanthogranuloma shows a lymphoid follicle with touton giant cells.

There are many treatments used to treat NXG, each with varying degrees of success. A combination of chlorambucil or melphalan with oral corticosteroids is one of the most commonly used therapies for NXG.² Interferon alfa-2b is another treatment that has shown good results.¹² Other treatments utilized with varying degrees of success include: cyclophos-

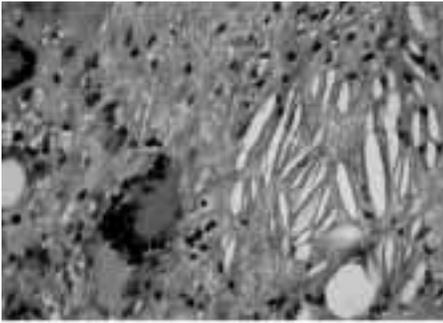


Figure 1d (H&E stain) at 400x magnification. Histologic findings of necrobiotic xanthogranuloma shows a cholesterol cleft and multinucleated giant cells.

phamide, methotrexate, nitrogen mustard, adrenocorticotropic hormone, systemic corticosteroids, intralesional corticosteroids, azathioprine, plasmapheresis, and radiation therapy.^{4,12} Extracorporeal photophoresis has been tried without any appreciable results.⁴ Ulcerations associated with NXG have been treated with thalidomide and etretinate with limited improvement.⁷ These medications however, do not help the xanthomatous

lesions of NXG.⁴ Finally, surgical excision of NXG lesions usually results in relatively rapid recurrence. However, there has been a report of a surgical excision of a single NXG lesion that has not recurred by one year follow-up.⁴

Course and Prognosis:

The pathogenesis of NXG as well as its link to paraproteinemia is unclear. The course of NXG is usually progressive and locally destructive. Prognosis of NXG depends on the severity of the disease, the extracutaneous involvement, and visceral tumors.²

In conclusion, we have presented an 84 year old female who was diagnosed with necrobiotic xanthogranuloma of the eyelid. Necrobiotic xanthogranuloma is a rare disorder that is associated with paraproteinemia and often with plasma cell and lymphoproliferative disorders including multiple myeloma. We have presented a review of the literature on necrobiotic xanthogranuloma. As previously discussed, because necrobiotic xanthogranuloma may result in dysfunction of the eyelids or extraocular muscles, and is associated with

potentially life-threatening systemic conditions, its recognition by the physician is extremely important.

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Furuncular Cutaneous Myiasis

Jere J. Mammino, DO

Myiasis is the infestation of mammalian tissues by dipterous (two-winged fly) larvae. The skin is the most common site, but other areas can be involved, including ocular, auricular, gastrointestinal, and genitourinary. Cutaneous myiasis may present in one of three ways: a superficial infection of larvae (maggots), a dermal slowly migrating erythematous patch, or as a furuncle. This article describes the furuncular form of cutaneous myiasis, and reports a recent case.

Case Reports

A 24-year-old white woman presented with a slowly enlarging tender nodule on her scalp. Her history is significant for traveling to the Central American country of Belize on vacation five weeks prior. She did much hiking and exploring of the countryside. On the plane back, she felt a small irritated bump on her scalp which she assumed was a mosquito bite. Over the course of a month this slowly enlarged which prompted a visit to her family physician. He astutely realized this presentation was unusual for an abscess so referred her for dermatologic consultation.

Physical examination revealed a mildly tender 2 cm area of erythematous indura-



Fig. 1. The lesion with the small central punctum.

tion with a central 0.2 cm pore (Fig. 1). Pressure on the lesion caused some slight serosanguineous fluid to be expressed. Myiasis was suspected, so the pore was covered with a thick layer of bacitracin ointment and she was asked to return in an hour. On reexamination a white parasite could be seen inside the pore. The central area of the lesion was injected with 2% Lidocaine and a 0.5 cm



Fig. 2. The extracted larva, released after incision and firm pressure

incision was made over the pore. Firm pressure was applied around the lesion and the larva was expressed (Fig. 2). Prophylactic antibiotics were prescribed, and she had a full recovery in a few days.

The larva measured 1.3cm in length and was elongate in appearance. The body had narrow belts of sparsely set, posteriorly pointing spines. The anterior end possessed prominent mouth-hooks and the posterior end was narrowed (Fig. 3). Consulting a parasitology text¹ confirmed this to be a mature third instar larva of *Dermatobia hominis*, a common type of botfly in the western hemisphere.

Discussion

This presentation of furuncular cutaneous myiasis in this patient is typical of the human botfly, *Dermatobia hominis* (Fig. 4). The flies are found in the forest and jungle areas especially around rivers and streams, and along the coastal



Fig. 3. Close up photo of the *D. hominis* third instar larva.



Fig. 4. The human botfly, *D. hominis*.

areas. It is a common parasitic infestation in endemic areas from central Mexico through Central and South America.² Cases have been reported in Canada and the United States from travelers who return from these areas. The botfly has both wild and domestic animals and birds as its normal hosts, although humans occasionally can become infected. In Africa, a similar type of furuncular cutaneous myiasis is caused by the tumbu fly.³

The human botfly has a fascinating and complicated life cycle (Fig. 5). The female fly can produce eggs but have no direct means of introducing them into a host. Instead the female captures another species of biting arthropod, usually mosquitoes, and by holding its wings with her legs she glues 15 to 30 eggs on its abdomen (Fig. 6).² She will then repeat many times over the next 8 to 9 days producing 100 to 400 eggs. If an

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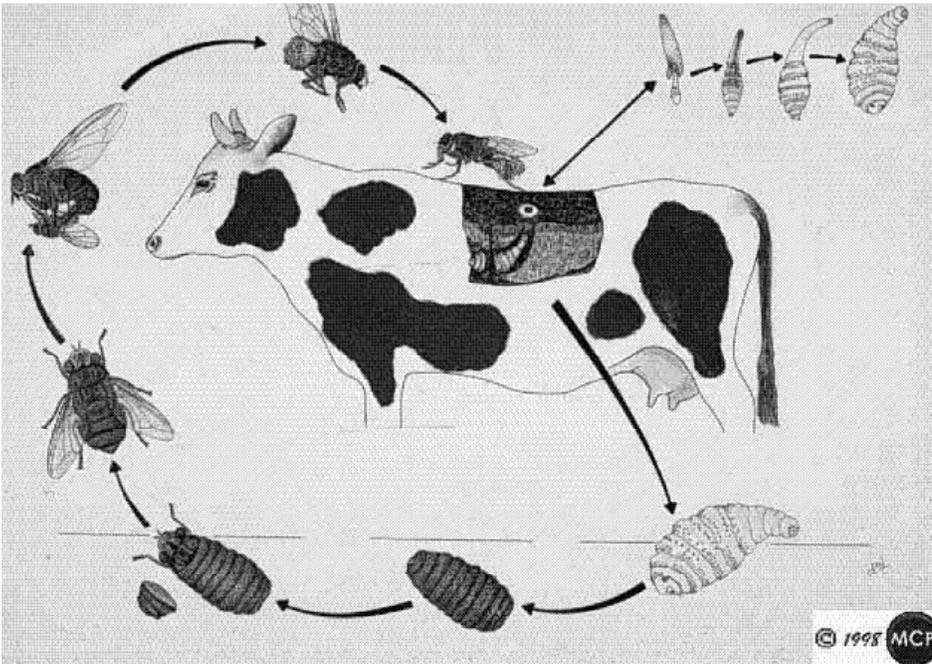


Fig. 5. Life cycle of *D. hominis*.



Fig. 6. The insect vector carrying the botfly's eggs.

insect vector cannot be found, the eggs are deposited on plant leaves which may come in contact with a host.

The insect vector is not harmed by carrying the eggs. When it bites a warm blooded animal, the heat from the mammal causes the larvae to hatch and escape from their eggshells. These burrow into the skin via the bite, a hair

follicle, or through intact skin⁴. The larvae are now safe to feed and grow, establishing a boil-like pouch below the dermis. A small opening is kept open to allow it to intermittently breathe through its respiratory tube. The larva undergoes three moltings in the next 5 to 12 weeks reaching a size of 2 cm or more in length.⁵ It then enlarges the pore and falls to the ground, spending 2 to 4 weeks in the soil to pupate. Finally an adult fly emerges completing the life cycle.

Clinically lesions of myiasis are found on exposed skin, most commonly the extremities, back, or scalp. Within 24 hours of a larva entering, a small erythematous papule appears. This gradually enlarges to form a furuncle-like lesion up to 3 cm in diameter surrounded by a larger area of induration. In the center a 2 to 3 mm breathing hole or punctum can be seen with serous, serosanguineous, or seropurulent exudate given off. Examination of the punctum may reveal move-

ment of the larva or small bubbles as the larva breaths. The patient's symptoms may range from mild pruritus to intermittent or constant sharp pain.

Different treatment methods have been described to remove the larva. The native method involves introducing tobacco juice and squeezing tightly.⁶ If the punctum is wide, an effective method is to occlude this opening causing the larva to migrate out of the skin as it attempts to breathe. Substances described as being effective include petroleum jelly, pork fat, nail polish, adhesive tape, chewing gum, bee's wax, butter and mineral oil.² Incising the lesion, as in our patient, is fast effective method. A small incision is made over the punctum and firm pressure with fingers or the ends of two tongue depressors can usually express the larva. This technique is similar to the removal of a pilar cyst on the scalp. Surgical excision with debridement of the cavity is required only if the above methods fail. Once the larva is removed, the site heals quickly leaving a small pigmented scar that fades over time.

In our age of more common international travel, the health professional must maintain a higher degree of suspicion to make an accurate diagnosis of cutaneous myiasis. Key points to assist in this diagnosis include one or more non-healing lesions on exposed skin, drainage from a central punctum, a white structure visible in the punctum, symptoms of tenderness, pruritis, or movement, and a history of recent travel to an endemic area.

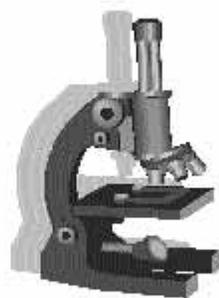
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* Treatment success was defined as a Physician's Static Global Assessment score of 0 or 1, plus a step-wise mean of 0, or a mean score of 0 or 1, and a 50% improvement of 1 or more lesions scored on a severity scale from 0 to 5.

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Cutaneous Anthrax and Bioterrorism

Peter A. Vitulli, D.O.,* Stanley E. Skopit, D.O., F.A.O.C.D.**

The name Anthrax is derived from the Greek word for coal, Anthracis, and refers to the typical black eschar seen on the skin of affected areas.

Bacillus Anthracis is a spore forming gram + bacillus that is found in soil. Endospores can survive for decades since they are very resistant to drying, heat, and ultraviolet radiation. *Bacillus Anthracis* is an endemic infection in animals.

Naturally occurring infection generally results from contact with contaminated fluids, hides, wool, leather, or contaminated meat, from the infected animals, usually Herbivores, via endospores and has been called wool-sorters disease³. Endospores are introduced into the body by abrasion (cutaneous), inhalation (respiratory), or ingestion (gastrointestinal) anthrax and are phagocytosed by macrophages and carried to regional lymph nodes. Endospores germinate inside macrophages and become vegetative bacteria. The vegetative bacteria are then released from the macrophages, multiply in the lymphatic system, enter the blood stream causing massive septicemia. This is mediated mostly via edema toxin and lethal toxin.

Edema toxin increases levels of intracellular CAMP. Increased intracellular CAMP levels cause disruption of water homeostasis and results in massive edema as seen in cutaneous anthrax.

Lethal toxin stimulates macrophages to release Tumor Necrosis Factor (TNF) and Interleukin 1B (IL1B). Increased levels of TNF and IL1B result in shock and death.¹ Clinically Anthrax presents as Gastrointestinal, Inhalation, and Cutaneous forms. Gastrointestinal anthrax has never been reported in the United States and is the result of ingestion of

undercooked contaminated meat. Symptoms appear 2-5 days after ingestion of endospores. Endospores presumably enter the mucosal lining resulting in ulceration and subsequent mesenteric lymphangitis of the upper and lower gastrointestinal tract. Fever, abdominal pain, acites, melena, hematemesis, meningitis, shock and death have been reported with mortality rates 50-60% in treated Gastrointestinal Anthrax. Inhalation Anthrax is rare in nature and is the most serious form of anthrax with mortality rates of 70-90%. It occurs after inhalation of endospores from contaminated animal hides or products. Symptoms usually develop in 10 days but may take up to 6 weeks to develop after exposure. Early symptoms include fever, non-productive cough, myalgias, malaise, and pluritic chest pain, all resembling a viral upper respiratory tract infection which can make early diagnosis difficult. Early in disease course chest radiographs show a widened mediastinum³ which is evidence of hemorrhagic mediastinitis and pleural effusions. Usually Inhalation Anthrax causes mediastinitis than pneumonia.

Symptoms progress rapidly over 24-72 hours with increasing fever, dyspnea, shock, and death, with mortality rates between 70-90%. Early diagnosis and treatment are key to survival and is often difficult, requiring a large index of suspicion.

Cutaneous Anthrax¹ in nature accounts for 95% of anthrax infections in the United States prior to 9/11/01. Anthrax infections in the United States prior to 9/11/01 is rare with less than 10 cases in the last 20 years. Patients often have an occupational history of contact with animals or animal products. Most common areas of involvement are areas of the skin not protected by clothing, where spores can land and be introduced by cut or abrasion, such as the head, neck, and extremities. Human to human transmission has not been documented. A few cases of transmission by insect bite

have been reported. The primary lesion of the skin is usually a painless, pruritic papule that appears 3-5 days after exposure to the endospore and in 28-36 hours undergoes central necrosis and drying leaving a characteristic dark brown-black eschar which is surrounded by an indurate, swollen area with vesicles. Regional lymph glands become enlarged and suppurative. These lesions are typically painless and non-purulent. If these lesions are painful and pustular this usually indicates secondary infection with staphylococcus or streptococcus, or a different etiology other than anthrax. In severe cases fever, extensive local edema, and shock may occur.

Mortality rate is 20% for untreated cases and <1% for treated cases. Anthrax Meningitis can complicate all forms of anthrax and is nearly always fatal.

Histopathology of Cutaneous Anthrax shows epidermal necrosis and peridermal inflammation with necrotizing vasculitis, numerous gram + thick bacilli are present.

So why was anthrax chosen as a bioterrorist agent. Anthrax has a history as a biological agent and was used by the Japanese Army in Manchuria in 1940.¹ Anthrax is odorless, tasteless, and virtually invisible. It is relatively inexpensive. The accidental aerosolized release of anthrax from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths. This demonstrated the lethal potential of anthrax aerosols.²

In 1993 a report by the US Congressional Office of Technology Assessment estimated between 130,000 and 3 million deaths could follow the aerosolized release of 100kg of the anthrax spores upwind of the Washington D.C. area- lethality matching or exceeding the hydrogen bomb.²

An economic model developed by the CDC suggested a cost of 26.2 billion per 100,000 persons exposed.² Based on the cost and lethal nature of anthrax it is an

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excellent biological weapon which would cause public panic, social disruption, mass casualties and marked economic loss.⁴

Since 9/11/01 there have been 11 cases of confirmed Inhalation Anthrax, 0 cases of confirmed Gastrointestinal Anthrax, and 12 cases of Cutaneous Anthrax - 4 suspected and 8 confirmed, the most recent, 3/12/02, being a lab worker in Texas who was testing samples from Florida and New York.⁶

Clinicians in the post 9/11 era must have a high index of suspicion for the diagnosis of anthrax and initiate early treatment. If Anthrax is suspected, the following is the Cutaneous Anthrax management.

Algorithm: Diagnosis of Cutaneous Anthrax

- * Notify the Department of Health regarding suspected Anthrax cases for any additional instructions before doing diagnostic tests
- * Swab exudates for gram stain and culture
- * Obtain two 4mm punch biopsies, one for permanent sections (formalin) and one for non-bacterial static (sterile saline) or in a bacterial culturette
- * Draw 5ml of blood in a red topped or serum separator tube, label tube R/O Anthrax save serum at \bar{n} 70 degrees centigrade
- * Draw 5mls of blood in a purple top tube. This tube should be refrigerated and held for potential PCR testing by the CDC
- * Obtain blood cultures for febrile or hospitalized patients
- * Notify lab regarding suspected Anthrax

The following are treatment Guidelines for Cutaneous Anthrax⁷

- * First line: Ciprofloxacin 500mg p.o. bid for 60 days
- * Alternative: Doxycycline 100mg p.o. bid for 60 days
- * Amoxicillin 500mg p.o. tid if a patient can not take a fluoroquinolone or tetracycline class drug
- * For extensive lesions: Extensive edema, signs of systemic involvement, or hand and neck lesions, the treatment is the same as for an inhalation anthrax infection
- * Pregnant women should receive the same treatment as adults. Note ciprofloxacin or tetracycline is not recommended during pregnancy but may be indicated for life threatening illness.
- * Immunocompromised persons should receive the same treatment as adults Pediatric Recommendations
- * Pediatric Treatment: Ciprofloxacin 15mg/kg q 12 hours max dose 1 gm /day in children for 60 days
- * Doxycycline is also a first line alternative pending sensitivities \bar{n} if > than 8 years and >45kg \bar{n} same as adult dose. If < 45kg 2.2mg/kg q 12 hours for 60 days
- * Note: Ciprofloxacin may cause arthropathy in children and doxycycline may cause dental pigmentation in children⁵

The following are treatment guidelines for inhalation anthrax infection.⁷

- * Adult treatment: Ciprofloxacin 400mg IV q 12 hours and switch to p.o. when clinically appropriate for a total treatment duration of 60 days; or Doxycycline 100mg IV q 12 hours and switch to p.o. when clinically appropriate for a total treatment duration of 60 days. In addition 1 or 2 other antimicrobials including

rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, or clorithromycin should be used concomitantly

- * Pregnant women: Same treatment as adults (Ciprofloxacin or tetracycline is not recommended during pregnancy but may be indicated for life threatening illness)
- * Immunocompromised persons same as children and adult recommendations
- * Pediatric treatment: Ciprofloxacin 10mg/kg IV q 12 hours (max 400mg/dose) for 60 days or Doxycycline : > 45kg - 100mg IV q 12 hours for 60 days 45kg - 2.2mg/kg IV q 12 hours for 60 days in addition, or 2 antimicrobials including rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, or clorithromycin should be used concomitantly

In Conclusion, as a dermatologist in the post 9/11 era we have to have a high index of suspicion for the diagnosis of anthrax. If a suspicious lesion is noted, 1st notify the Health Department and do the appropriate diagnostic studies based on the Health Departments recommendations and initiate early treatment.

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Porokeratosis Palmaris et Plantaris Disseminata: A case report

Eric Adrien Adelman, D.O.*

Introduction

Porokeratosis is a group of chronic disorders of keratinization that has an autosomal dominant inheritance, and is characterized by a common histological picture of an epidermal ridge formed by a thickened column of abnormal keratinocytes called a cornoid lamella. The porokeratosis disorders are classified into five disease processes: (1) Porokeratosis of Mibelli; (2) Disseminated superficial actinic porokeratosis; (3) Porokeratosis palmaris et plantaris disseminata; (4) Punctate porokeratosis; and, (5) Linear porokeratosis.¹

Porokeratosis palmaris et plantaris disseminata was first discovered by Guss et al,^{iv} in 1971 based on findings of eight members from four generations who had multiple porokeratoses on the palm, soles, and trunk. It was found that this disease process occurred most commonly in the young teens and early twenties. It had a familial aspect with transmission in an autosomal dominant fashion, and began on the palms and soles, unlike any form of porokeratosis classified. Clinically the lesions are bilateral, symmetrical, and mostly uniform in nature. The lesions are seen on both sun-exposed and non-sun exposed skin with the more hyperkeratotic representative lesions on the palms and soles. This disease process has been documented to occur most often on the palms, soles and trunk, although there have been documented cases involving all skin and mucosal surfaces.¹

Case Report

A 28 year-old female with no prior past medical history presented to our office with complaints of multiple scaling plaques on bilateral palms, soles, and shins. The patient first developed a few of these lesions in her mid-teens on small areas of her palms and soles. Over

the course of the last decade these lesions have increased in number and distribution to include her entire palms and soles with sporadic lesions on bilateral lower extremities. The lesions are most troublesome to the patient visually, although a few lesions are painful and itch at which point the patient shaves the specifically painful lesions with a kitchen knife causing relief for a period of time. The patient has been increasingly frustrated due to previously failed attempts at finding a diagnosis.

The patient's mother, who is sixty-three, also has a history of similar undiagnosed lesions on her palms and soles. The mother first saw the development of this disease process in her early twenties, with slow progression over the last forty years. The mother's lesions are not as pronounced as her daughters. The patient's younger brother, twenty-four, began developing scaling plaques a few years ago on his palms and soles. The mother and brother of the patient were unable to be examined due to geographic location, but were interviewed via phone. Both deny pain or itching of lesions. The patient's father has no history of the disease process and grandparents of the mother were unable to be evaluated due to both dying at a very young age of unknown causes.

Physical examination reveals extensive scaling annular and gyrate 2 to 3 mm plaques with hyperkeratotic scaling borders on bilateral soles and upper ankles. The plaques have a hyperpigmented depressed or atrophic center. Bilateral palms show scaling annular and gyrate plaques with a lesser degree of central depression and hyperkeratotic borders. The remainder of the physical examination was without consequence.

Histological findings

The biopsies taken showed classical representations of porokeratosis with acanthosis, orthokeratosis, and a mildly dense inflammatory infiltrate in the dermis. The epidermis showed multiple columns of parakeratotic cells reaching above the uniform orthokeratosis, the

histological hallmark of porokeratosis the cornoid lamella. Below the cornoid there were vacuolated keratinocytes and decrease in the thickness of the granular cell layer.

Treatment

Due to the patient's age, diffuse nature of disease process, and the possibility of reproduction, the patient will await treatment with the only proven efficacious long-term control of the disease, oral retinoids.^v In the interim, the patient has been using Tazorac 0.05% cream and keratolytics with moderate results relieving pain in select areas.

Discussion

The first porokeratosis discovered was in 1893 by Mibelli and Resphighi and classically named Porokeratosis of Mibelli. This type is characterized by a plaque-like formation of irregular atrophic patches with a well-demarcated hyperkeratotic border. It occurs early in life, is autosomal dominant like all the porokeratosis types, is slowly progressive, persists indefinitely, and is usually localized and found on practically any body surface. The second disorder of porokeratosis was described in 1966 by Chernosky, called disseminated superficial actinic porokeratosis (DSAP).^{vi} The type occurs in an older population, is most prominent in sun-exposed areas, and is more generalized with multiple superficial and relatively uniform hyperkeratotic papules. DSAP is often found bilaterally and in a symmetric fashion. This type of porokeratosis, unlike the others is found more commonly in women.ⁱⁱ Linear porokeratosis is found from birth to adulthood, consists of lesions that mimic porokeratosis of Mibelli and is seen exclusively in a unilateral and linear fashion. It has the highest risk of the group for developing malignancy, and is most commonly found on the distal extremities.ⁱⁱⁱ Punctate porokeratosis is usually associated with linear or the Mibelli forms of porokeratosis showing plaques or a linear distribution of hyperkeratotic discrete lesions.

According to Guss et al^{iv} in 1971 and

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McCallister et al^{vi} patients with Porokeratosis palmaris et plantaris disseminata experienced exacerbation of symptoms including pain and itching during the summer months, and had less hyperkeratotic plaques on areas of the trunk and extremities. In our patient's case the less hyperkeratotic areas of the disease presented on her palms, and as far as she can remember our patient has not experienced this summer phenomenon.

There are many theories on the cause of porokeratosis palmaris et plantaris disseminata. Reed and Lanai^v believed that the cornoid lamella of the porokeratosis was due to abnormal clones of keratinocytes causing an increased turnover of epidermal cells. The tendency of this abnormality could possibly be either inherited or due to actinic exposure or unrelated reason. Because Wade and Ackerman^{viii} observed cornoid lamella in inflammatory and neoplastic disorders, they proposed that cornoid lamella were expressions of disordered epithelial metabolism. The status is still unclear.

As far as treatment is concerned, most attempted modalities have been inadequate in results. Topical steroids

and sulfur-salicylic acid creams had no effect. The use of Fluorouracil improved pain and decreased hyperkeratosis, but had little other effects.^{iv} Topical retinoids showed reduction in hyperkeratotic lesions.^{ix} The only modality that has shown long-term beneficial response and possible protective effects against malignancy is the oral retinoids. Although there is documentation showing excellent results with retinoid therapy, there also have cases where retinoids have worsened the disease.^x The dosage varies per patient and relapse occurs soon after the medication is stopped. Although retinoid therapy is conflicting, it seems to be the best therapy at this time.

Squamous cell carcinoma has been reported in multiple cases of porokeratosis palmaris et plantaris.^{ix,x} The cause of this is not known at this time, but is theorized to be due to a high rate of abnormal DNA-ploidy in abnormal keratinocytes of porokeratosis, and by phenotypic features of overexpression of p53.^x

Conclusion

This patient's case is consistent with

the reported findings of porokeratosis palmaris et plantaris. The historical, physical, and histologic findings define it from other specific porokeratoses. The rarity of this disorder and limited treatment options, along with its possible propensity as a precursor to squamous cell carcinoma, leave us with a challenge for the present and future.

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As with other retinoids, when tazarotene was given **orally** to experimental animals, developmental delays were seen in rats; and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 3.5 and 85 times, respectively, the maximum exposure (AUC₀₋₂₄) seen in acne patients treated topically with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area in a controlled pharmacokinetic study.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation day 7. A low incidence of retinoid-related malformations at that dose were reported to be related to treatment. That dose produced an AUC₀₋₂₄ that was 11 times that observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

There were three reported pregnancies in patients who participated in the clinical trials on acne with tazarotene cream 0.1%. Two of the patients were found to have been treated with tazarotene cream and the other had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy. The other gave birth to an apparently normal, healthy child at 36 weeks gestation. Seven pregnant women who were inadvertently exposed to topical tazarotene during other clinical trials subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

TAZORAC® Cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. (see also PRECAUTIONS: Pregnancy; Teratogenic Effects).

TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS:

Pregnancy Category X. See CONTRAINDICATIONS section. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period.

PRECAUTIONS:

General: TAZORAC® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC® Cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC® Cream. Patients with sunburn should be advised not to use TAZORAC® Cream until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC® Cream and ensure that the precautions outlined in the Information for Patients subsection of the full package insert are observed.

TAZORAC® Cream should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established. Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC® Cream.

Drug Interactions: Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® Cream is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

A long term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to

rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 2.0 times the maximum AUC₀₋₂₄ seen in acne patients treated with 0.1% tazarotene cream at 2 mg/kg/cm² over 15% body surface area in a controlled pharmacokinetic study. In evaluation of photo-co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure (AUC₀₋₂₄) at the highest dose was 13 times the maximum AUC₀₋₂₄ seen in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area in a controlled pharmacokinetic study.

Tazarotene was found to be non-mutagenic in the Ames assays using *Salmonella* and *E. coli* and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC₀₋₂₄ observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area in a controlled pharmacokinetic study.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an AUC₀₋₂₄ that was 6.3 times the maximum AUC₀₋₂₄ observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an AUC₀₋₂₄ that was 11 times the maximum AUC₀₋₂₄ observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC₀₋₂₄ observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm² over 15% body surface area.

Pregnancy: Teratogenic Effects: Pregnancy Category X:

See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

Nursing mothers:

After single topical doses of ¹⁴C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of tazarotene cream have not been established in patients with acne under the age of 12 years.

Geriatric Use:

Tazarotene cream for the treatment of acne has not been clinically tested in persons 65 years of age or older.

ADVERSE REACTIONS:

In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity, or photoallergy.

The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne, occurring in 10-30% of patients, in descending order included desquamation, dry skin, erythema, and burning sensation. Events occurring in 1 to 5% of patients included pruritus, irritation, face pain, and stinging.

OVERDOSAGE:

Excessive topical use of TAZORAC® Cream 0.1% may lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General).

TAZORAC® Cream 0.1% is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.

Rx only

U.S. Patent Number 5,089,509



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Cutaneous Manifestations of Biological Terrorism

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Abstract

*This paper is intended to discuss the biological agents and diseases and their cutaneous manifestations that are designated as Category A by the CDC. Category A is defined as agents that pose a high risk to national security because they can be easily disseminated from person to person, result in high mortality rates and have the potential for major public health impact, might cause public panic and social disruption, and require special action for public health preparedness. In light of the recent terrorist attacks the CDC recommends that healthcare providers must be prepared to address these pathogens rarely seen in the United States.*¹

Anthrax History

Research on anthrax as a biological weapon began more than 80 years ago. Anthrax has been used, unsuccessfully, by the terrorist group Aum Shinrikyo on at least 8 occasions without result in illness. An accidental release in Sverdlovsk in 1979 resulted in 79 cases of anthrax and 68 deaths. The aerosol is odorless and invisible and can travel many kilometers before disseminating. The WHO in 1970 released a report estimating the theoretical aircraft release of 50 kg of anthrax over an urban population of 5 million would result in 250,000 casualties, of which 100,000 would die without treatment. In 1993 a report by the U.S. Congressional Office of Technology Assessment estimated that between 130,000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington D.C. area which is a lethality matching or exceeding that of a hydrogen bomb. 17 nations currently have offensive biological weapon programs but it is not known how many are working with anthrax. Iraq has acknowledged producing anthrax weapons.

Epidemiology.

Anthrax can be acquired through contact of anthrax containing animals or animal products. The disease most commonly occurs in herbivores, which are infected by ingesting spores from soil. Animal vaccination programs have dramatically reduced animal mortality.

Three types of the disease occur in humans: inhalational, cutaneous, and gastrointestinal with cutaneous being the most common form. Wool sorters were historically at greatest risk for inhalational disease. Until the 2001 attacks, no cases of inhalational disease were reported. Cutaneous anthrax is the most common naturally occurring form. Until the anthrax attacks of 2001 there were 224 cases of cutaneous anthrax reported between 1944 and 1994. Gastrointestinal anthrax is the least common form with most of the reported cases occurring in Africa and Asia. It follows the ingestion of insufficiently cooked meat.²

Microbiology.

Anthrax infection is caused by *Bacillus anthracis*, a large aerobic, encapsulated, gram-positive, square ended rod that forms spores in unfriendly environment.³ It is derived from the Greek word for coal, *anthrakis*, because of the coal like skin lesions. Spores may persist for many years in cutaneous products of these animals and in pastures where they live. Spores can be grown readily on all ordinary laboratory media at 37 degrees Celsius with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial appearance. The spores will germinate in nutrient rich environments and from spores only after the supply is exhausted. Reservoirs of infection have been virtually eliminated in the United States due to vaccination and animal control programs but imported animal products introduce spores into selected industrial environments. Up until recently infections in the United States were limited to persons working in animal product-associated industries, particularly individuals handling raw materials in wool factories.

Pathogenesis and Clinical Manifestations.

Cutaneous anthrax occurs following deposition into the skin with previous cuts or abrasions making one more susceptible to infection. After the spore germinates in skin tissue, toxin production results in local edema followed by ulcer formation by the second day. 1 to 3 mm vesicles may appear that discharge clear fluid containing numerous organisms. This is followed by painless, black eschar formation with extensive local edema. The eschar dries, loosens, and falls off in the next 1 to 2 weeks. Lymphadenopathy can occur with associated systemic symptoms. Without antibiotic therapy, the mortality rate has been reported as high as 20%; however, with antibiotic treatment death is rare.⁴

Inhalational anthrax occurs following deposition of spore-bearing particles into alveolar spaces. The spores are ingested by macrophages and those that survive are transported to the mediastinal lymph nodes where germination may occur up to 60 days later. Once the germination occurs, disease follows rapidly. The bacteria release toxins leading to hemorrhage, edema, and necrosis. The disease has two stages. The first stage has a spectrum of nonspecific symptoms such as fever, dyspnea, cough, headache, and chest pain. This stage can last from hours to a few days. The second stage develops abruptly with fever, dyspnea, diaphoresis, and shock. Chest X-ray shows a widened mediastinum consistent with lymphadenopathy. Up to half of the patients develop hemorrhagic meningitis with delirium and obtundation. The mortality rate before the development of critical care units was 89%.

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Gastrointestinal anthrax occurs due to deposition and germination of spores in the GI tract. Two forms may occur: oral-pharyngeal form and lower GI form. The oral-pharyngeal has oral or esophageal ulcers with regional development of lymphadenopathy, edema, and sepsis. The lower GI form presents with nausea, vomiting, and malaise which progresses to an acute abdomen or sepsis.

Diagnosis.

If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid should be obtained. If the Gram stain is negative or the patient is taking antibiotics already, punch biopsy should be performed and specimens sent to a laboratory with the ability to perform immunohistochemical staining or polymerase chain reaction assays. Blood cultures should be obtained and antibiotics should be initiated pending confirmation of the diagnosis of cutaneous anthrax. The differential diagnosis must include tularemia, scrub typhus, rickettsial spotted fevers, rat bite fever, ecthyma gangrenosum, arachnid bites, and vasculitides.

In cases of inhalational anthrax chest x-ray should be obtained. The most useful microbiologic test is the standard blood culture which will show growth within to 24 hours. Sputum culture and Gram stain are unlikely to be diagnostic.

Treatment.

Treatment for cutaneous anthrax is Ciprofloxacin 500mg twice daily for 60 days or Doxycycline 100mg twice daily for 60 days in adults and pregnant women. For children more than 8 years of age or 45kg, a dose of ciprofloxacin 10-15mg/kg every 12 hours or doxycycline 100mg every 12 hours is recommended. For children less than 45kg or less than 8 years of age, 2.2mg/kg every 12 hours is the recommended dose.² For inhalational anthrax, treatment with ciprofloxacin 400mg every 12 hours or doxycycline 100mg every 12 hours IV with change to oral forms when clinically appropriate for 60 days is recommended. There were 22 cases confirmed or suspected cases that resulted from the anthrax attacks of 2001. Eleven of these cases were inhalational anthrax, of which 5 died. The remaining 11 were cutaneous anthrax infection. Anthrax can be delivered as the letter attacks were or in aerosol form giving the ability for larger area coverage.

The U.S. anthrax vaccine, named anthrax vaccine absorbed (AVA), is an inactivated cell-free product. It is licensed to be given in 6 dose series. It is made from cell-free filtrate of a nonencapsulated attenuated strain of B anthracis.²

Smallpox

Smallpox represents a serious threat if used as a biological weapon because of its case-fatality rate of 30% or more among unvaccinated persons and the absence of specific therapy. In today's highly susceptible, unvaccinated, mobile population smallpox would be able to widely and quickly spread through this country.

History.

Smallpox was probably first used as a weapon during the French and Indian Wars (1754-1767) by British forces in North America. Soldiers distributed blankets that had been used by smallpox patients with the intent of initiating outbreaks among American Indians. Epidemics did occur killing more than 50% of affected tribes. The threat of smallpox being used as a weapon was greatly diminished when in 1796 Edward Jenner demonstrated that an infection caused by cowpox protected against smallpox. Many people were vaccinated with cowpox inoculation. Smallpox was eradicated in 1977. Many research labs retained stocks of variola virus including the United States and the USSR. The variola virus can be released by an aerosol method and due to the stability of the virus wide dissemination would be possible. Also the infectious dose is small.⁵

Epidemiology.

There were two principal forms of smallpox, variola major and a milder form variola minor. Variola major predominated throughout the world through the 19th century. Smallpox is spread from person to person, primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. There are no animal vectors or reservoirs and the virus can spread through clothing and bed linens. The transmission of smallpox does not occur until the onset of the rash by which time the affected person is confined to bed due to prodromal illness restricting contact to household residents. The patient is most infectious from the onset of the rash through the first 7 to 10 days of rash. The age of distribution has been historically children since in the past the adults had been immunized or already contracted the disease as children. This of course would change since immunizations have stopped.⁶

Microbiology.

Smallpox is a DNA virus and a member of the genus orthopoxvirus. The virion has a brick-shaped structure with a diameter of 200nm. This group contains 3 other members that can infect humans

which are the monkeypox, vaccinia, and cowpox. Only smallpox is readily transmitted from person to person.

Pathogenesis and Clinical Manifestations.

Smallpox is an acute exanthematous disease caused by infection with poxvirus variolae. The main clinical features of this disease are a 3-day prodromal illness and a generalized centrifugal rash with rapidly successive papules, vesicles, pustules, umbilication, and crusting within 14 days. Through vaccination policies and intensive case finding eradication of smallpox was officially announced in 1979. Until the advent of the Jennerian vaccination, smallpox was a major threat with widespread attack rates, persistent infection within a community, and a high mortality rate. The poxvirus variola infection follows contact with another infected human being primarily by respiratory transmission but skin inoculation and fomite spread may also play a role. Following contact, an asymptomatic period of 12 to 13 days with massive viral replication occurs. The virus following introduction via the respiratory tract, undergoes local multiplication in the respiratory mucosa and regional lymphoid tissue. Viremia occurs which spreads the virus widely throughout the reticuloendothelial system, where massive multiplication occurs. A second viremia then occurs which begins the onset of prodromal illness with spread to organs and tissues and primary manifestation in the skin.

An influenzal illness shortly after contact has been described as an illness contact. A history of contact is essential. A vaccination history and interval to symptoms are very important, as the disease pattern may be altered. Prior to onset of skin lesions, a prodromal period of 3 days' duration occurs characterized by apprehension, sudden prostrating fever, severe headache, back pain, and vomiting. A prodromal rash is not uncommon; it is a macular and papular or petechial, and when it occurs in the characteristic "swimming trunk" distribution, it is felt to be pathognomonic.⁷

The disease may take several courses. In the nonvaccinated, a discrete pox eruption is the most frequent form of illness. Severe forms of the disease are associated with confluent eruptions and/or cutaneous hemorrhage. Infrequently variola may occur without eruption, or with just a few pocks. A flat erythematous macular rash may precede the appearance of tense, deep-seated papules that rapidly vesiculate. These lesions are firm and more deep-seated than those of chickenpox. The rash may be sparse, or individual vesicles may

become confluent to form large patches. As the lesions mature, the classic "pustule" occurs. These lesions do not contain bacteria, and the cloudiness represents accumulated white blood cells, debris, and protein. Central umbilication is characteristic and eventually the lesion crusts over and heals with scar formation. This is the classic appearance of the disease. Those with previous vaccination may present with variations such as flat disklike appearance or may undergo resolution without passing through vesiculopustular stage. There are two hemorrhagic forms of the disease; one in which hemorrhage occurs in association with prodromal symptoms but death supervenes before any of the characteristic skin lesions can occur; and a second, characterized by hemorrhage into preexisting lesions. Both have almost universally fatal outcomes, the first within a week and the second after 8 to 12 days. Other common secondary physical findings are ulceration of the cornea, laryngeal lesions with symptoms of obstruction in the upper part of the airway, central nervous system involvement with encephalitis or acute psychotic behavior, and, less commonly, osteomyelitis, pneumonia, and orchitis.⁸

Diagnosis.

Histopathology shows deep vesicles with leukocyte infiltration. Also typical cytoplasmic inclusion bodies have been described known as Guarnieri's bodies.⁽⁹⁾

Differential diagnosis should include chickenpox, coagulation disorders, typhus, and in the preruptive phase of the disease must be distinguished from dengue, measles, enterovirus, and other febrile illnesses. Rapid laboratory means of diagnosis include light microscopic identification of elementary bodies with appropriate stains, electron microscopic identification of virus in vesicular fluid or scrapings from the base of a papule or early vesicle, and fluorescent antibody staining of the virus from same material. All of these tests yield rapid results but definite diagnosis can be achieved only by isolation of the virus in the embryonated egg or in appropriate tissue culture systems and specific identification of the virus by neutralization with variola or vaccinal antiserum. Smallpox is best diagnosed by clinical picture and adequate history of exposure, observation of an approximately 2-week incubation period followed by a severe 3 day prodrome, ultimately terminating in a typical rash with centrifugal distribution and all lesions in the same stage of development.

Treatment.

Treatment for the disease is limited

with best efforts aimed at prevention with the Jennerian vaccination. Thiosemicarbazone and antivariola or antivaccina serum and immune globulin failed in the therapy of established smallpox. Care should be supportive and prevention of secondary bacterial infection a must. The overall mortality of smallpox is 25 percent with confluent disease representing a greater risk than discrete eruptions. Fulminant smallpox is universally fatal, as are the hemorrhagic forms of the illness. Since the aerosol release of smallpox to as little as 50 to 100 persons would rapidly spread in a now highly susceptible population, the infected would rapidly expand to 10 to 20 times the first generation. Therefore, vaccination within the first few days of exposure and even as late 4 days can prevent or ameliorate subsequent illness.

Also of note are the vaccine complications. Vaccine can be safely administered to persons of all ages, from birth onward. The vaccination is performed using a bifurcated needle that is dipped into an ampule of reconstituted vaccine. This needle is then rapidly stroked onto the arm 15 times in 5mm diameter. After 3 days a red papule appears at the site and becomes vesicular on about the 5th day. On the 7th day it becomes the Jennerian pustule, a whitish, umbilicated, multilocular, containing turbid lymph and surrounded by an erythematous areola that may continue to expand for 3 more days. This can be associated with fever and lymphadenopathy. The pustule dries and falls off in about 3 weeks.

Complications.

Postvaccinial encephalitis occurs at a rate of 1 in 300,000. One fourth of these cases are fatal. Between 8 and 15 days after vaccination, encephalitic symptoms developed such as fever, headache, vomiting, drowsiness, and sometimes spastic paralysis, meningitic signs, coma, and convulsions. Recovery is either complete or with residual paralysis and other CNS symptoms. There is no treatment.

Progressive vaccinia (*Vaccinia Gangrenosa*) can occur in primary or revaccines. It was frequently a fatal complication in those with immune deficiency syndromes. The vaccinal lesion failed to heal and progresses to skin necrosis spreading to bones and viscera. VIG has been used for this problem.

Eczema vaccinatum occurs in which vaccinal skin lesions extended over areas currently afflicted with eczema. VIG was therapeutic.

Generalized vaccinia follows primary vaccination in which the virus becomes blood-borne and lesions appear 6 to 9 days after vaccination and were few in number or generalized. This condition is usually self-limited but in severe cases VIG can be used.

Inadvertent inoculation occurs from close contacts or autoinoculation to face, mouth, eyelid, and genitalia. Most lesions heal without incident, but VIG may be used.

There are 5 groups at risk for the above complications: 1. Persons with eczema or exfoliative skin condition; 2. Persons with leukemia, lymphoma, or generalized malignancy receiving therapy that causes immunosuppression; 3. HIV patients; 4. Hereditary immune disorders; and 5. Pregnant women. VIG may be given simultaneously with vaccination in these individuals.⁵

Tularemia

The causative agent of tularemia is *Francisella tularensis* and is one of the most infectious pathogenic bacteria known requiring inoculation or inhalation of as few as 10 organisms to cause disease. Tularemia is widely considered a dangerous potential biological weapon because its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death.

History.

Tularemia was first described as a plaguelike disease of rodents in 1911 and, shortly thereafter, was recognized as a potentially severe and fatal illness in humans. It has been studied for military purposes in both the east and west. It has been suggested that tularemia outbreaks affecting tens of thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use. Following the war research was developed to study the use of tularemia as a weapon in the United States, Soviet Union and other countries. In 1969, a World Health Organization expert committee estimated that an aerosol dispersal of 50 kg of virulent *F. tularensis* over a metropolitan area with 5 million inhabitants would result in 250,000 incapacitating casualties, including 19,000 deaths.¹⁰

Epidemiology.

Tularemia is mostly a rural disease and occurs throughout much of North America and Eurasia. In the United States human cases have been reported from every state except Hawaii; however most cases occur in south central and western states. In Eurasia the disease is

widely endemic with the greatest numbers of human cases reported in northern and central Europe. Natural reservoirs of infection include mammals such as voles, mice, water rats, squirrels, rabbits, and hares that acquire infection through bites by ticks, flies, and mosquitoes or through contaminated environments such as water, soil, and vegetation. Humans can become infected by various modes including bites by arthropods, handling infectious animal tissue or fluids, direct contact with or ingestion of contaminated water, food, or soil and inhalation of infective aerosols. All ages and sexes are equally susceptible with those who hunt, trap, handle infected animals, and farm having a higher incidence. No person-to-person transmission has been documented. Less than 200 cases were reported in the United States in the 1990s with most occurring in June through September when arthropod transmission is most common.¹¹

F tularensis could be used as a weapon in a number of ways, but experts believe that an aerosol release would have the greatest adverse medical and public health consequences. Release in a densely populated area would result in an abrupt onset of large numbers of cases of acute, nonspecific febrile illness beginning 3 to 5 days later with pleuropneumonitis developing in a significant proportion of cases during the ensuing days and weeks.

Microbiology.

F tularensis is a small, nonmotile, aerobic, gram-negative coccobacillus. It has a thin lipopolysaccharide-containing envelope and is a hardy non-spore-forming organism that survives for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses. It is divided into two major subspecies (biovars) by virulence testing, biochemical reactions and epidemiological features. Type A is highly virulent in humans and animals, produces acid from glycerol, demonstrates citrulline ureidase activity, and is the most common biovar isolated in North America. Type B is relatively avirulent, does not produce acid from glycerol, and does not demonstrate citrulline ureidase activity.

Pathogenesis.

F tularensis can infect humans through skin, mucous membranes, GI tract, and lungs. It is a facultative intracellular bacterium that multiplies within macrophages. Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to regional lymph nodes and further multiply, and may then disseminate to organs throughout the body.

Clinical Manifestations.

Primary disease presentations include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, and septic forms. The onset of tularemia is usually abrupt, with fever, headache, chills and rigors, generalized body aches, coryza and sore throat. Nausea, vomiting, and diarrhea sometimes occur. Sweats, fever and chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness. Without antibiotics the overall mortality rates range from 5% to 15% and fatality rates as high as 30% to 60% were reported for untreated forms of the pneumonic and severe systemic forms of disease.

The ulceroglandular type begins with a primary papule or nodule that rapidly ulcerates at the site of infection. This can occur from contact with tissues or body fluid of infected mammals via abrasion or scratch or by bites of a tick such as *Dermacentor andersoni* or of a deer fly *Chrysops discalis*. The primary ulcer is tender, firm, indolent, and punched-out, with a necrotic base that heals with scar formation in about six weeks. Lymphangitis spreads from the primary lesion. The regional lymph glands become swollen, painful, and inflamed, and tend to break down, forming subcutaneous nodules resembling those of sporotrichosis. Other symptoms include fever at first continuous then remissions and back to normal. Erythema multiforme and erythema nodosum often occur as well.¹²

In the typhoidal type the site of inoculation is not known and there is no local sore or adenopathy. Persistent fever, malaise, GI symptoms, and presence of specific agglutinins in the blood serum after the first week characterize this form. Also oculoglandular which is primary conjunctivitis and an oropharyngeal form may occur. The oropharyngeal form occurs after ingesting infected inadequately cooked meat. The glandular type has no primary site of infection but enlargement of regional lymph glands followed by generalized involvement occurs.

Diagnosis.

A diagnosis can be made by direct examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains. It can also be cultured on special media containing cystine glucose blood agar or other selective media.¹¹ The most reliable diagnostic procedure is the agglutination test which is positive after two weeks of illness and diagnostic with a fourfold rise in titer.

Histopathology shows granulomatous formation with central necrosis and nuclear dust. There is a nonspecific inflammatory infiltrate associated with the granulomatous reaction.¹³

The differential of the primary lesion should include furuncle, paronychia, ecthyma, anthrax, *P multocida* infection, or sporotrichosis. The regional adenopathy suggests cat-scratch disease, plague, melioidosis, Eastern hemisphere spotted fever, or lymphogranuloma venereum. The febrile illness must be differentiated from Lyme disease, Rocky Mountain spotted fever, or community pneumonias.¹¹

Treatment.

IV Streptomycin is the drug of choice with Gentamicin being an acceptable alternative. Treatment should be continued for ten days. Other treatments include tetracyclines, ciprofloxacin, and chloramphenicol. These all may also be used in children. Short courses of gentamicin may be used in pregnant women. In the United States a live attenuated vaccine derived from avirulent live vaccine strain has been used for laboratory workers and is under review by the FDA. It does not protect all recipients against aerosol challenges in studies and did not reduce incidence of ulceroglandular disease but did reduce signs and symptoms. Exposed persons should be treated prophylactically with 14 days of oral doxycycline or ciprofloxacin.¹⁰

Botulism, Plague, and Viral Hemorrhagic Fevers

Botulism. *Clostridium botulinum* is a spore-forming, obligate anaerobe whose natural habitat is soil from which it can be isolated without undue difficulty. Botulinum toxin exists in 7 distinct antigenic types that have been assigned the letters A through G. Botulinum toxin is the most poisonous substance known. One gram of crystalline toxin, evenly dispersed and inhaled, would kill more than one million people, although technical factors would make such dissemination difficult.

Three forms of naturally occurring human botulism exist: foodborne, wound, and intestinal. Less than 200 hundred cases are reported annually in the United States. All forms result from absorption of toxin from mucosal surface or wound. It does not penetrate intact skin. Once absorbed the bloodstream carries the toxin to peripheral cholinergic synapses at neuromuscular junctions where it binds irreversibly. The toxin is internalized and enzymatically blocks acetylcholine release. Symptoms include cramps, nausea, vomiting, or diarrhea for GI trans-

mission then progressing to an acute a febrile, symmetric, descending flaccid paralysis that always begins in bulbar musculature. Patients present with difficulty seeing or swallowing. Other symptoms include ptosis, diplopia, blurred vision, dysarthria, dysphonia, and dysphagia. Recovery results form new motor axon twigs that sprout to reinnervate paralyzed muscle fibers, a process that, in adults, may take weeks or months to complete.

The use of botulinum toxin as a weapon began as early as 60 years ago by Japan in Manchuria on prisoners who were fed toxin during Japan's occupation. It was used in aerosol form in the mid-1990s in Japan by the cult Aum Shinriky that failed due to faulty technique and internal sabotage. Currently Iraq has 19000 L unaccounted for which constitutes approximately 3 times the amount needed to kill the entire population by inhalation.¹⁴

The diagnosis of botulism is with the standard diagnostic test of specimen and food with mouse bioassay in which type specific antitoxin protects mice against any botulinum toxin present in the sample. This test yields results in 1 to 2 days and must be done in untreated specimen.

Treatment of botulism is supportive and passive immunization with equine antitoxin. The antitoxin will not reverse existent paralysis but will neutralize existing toxin.

Plague.

This disease occurs in 3 forms that are bubonic, bubonic-septicemic (a more acute and severe form of bubonic plague with bacteremia and delerium), and pneumonic. The plague is caused by *Yersinia pestis* an aerobic gram-negative bacillus with "safety-pin" bipolar staining. The disease is transmitted by fleabites of *Xenopsylla cheopis* and in the United States by the *Diamanus montanus*, *Chrsis bacchi*, and *Opisocrostis hirsutus* all of which are species that live on the host rodents such as squirrels, rats, prairie dogs, chipmunks, marmots, skunks, deer mice, wood rats, and hares. Infection can also be transmitted through contact of infected animals, humans, pneumonic spread and infected exudates.

The clinical manifestations of bubonic plague include an initial fleabite (if visible). Painful, tender, enlarged lymph nodes are present in the area draining the bite site. The nodes become matted (buboes) with extensive surrounding edema. Other symptoms include fever, headache, nausea, vomiting, tachycardia, and abdominal pain. Pneumonic plague

presents with symptoms of other bacterial pneumonias and must differentiated from such. The differential diagnosis includes tularemia, lymphogranuloma venereum, cat-scratch disease, Eastern Hemisphere spotted fever, and supportive lymphadenitis. The diagnosis can be firmly established by examination of Gram and Wayson-stained smears of infected material and by culture of the organism from blood, sputum, or aspirated buboes. Also a convalescent passive hemagglutination titer of greater than 1:16 is strongly suggestive of a diagnosis.

The treatment of all forms is IM streptomycin. Alternatives include chloramphenicol and tetracycline that can be added if resistant strains are found. Bubonic plague if untreated has a mortality rate of 30 to 70% while pneumonic and septicemic plague is universally fatal. Early antibiotic treatment can reduce the mortality rate to 5 to 10%.^{15,16}

The first plague pandemic began in Egypt in AD 541 and swept across Europe with population losses of between 50 and 60%. The second plague pandemic began in 1346 and killed 30 to 40 million people in Europe. The third pandemic began in China in 1855 and killed more than 12 million people in India and China. In World War II Japan dropped plague-infected fleas over populated areas of China causing outbreaks of plague. The United States and Soviet Union developed aerosol forms of the disease eliminating the unpredictable flea vector in later years. The WHO in 1970 reported that in a worst-case scenario if 50g of *Y pestis* were released by aerosol over a city of 5 million, 150,000 persons would develop pneumonic plague with 36,000 deaths. It is unknown currently if any countries have

the ability of the use of plague as a bioweapon.¹⁷

Viral Hemorrhagic Fevers.

The viral hemorrhagic fevers refer to a clinical illness associated with fever and a bleeding diathesis caused by a virus belonging to 1 of 4 distinct families which are Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae. Not all of the viruses of these families pose a serious threat as biological weapons due to their characteristics. Those that do pose a serious threat, include Ebola and Marburg viruses (Filoviridae), Lassa fever and New World arenaviruses (Arenaviridae), Rift Valley fever (Bunyaviridae), and yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease (Flavoviridae). All of the HFVs are RNA viruses with lipid envelopes. These diseases are described in the table below.

The methods of diagnosing of HFVs include antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody detection by antibody-capture ELISA, RT-PCR, and viral isolation. The lab testing requires time so a diagnosis will rely heavily on clinical judgment.

The treatment, as shown above, is largely supportive. Studies are currently being done on antiviral therapies as well as vaccines. There is a vaccine for yellow fever called the yellow fever live attenuated 17D vaccine which is highly effective when administered to travelers to endemic areas but would be ineffective for post exposure treatment due to the short incubation period of yellow fever since neutralizing antibodies take longer to appear.

HFVs have been weaponized by the

Table 1

Virus	Disease	Vector	Geographic Distribution	Person to Person Transmission
Ebola	Ebola Hemorrhagic Fever	Unknown	Africa	Yes
Marburg	Marburg Hemorrhagic Fever	Unknown	Africa	Yes
Lassa	Lassa Fever	Rodent	West Africa	Yes
New World Arenaviridae	New World Hemorrhagic fever	Rodent	Americas	Yes
Rift Valley	Rift Valley fever	Mosquito	Africa, Saudi Arabia, Yemen	No
Yellow fever	Yellow fever	Mosquito	Africa, tropical Americas	No
Omsk hemorrhagic fever	Omsk hemorrhagic fever	Tick	Central Asia	No
Kyassanur Forest disease	Kyassanur Forest disease	Tick	India	No

Disease	Incubation	Features	Mortality	Treatment
Ebola hemorrhagic fever	2-21 days	High fever, diffuse maculopapular rash by day 5 of illness. Bleeding and DIC common.	50 - 90%	Supportive
Marburg hemorrhagic fever	2-14 days	High fever, myalgia. Nonpuritic maculopapular rash of face, neck, trunk, and arms. Bleeding and DIC common.	25-70%	Supportive
Lassa fever	5-16 days	Gradual onset of fever, anorexia, abd. Pain, severe sore throat, cough, conjunctivitis, ulceration of buccal mucosa, mandibular pharyngitis, and cervical lymphadenitis. Late signs include severe swelling of the head and neck, pleural and pericardial effusions.	15-20%	Ribavirin, supportive
New World Hemorrhagic fever	7-14 days	Gradual onset of fever, myalgia, anorexia, abd. Pain, conjunctivitis, flushing of face and trunk, and generalized lymphadenopathy. May develop petechiae, bleeding, and CNS dysfunction.	15-30%	Ribavirin, supportive
Rift Valley fever	2-6 days	Fever, headache, retro-orbital pain, photophobia, and jaundice. Less than 1% develop hemorrhagic fever or encephalitis. Meningitis effluvia approx. 10% which may occur at time of acute febrile illness or up to 4 weeks later.	<1%	Ribavirin, supportive
Yellow fever	3-6 days	Fever, myalgia, facial flushing, and conjunctival injection. Patients either recover or enter short incubation followed by fever, relative bradycardia, jaundice, renal failure, and hemorrhagic complications.	20%	Supportive
Creek hemorrhagic fever	2-9 days	Fever, cough, conjunctivitis, papulovesicular eruption on the soft palate, marked hypotonia of the face and trunk (no rash), generalized lymphadenopathy, and splenomegaly. Some develop pneumonia and CNS dysfunction.	5-10%	Supportive
Kyasanur Forest disease	2-9 days	Similar to Creek but biphasic illness: first phase lasts 6-11 days and is followed by an afebrile period of 9 to 21 days. Up to 50% of patients relapse and develop meningoencephalitis.	3-10%	Supportive

Table 2

former Soviet Union, United States and Russia. Several studies show the successful infection of nonhuman primates by aerosol preparations of Ebola, Marburg, Lassa, and New World arenaviruses. The United States discontinued its program in 1969 and Russia

stopped production in 1992.¹⁸

The VHF's transmission is still poorly understood. Studies continue on developing rapid diagnostic techniques, therapies, and vaccines.

In conclusion, this paper serves as a summarization of Category A agents and in the event that a healthcare provider suspects such a diagnosis they should contact both the CDC and the local health department for correct procedures. Ongoing research on therapies, diagnostic testing and vaccination will hopefully lead to lessen the threat of such attacks.

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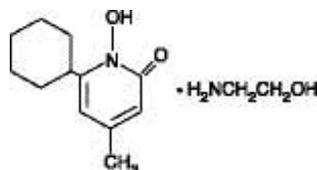
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First Documented Case of Fournier's Gangrene After Dilatation and Curettage

Alpesh D. Desai, D.O., Tejas D. Desai, D.O., David Horowitz, D.O.,* Mark Horowitz, D.O.**

Abstract

Fournier's gangrene is a rapidly progressive necrotizing fasciitis of the perineum. Aggressive management is desired in order to prevent mortality. We present a case of Fournier's gangrene in a 71-year-old female with diabetes. The etiology of her infection was due to a dilatation and curettage for post-menopausal bleeding. Gangrene Severity Index was noted to be 7, which correlated to a 78% survival rate. The patient succumbed 41 days after admission from a pulmonary embolism. This is the first reported case of Fournier's gangrene following a dilatation and curettage to date. Dermatologists should recognize and be familiar with the signs and symptoms of Fournier's gangrene in order to prevent morbidity and mortality.

(Key Words: Fournier's gangrene, necrotizing fasciitis, perineum, dilatation and curettage)

Introduction

There are approximately 850 cases of Fournier's gangrene (FG). It was first described in 1883 by Jean Alfred Fournier, a French venerologist, as a rapidly progressing gangrene of the penis and scrotum that occurs in young, healthy males.¹ Today, these infections are often seen in debilitated patients with comorbid conditions, most notably diabetes mellitus (DM) and alcoholism. A precipitating cause is often identifiable.² Prior to 1979, there were only two cases of FG in females reported in the literature.^{3,4} The incidence of FG has increased in women from 1979 to 1988, with 14% of the patients reported to have been women and this trend represents a divergence from the traditional diagnostic criteria for this condition.⁵ Fournier's gangrene is aggressive and has a mortality of 49% in females.⁵ This is significantly greater than male mortality. When patients with obstetrical causes were excluded, the overall mortality of both sexes was not significantly different. This suggests that the pathophysiology of this condition is similar in both sexes. We present a unique case of FG in a 71-year-old female status post dilatation and curettage (D&C) with insulin dependent DM (IDDM), congestive heart failure (CHF), and peripheral vascular disease (PVD).

Case Report

A 71-year-old female was admitted to the hospital with a chief complaint of a bloody vaginal discharge that was noticed by the patient's family upon routine bathing. The discharge was described as green and malodorous. She denied any dysuria, nausea, vomiting, or constipation. The patient had been experiencing brown diarrhea a few days prior to admission.

Past medical history was significant for hypertension (HTN), congestive heart failure, insulin dependent diabetes mellitus, two past cerebral vascular accidents (CVA), with the most recent CVA resulting in a right-sided hemiparesis; in addition, the patient was diagnosed with peripheral vascular diseases and rheumatoid arthritis (RA). Past surgical history revealed a right hip replacement. Family history was significant for HTN, IDDM, and myocardial infarction (MI).

Physical examination revealed the patient to be 5'11" and 168 lbs., BP 136/79, pulse 95, respiratory rate 20, and temperature was 36.8 oC. Head, eyes, ears, nose, and throat examination revealed bilateral cataracts and cerumen impaction bilaterally. The neck, heart, lungs, and abdomen were unremarkable. An examination of the extremities revealed right-sided hemiparesis with the right hand held in a flexed position. Left muscle strength of upper and lower extremity showed weakness of 4/5. The genital, pelvic, and rectal examination were unremarkable. Osteopathic structural examination revealed a type II dysfunction on the right from T2-T12 with

associated muscle bogginess and hypertrophy.

The following day a pelvic ultrasound showed a uterine fibroid mass measuring 11.8 X 17.1 cm, which had increased in a size from a previous study two years earlier. A gynecological evaluation by hysteroscopy demonstrated a fundal uterine polyp. No evidence of hyperplasia or fibroids were noted. There were no cervical abrasions or vaginal lacerations visualized. Polypectomy and D&C were performed. Pathologic reports described endometrial cystic hyperplasia with focal tubal metaplasia.

One week post D&C, a vulvar abscess was noted which communicated with the left groin toward the anterior superior iliac spine (ASIS). In addition, there were multiple ulcerations on the mons pubis and a white-green, malodorous discharge. The patient's temperature was 36.1 oC, pulse 140, and respiratory rate of 24. Hematological studies revealed a white count of 27.8 th/cm and a hemocrit of 23.3%. Electrolyte levels were as follows: sodium 133 mmol/L, potassium 3.8 mmol/L, bicarbonate 22 mg/100mL, and serum creatinine 0.8 mg/100mL. Because of the notable skin changes in the vulvar region, a dermatology consult was obtained and a diagnosis of Fournier's gangrene was made due to edema, erythema, necrosis, crepitus, and bullae formation. Surgical consult was also obtained and the patient was taken to surgery. A right radical hemi-vulvectomy was performed with dissection carried down to the right femoral sheath and the upper extent to

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the right side of the abdomen. The surgical wound was left open with packing. A right direct, indirect, and femoral hernia were also identified.

The patient was placed on metronidazole, fluconazole, and piperacillin/tazobactam, along with daily dressing changes with half strength Dakin solution. Pathological reports identified the excised right vulva measuring 17.0 x 15.0 x 5.5 cm. It was described as gelatinous and purulent with no nodules, masses, or hemorrhage. The deep margin of the excised tissue showed an area of pus-like change consistent with the anterior surface measuring 4.0 x 2.5 cm. This specimen also revealed necrosis, suppurative inflammation, and gangrenous pockets, consistent with fasciitis. Cultures obtained immediately preoperatively indicated: Enterococcus species, alpha-hemolytic Streptococci, Lactobacillus species, and yeast. Vulvar cultures revealed: Enterococcus species, alpha-hemolytic Streptococci, and Escherichia coli.

The patient received daily hyperbaric oxygen (HBO) treatments to improve granulation of the extensive debridement zone for 21 days. Twenty one days post-operatively, the patient and family agreed for a diverting colostomy. A left ovarian mass was discovered resulting in a left oophorectomy along with a supracervical hysterectomy.

A radical debridement was also performed and a full thickness skin flap was constructed to allow for closure of the right vulvar region. Pathological report noted the uterus to contain a 14.0 x 12.0 x 9.5 cm subserosal leiomyoma, with hyalinization, ischemia, and cystic degeneration. The endometrium showed hyperplasia without atypia. The ovary mass was predominately adipose tissue. Nine days after skin flap closure, the patient sustained an acute pulmonary embolus resulting in her demise.

Discussion

Fournier's gangrene is a rapidly progressing fasciitis of the perineum. The terminology used to describe these infections have expanded over the years. Examples include synergistic gangrene, necrotizing fasciitis,⁶ and synergistic necrotizing cellulitis.⁷ The initial portal of entry for FG most commonly occurs from local trauma, extension of an urinary tract infection, or extension of a perianal infection.³ There have been many cases associated with other mechanisms, such as Crohn's,⁸ rectal adenocarcinoma,⁹ ulcerative colitis,¹⁰ operative procedures such as circumcision, vasectomy, and hernia repair.¹³ A review of the literature indicated the most common surgical

cause to be an episiotomy.⁵ Most patients are affected by severe comorbid states, such as IDDM, alcoholism, or intravenous drug use, all of which hinders immunologic defenses.³ Although a rare condition, FG must be aggressively managed due to its high morbidity and mortality. The gangrene can spread rapidly into the abdomen through the inguinal canal or spread in between Colles' and Scarpa's fascia. Symptoms of FG include localized perineal pain, fever, and disorientation. Dermatologic changes are the most apparent and should be identified immediately by a dermatologist. The skin changes include pale erythema, with or without crepitation and, subsequently, a blue-to-brown ecchymotic discoloration.¹³ Pain usually is prominent early in the course of this condition, but gradually is replaced by numbness and analgesia due to compression and destruction of the cutaneous nerves. In advanced stages of the disease, prostration may be severe. Bacteremia is common, but not uniformly present. This patient illustrated the majority of these signs and symptoms after her D&C.

We believe that this patient's infection developed as a result of a vaginal abrasion from the D&C that subsequently became infected and burrowed between Colles' and Scarpa's fascia. This site was undoubtedly complicated by her IDDM, which resulted in susceptibility to bacterial infections, defective phagocytic function, increased incidence of urinary tract infections secondary to diabetic neuropathy, and small vessel disease.¹⁴ Moreover, the previous CVAs contributed to the maintenance of this infection by impairing adequate fecal and urinary function. As a result, urinary and fecal material were constantly being introduced into the abrasion site. After a review of the literature, we could not identify a known cause of FG after D&C.

Fournier's gangrene is primarily a multi-organism infection. Typical bacteria include E. coli, Bacteriodes, Proteus, anaerobic streptococci, and Clostridium.^{5,15} Most cases reviewed show E. coli to be the most prevalent organism.^{15,16} Although a study has shown no statistical significance between bacteriologic findings and mortality rate, broad spectrum antibiotics must be utilized due to FG's rapid and fulminant course.¹⁶ A reasonable choice would be the combined use of gentamycin and metronidazole. With proper surgical debridement, antibiotic therapy is not necessary after 5-7 days.³

The ability of this patient to fight infections was severely hampered by her IDDM. As noted, urinary and fecal control were critical issues in the management of

this case. Fecal and urinary diversion are recommended if the source of the FG is believed to be genitourinary or colorectal. Initially, family wishes were against the implementation of a colostomy. Since the patient had total incontinence of her anal sphincter and bladder, it was critical to utilize rectal and urinary catheters, thereby preventing re-infection into the debrided areas. After continued discussions with the family and continued contamination of the wound by fecal material, the family elected for a diverting colostomy. In this situation, the use of a colostomy appeared logical and practical; however, a study by Clayton et al.¹⁶ showed a greater survival rate in patients that did not undergo a colostomy compared to patients that elected for this procedure.

Treatment with hyperbaric oxygen was used because HBO facilitates phagolytic function, promotes angiogenesis, and assists with wound healing. It also has a direct toxic effect on the anaerobic organisms by increasing free-radicals.¹⁷ One study demonstrated a zero mortality rate in 11 patients diagnosed with FG that underwent HBO therapy.¹⁷ Care must be taken with diabetic patients using HBO therapy, since this procedure can cause hypoglycemia.¹⁷ Kovalcik et al.¹⁸ reported a rapid drop of fever and leukocytosis after HBO treatment was initiated.

The extent of body surface involved is not a statistical factor when assessing mortality.^{16,19} However, patients who are diabetic and have FG seem to have an increased mortality rate of two to three times higher.¹⁵ Another study showed a 52% mortality rate in FG caused by surgical procedures and a significantly greater mortality rate for females when compared to males.⁵ Other prognostic factors of mortality include blood urea nitrogen (BUN) greater than 50 mg/dl upon presentation and advanced age.¹⁶ Interestingly, FG has a lower mortality rate when compared to other forms of necrotizing fasciitis.³

Laor et al.¹⁹ created a Fournier's Gangrene Severity Index (FGSI), which is based on the treatment outcomes of 30 patients over a 15 year period. They used 9 parameters and denoted a score for each parameter (Table 1). According to this index, a FGSI score greater than 9 corresponds to a 75% probability of death, whereas a score of less than 9 corresponds to a 78% survival rate. Our patient scored a 7 on the FGSI and, unfortunately, succumbed to a pulmonary embolus.

Although not used in the treatment protocol for this case, some clinicians believe in the application of unprocessed honey. Efem²⁰ managed 20 consecutive

Table 1. Fournier's gangrene severity index

	High Abnormal Values			Normal		Low Abnormal Values			
Point Assign.	+4	+3	+2	+1	0	+1	+2	+3	+4
Temp. (C)	>41	39-40.9	--	38.5-38.9	36-38.4	34-33.9	32-33.9	30-31.9	<29.9
Heart rate	>180	140-179	110-139	--	70-109	--	55-69	40-54	<39
Resp. rate	>50	35-49	--	25-34	12-24	10-11	6-9	--	<5
Serum Na	>180	160-179	155-159	150-154	130-149	--	120-129	111-119	<110
Serum K	>7	6-6.9	--	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	--	<2.5
Serum Cr	>3.5	2-3.4	1.5-1.9	--	0.6-1.4	--	<0.6	--	--
Hemocrit(%)	>60	--	50-59.9	46-49.9	30-45.9	--	20-29.9	--	<20
WBC	>40	--	20-39.9	15-19.9	3-14.9	--	1-2.9	--	<1
Serum HCO3	>52	41-51.9	--	32-40.9	22-31.9	--	18-21.9	15-17.9	<15

--Bold Print indicates patient's values. These added to a FGSI score of 7. Table adapted from Laor et al.

cases of FG with systemic antibiotics and daily application of unprocessed honey to the infection site (Group A) and compared them to 21 similar cases of FG (Group B) managed by traditional treatment (incision and drainage, debridement, wound excision, skin grafting). Three deaths occurred in Group B, while no deaths were recorded in Group A. In addition, Group A patients did not have to undergo any extensive surgical operations and the associated risks (i.e., general anesthesia, post-operative complications, etc.). The actions of honey are multiple which include the ability to chemically sterilize infected wounds, decrease edema from the wound site, induce enzymatic debridement of necrotic tissue, and stimulate epithelialization.²⁰ Along with its cost effectiveness and noninvasive implementation, honey may revolutionize the treatment of FG in the future.

Fournier's gangrene is a rare disease, however, physicians and other health care workers are vital in early recognition of this condition. Delay in diagnosis or recognition of perineal infection can be deadly. There should always be a suspicion of FG in a debilitated patient with fever of unknown origin. A study of 12 patients with FG showed that the perineum was improperly examined during the assessment of a patient.²

Conclusion

Our case of FG was unique in that it occurred in a female after a D&C, which to our knowledge and review of the literature has never been documented. FG should be considered in any debilitated patient following a gynecological procedure with a fever of unknown origin. Dermatologists, in particular, should be familiar with the skin changes associated with this condition. Proper postoperative diagnosis and recognition are critical to the prevention of complications. The hallmark of treatment has been adequate resuscitation, drainage, debridement, and systemic antibiotics and HBO therapy. Despite acceptance of this approach to treatment, the mortality rate of 20% to 40% has remained constant.²¹

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Stevens-Johnson Syndrome: Treatment with Intravenous Immunoglobulin, A Case Report and Review

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ABSTRACT:

Stevens-Johnson Syndrome (SJS) is a mucocutaneous disorder due to an immune-complex-mediated hypersensitivity reaction. It is characterized by prodromal symptoms followed by mucous membrane erosions then widespread vesicles arising on erythematous macules. More than fifty percent of SJS are related to drug exposure. In contrast, there are very few reports of SJS occurring after vaccination. Treatment of SJS is usually supportive. Reports of the usage of intravenous immunoglobulin in SJS are few. We report a patient who received Amiodarone, Allopurinol and influenza vaccine within one month of the onset of prodromal symptoms of SJS. Treatment with intravenous immunoglobulin resulted in significant improvement. This paper reviews SJS and how to differentiate it from Erythema Multiforme and Toxic Epidermal Necrolysis based on clinical findings. In addition, the usage of intravenous immunoglobulin in SJS will be discussed.

Stevens-Johnson syndrome (SJS) is a mucocutaneous disorder due to immune-complex-mediated hypersensitivity reaction. It is characterized by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric macules.¹ It most commonly occurs during the second through fourth decades of life. It affects both sexes with a male to female ratio of 2:1. The incidence is 0.4-1.2 per million person-years. Treatment is usually supportive. The use of corticosteroid therapy is controversial.² Reports of usage of intravenous immunoglobulin (IVIg) in SJS are few. It has been reported in an immunocompetent adult³, two patients with AIDS⁴ and fifteen pediatric cases^{5,6,7,8}. We report a patient with SJS who was treated with both intravenous steroids and immunoglobulin with significant improvement.

A Case Report

A 67 year old African American male was admitted in the hospital for gastroenteritis and dehydration. He had a two day history of recurrent nausea, vomiting, diarrhea and abdominal pain. He received an influenza vaccine two days prior to admission and he has complained of malaise since then. He has been receiving influenza vaccine yearly for five years without any problems. He denied fever, chills, cough, myalgia or cold sores.

His past medical history was complicated by oxygen and steroid dependent COPD, CAD, HTN, CVA with minimal deficits, BPH, chronic renal insufficiency, gout and atrial fibrillation. He had no history of blistering diseases. He had no known drug allergies.

Medications included Lotrel (amlodipine/benazepril), Lasix (furosemide), Zaroxolyn (metolazone), K-dur (potassium chloride), Coumadin (warfarin), Vistaril (hydroxyzine), Proventil inhaler (albuterol), Imdur (isosorbide mononitrate), prednisone and Uniphyll (theophylline) during the last five years. Nineteen days prior to admission, the patient started Allopurinol for his left toe gout. Moreover, Amiodarone was added two days before having his symptoms.

Family history was unremarkable. Physical exam on the day of admission revealed a well-developed male in no acute distress with a temperature of 99.3 F°. His mucous membranes were dry with no ocular, oral and genital lesions. Dermatological exam was unremarkable.

Laboratory test results were as follows: WBC 3.1 (nl 4.5 – 11.0 K/CU MM), Platelets 142 (nl 150-450 K/CU MM), neutrophils 33 (nl 45-75%), Band % 9 (nl 0-7%), lymph % 41 (20-40%), mono % (2-10%). BUN was 38 (nl 7-26 mg/dl) and creatinine 1.8 (0.6-1.5 mg/dl). LFT was unremarkable. His chest and abdominal radiological studies were unremarkable.

During the course of his hospital stay, his fever continued to rise (Fig. 1). In addition, he developed conjunctival injection on day 4. At this time Neosporin ophthalmic drops were instituted for his conjunctivitis and Levaquin (levofloxacin) for the fever due to presumed infection. Blood cultures were obtained.

His oral intake had declined due to mouth pain and dysphagia. Because he was prednisone dependent and his oropharynx had extensive whitish-yellowish exudates with bloody weeping discharge, oropharyngeal candidiasis was strongly considered. At this time, he was started empirically on Mycelex (clotrimazole) troches and intravenous

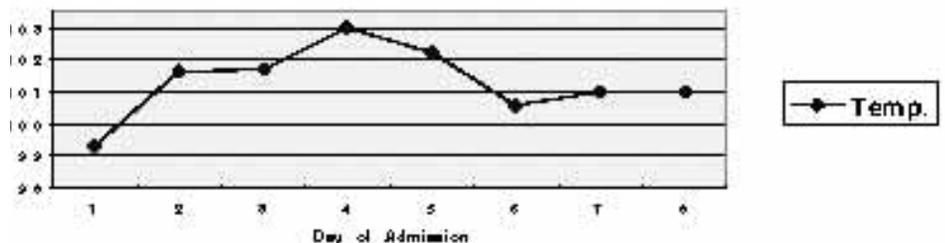


FIGURE 1: TEMPERATURE IN FAHRENHEIT
Day 4 of admission- Fever continued. Onset of ocular lesions. Levaquin was started.
Day 5 of admission- Onset of oral lesions.
Day 7 of admission- Transfer to ICU due respiratory failure.
Day 8 of admission- Onset of cutaneous lesions.

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Diflucan (fluconazole) after obtaining bacterial and fungal throat cultures. Due to his worsening clinical picture, Levaquin was discontinued. HIV 1 antibody was negative by EIA screen.

His oxygen requirement increased and his clinical picture declined on the seventh day. He was transferred to the intensive care unit for pending respiratory failure, difficulty swallowing and clearing his secretions. He was started on total parenteral nutrition due to his impaired alimentation.

On day 8, he developed a “petechial rash” on his abdomen, arms and legs. Erosions on his scrotum were also evident and Silvadene cream was started. At this time SJS was suspected and all of his medications were all discontinued. He was started on intravenous Solu-medrol 30mg every 12 hours. His “rash” continued to spread to his hands and feet. His right third finger became necrotic and orthopedics was consulted for debridement.

On the tenth day, dermatology was consulted for suspected SJS. Physical examination revealed an ill-appearing, febrile 286lb man (Fig. 2) with multiple erosions on erythematous base on his forehead and cheeks. He also had ill-defined violaceous patches with dusky center on his cheeks. Points of contact, such as the nasal bridge where his oxy-

Fig. 2 – Ill appearing 67yo male in moderate distress.



Fig.3. Hemorrhagic crust overlying erosions on lips



gen mask is placed, reveal epidermal detachment. He had well-defined erosions on his upper and lower lips with overlying hemorrhagic crusts (Fig. 3).

His buccal mucosa, gingival and

Fig. 4. Purulent erosions on scrotum



oropharynx had bright red erosions covered with yellow exudates. His conjunctiva were severely injected with yellow discharge. Genital mucosa had purulent erosions (Fig. 4).

In addition, he had widespread viola-



Fig. 5- Violaceous patches on arms.



Fig. 6- Erythematous macules with dusky centers on chest.

ceous patches with dusky centers on bilateral upper and lower extremities (fig. 5), chest (fig. 6) and abdomen (fig. 7). His right third finger had well-defined erosions. Some erythematous macules



Fig. 7- Violaceous macules coalescing into patches with dusky centers on abdomen.



Fig. 8- Erythematous patches on plantar aspect of feet.



Fig. 9- Erythematous patches on palmar aspect of hands.

coalesced into patches. These lesions were tender to touch.

His palms and soles were covered with ill-defined dusky to erythematous patches (Fig. 8 and 9).

There were violaceous vesicles on erythematous base on his cheeks. On his forehead, there was evidence of erosions with overlying crusts. (Fig. 10)

His upper back had coalescing violaceous macules with epidermal detachment. It involved less than 10% of his body surface area (BSA). Clinical diagnosis of Stevens-Johnson syndrome was made. Silvadene cream was discontinued. Then, he was immediately treated with IVIg 500mg/kg/day or 65



Fig. 10 - Violaceous vesicles on erythematous base on cheeks. Erosions with overlying crusts on forehead.



Fig. 11 - Inflammatory cell infiltrate at the DEJ.



Fig. 12 - Band-like lymphocytic infiltrates.

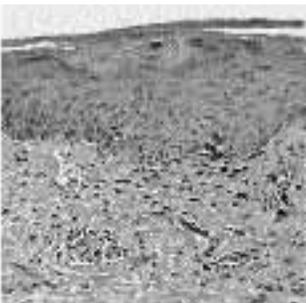


Fig. 13 - Necrotic keratinocytes at the lower epidermis.

g/day for four days.

Ophthalmology, Ear/Nose/Throat, pulmonology, gastroenterology were all involved in his care. His oral mucosa was treated symptomatically with Vibramycin (doxycycline) liquid/mycostatin (nystatin) suspension/Benadryl/Decadron (dexam-

ethasone) solution to swish and gargle four times a day. His lips were cleansed gently with sterile normal saline. His secretions were handled by gentle suctioning. For symptomatic relief of his genital erosions, Burrow's soaks and sitz bath were used. His ocular treatment consisted of pred forte and Tobrex (tobramycin) eye drops. His cutaneous erosions were gently cleansed with sterile normal saline and followed by bacitracin ointment twice a day.

Skin biopsies were performed for frozen section, H&E and direct immunofluorescence and fresh tissue culture. Histological examination showed inflammatory cell infiltrate at the dermal-epidermal junction

Fungal and viral cultures from his oral, genital mucosa and fresh tissue biopsy specimen revealed no growth. Oral and third digit bacterial cultures were positive for Staphylococcus aureus. His genital cultures were positive for Staphylococcus haemolyticus. Unasyn (ampicillin/ sulbactam) were added for empiric treatment.

Twenty four hours after IVIg treatment, he became afebrile and started feeling better (Fig. 14). Twenty four hours after the first IVIg treatment, his mucosal lesions have dramatically improved. The erosions and hemorrhagic crusts have decreased (Fig.15).

His palmar and plantar lesions have also improved. (Fig. 16). However, on his abdominal and upper extremities, atypical target lesions were more apparent. These are represented by round macules with two zones of poorly defined border and central vesiculous central zone. (Fig.17, 18.)

He also remained afebrile. Four days after his IVIG treatment, TPN was discontinued since he started eating solid food. Unasyn was also discontinued since his right finger had improved. Because of his history of chronic renal insufficiency, his renal function was carefully monitored. His BUN and creatinine had increased to a maximum of 152 and 5.0 respectively. At this time nephrology was consulted for acute renal failure. The patient was treated with IV fluids and his



Fig. 15- 24 hours after 1st dose of IVIg. Healing erosions on oral mucosa. Decreased hemorrhagic crust. Improved conjunctival injection.



Fig. 16. Improved plantar lesions 24 hours after 1st dose of IVIg.

renal function normalized without requiring hemodialysis. He was discharged 15 days after starting IVIg in stable condition. (Table 1)

Discussion and Clinical Review

Stevens-Johnson Syndrome was first described by Stevens and Johnson in 1922 as a new eruptive fever associated with severe erosive stomatitis and ocular lesions in 2 children.¹⁰ The first case reported was an 8 year old febrile boy with edematous eyelids and thick purulent discharge in his



Fig. 14. Temperature in Fahrenheit.

Day 10 of Admission: Intravenous immunoglobulin started. 0.5g/kg x 4 days.
Day 11 of Admission: Mucosal lesions improving. Temperature declined.
Day 15 of Admission: Cutaneous lesions with atypical targets.
Day 25 of Admission: Patient discharged to home.



Fig. 17. 24 hrs. after 1st dose of IVIg. Atypical targets with vesiculous central cone and two surrounding zones.



Fig. 18. 24 hrs after 1st dose of IVIg. Atypical targets with with illdefined borders.

eyes. Scattered diffusely on his face and body were multiple purple papules, some with necrotic centers. The other case reported by Stevens and Johnson was a 7 year-old boy with fever, conjunctivitis and hemorrhagic cutaneous lesions that were evenly distributed on his body. The patient suffered total blindness thereafter.

Bateman described the first erythema multiforme (EM) target lesion in 1814. In 1956, "toxic epidermal necrolysis" was used by Lyell to describe patients with epidermal necrosis resulting in skin surface looking scalded.¹¹

Table 2. Course of Stevens-Johnson Syndrome

DAY 1-14: PRODROMAL SYMPTOMS-
Fever, cough, sorethroat, headache, malaise, vomiting, diarrhea
MUCOSAL LESIONS- sudden onset
Oral: buccal mucosa, palate and vermillion border of lips
Symptoms: pain, dysphagia, hypersalivation
Edema, erythema, blisters, erosions, hemorrhagic crusts
Ocular: symptoms: photophobia, burning sensation, blindness
Hyperemia, painful erosions and ulcerations, anterior uveitis,
Anogenital: glans penis, vulva, vagina
Symptoms: dysuria
Hemorrhagic or purulent erosions
Other: tracheal, bronchial, gastrointestinal epithelium
CUTANEOUS LESIONS-
Face, neck, trunk, palms, soles, dorsum of hands, extensor surfaces.
Erythematous to violaceous macules with dusky center
May evolve into vesicles and bullae. + Nikolsky sign
Atypical targets with surrounding two zones
High tendency to coalesce
If severe, epidermal detachment

Table 1. Hospital Course

DAY 1 (prehospital day 1)
Received influenza vaccine
Nausea, vomiting, diarrhea, abdominal pain, malaise
Hospital DAY 1
Admission to hospital for dehydration, gastroenteritis, low grade fever
Hospital DAY 4
OCULAR LESIONS: conjunctival injection
High fever: started on Levofloxacin
Hospital DAY 5
ORAL LESIONS: white-yellow thick exudates with bloody weeping discharge.
Presumed candidiasis: started on mycelex troches and IV diflucan.
Decreased oral intake.
Levofloxacin was discontinued.
Hospital DAY 7
Transfer to ICU due to respiratory failure, difficulty swallowing and clearing secretions.
TPN was started.
Hospital DAY 8
CUTANEOUS LESIONS: widespread erythematous macules on abdomen.
Erosions on scrotum. Necrosis of distal right third finger.
SJS suspected.
All medications were discontinued
IV salivamedrol started.
Hospital DAY 10
Dermatology and ophthalmology consulted
IVIg started
Skin biopsies performed. SJS confirmed.
Hospital DAY 14
Improvement of oral and cutaneous lesions.
TPN discontinued
Fever resolved
Renal function worsened. Reversed with IV fluids.
Hospital DAY 25
Patient discharged to home in stable condition.

Clinical Features

Patients with SJS usually present with prodromal symptoms of fever, cough, sorethroat, headache, vomiting or diarrhea (Table 2). These symptoms precede mucocutaneous lesions by 1-14 days. In our patient, his prodromal symptoms preceded his mucocutaneous lesion by 6 days. Patients most often feel ill and receive antimicrobial and anti-inflammatory treatment that may cause difficulty in determining the offending factor later on.¹² In contrast, prodromal symptoms are usually absent in erythema multiforme (EM).

About 90% of patients with SJS or TEN will have a sudden onset of mucosal lesions that usually precede cutaneous lesions. His mucosal lesions preceded his cutaneous lesions by 4 days. The oral cavity is most often affected, particularly the buccal mucosa, hard and soft palate and vermillion border of the lips. Patients may complain of burning sensation and soreness of the mouth. Edema and erythema then occur. Finally, blisters occur and sometimes rupture forming red erosions or ulcers. The characteristic hemorrhagic crusts cover the lips. These oral lesions are extremely painful and, if severe enough, cause difficulty swallowing and hypersalivation. Severe cases may also involve the tracheal, bronchial and gastrointestinal epithelium¹³ as occurred in our patient.

Conjunctival involvement is present in 85% of SJS-TEN patients.¹⁴ Symptoms

include photophobia, burning of eyes and blindness. Conjunctival lesions may present as hyperemia, inflammation, painful erosions, and even corneal scarring.¹⁵

Genital involvement present as hemorrhagic or purulent erosions of the glans penis in males or vulva and vaginal cavity in females.¹² The anus is less frequently involved. Patients may complain of dysuria.

Cutaneous lesions begin as erythematous to violaceous macules that may develop into vesicles or bullae. The most frequent complaint is asthenia and skin tenderness. The lesions begin diffusely on the face, neck and central trunk areas¹⁷ that later on spread to the extremities. Palms, soles, dorsum of hands, extensor surfaces are most commonly affected.⁸ The initial lesions are irregularly shaped erythematous to violaceous macules with dusky centers. Individual lesions represent "atypical targets" which are ill-defined purpuric macules with a central blister. These "atypical targets" resemble EM target lesions, however, in SJS, only two zones are identified. Erythema multiforme target lesions consist of three concentric zones. The lesions of SJS are often larger and flatter than target lesions. A positive Nikolsky sign is also present on erythematous areas.¹⁶ The lesions have a tendency to enlarge and spread. The lesions have a striking tendency to coalesce.¹² Confluence is widespread in TEN while only limited to chest, neck and face in SJS. The epidermis may detach following minimal trauma exposing oozing and intensely red dermis. Pressure points such as the back and shoulders are common areas of epidermal detachment. Maximal disease expression is usually reached within 4 to 5 days.¹²

What's in a Name?

There is disagreement whether EM, SJS and TEN are different diseases or variants within a continuous spectrum.¹⁹ A recent clinical classification has been proposed as follows:

- BULLOUS EM:** detachment <10% of body surface area (BSA)
- SJS:** detachment <10% of BSA
- OVERLAP SJS/TEN:** detachment 10-30% of BSA Widespread purpuric macules or flat atypical targets
- TEN with SPOTS:** detachment >30% of BSA Widespread purpuric macules or flat atypical targets
- TEN w/o SPOTS:** detachment >10% of BSA Large epidermal sheets and without purpuric macule or target. (Fig. 19)

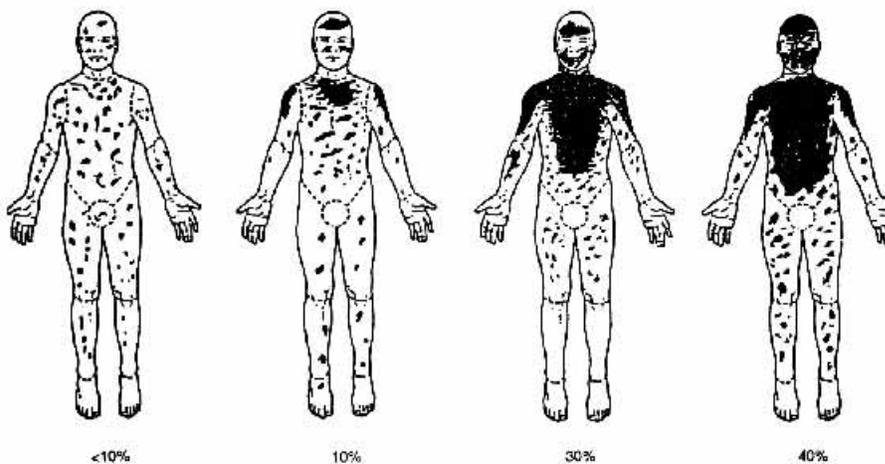


Fig. 19. Body surface area. Distribution of detachment in SJS-TEN. *From Bastuji et al. Clinical Classification of Cases of toxic epidermal necrolysis, Stevens-Johnson Syndrome and Erythema Multiforme. Arch Dermatol. 1993;129:92-96. (with permission)

Stevens-Johnson syndrome is sometimes called erythema multiforme major causing more confusion. It has been suggested that EM with mucosal lesions and SJS are two distinct clinical entities. If classification is based only on the pattern and distribution of skin lesions, SJS should be used for a syndrome characterized by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric maculae that are different from classic targets of EM.²⁰

Typical target is characterized by three different zones:

1. erythematous central disc with or without blister
2. edematous intermediate ring
3. erythematous outer ring (Fig. 20)^{19,20}

The target lesions of SJS are considered atypical due to the lack of the third concentric ring.1 (Fig. 21) The mucosal lesions of EM and SJS are similar. It should be noted that SJS is usually associated with systemic symptoms and internal organ involvement while EM is not. (Table 3).



Fig. 20 - Erythema multiforme target lesions. *From Dermochromes-1, Kingsbury J. 1914

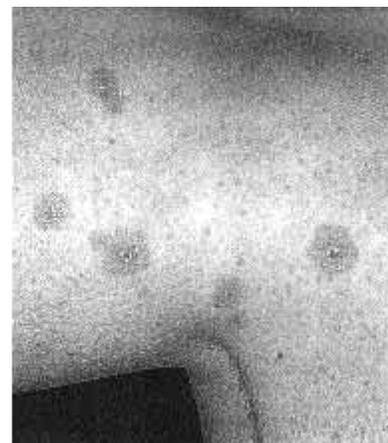


Fig. 21- SJS atypical target lesions. *From Assier et al. Arch Dermatol 1995; 131:541.

The etiology of SJS is most likely drug exposure accounting for >50% of patients. Eighty to ninety five percent of TEN cases are drug induced. More than 100 different compounds have been thought to cause SJS-TEN. The most frequently associated drugs are listed on Table 4.⁹ Other drugs have also been reported including phenytoin, penicillin, nystatin (Mycostatin)²¹, azithromycin and trimethoprim-sulfamethoxazole³, dapsone, cocaine, doxycycline²², terbinafine²³, griseofulvin²⁴, etretinate²⁵ ciprofloxacin²⁶ and theophylline. The most common drugs include co-trimoxazole, Fansidar-R-sulfadoxine, pyrimethamine and carbamazepine. Stevens-Johnson syndrome/Toxic epidermal necrolysis caused by drugs usually begin one-three weeks after initiation of therapy. However, rechallenge with the same or related drug results in more rapid onset of SJS.²⁷ It has been suggested that EM is

EM	SJS-TEN
Rare prodromal symptoms	common prodromal flu-like symptoms
Oral mucosal involvement	2-3 mucosal site involvement
Diffuse	diffuse/confluent
Acral extremities, face	trunk, extremities, face, neck
Target lesions with three concentric zones	Atypical target lesions with two zones
Blisters, Nikolsky sign (-)	macules, blisters, Nikolsky sign (+)
<10% body surface area affected	<10%->30% BSA affected
Absent internal organ involvement	frequent internal organ involvement
1-3 weeks duration	>2-6 week duration

Table 3. Comparison of Clinical Features of EM and SJS-TEN

Table 4. Drugs associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

DRUGS MOST FREQUENTLY ASSOCIATED*	DRUGS ALSO ASSOCIATED
Sulfadoxine	Cephalosporins
Sulfisidazine	Fluoroquinolones
Sulfasalazine	Vancomycin
Co-trimoxazole	Rifampin
Hydrocortis	Ethambutol
Carbamazepine	Fenbufen
Barbiturates	Tenoxicam
Benoxaprofen#	Tiaprofenic acid
Phenylbutazone	Diclofenac
Ioxicam#	Sulindac
Piroxicam	Ibuprofen
Chlormezonone	Ketoprofen
Allopurinol	Naproxen
Amithiazole	Thiabendazole
Aminopenicillins	

*Together these drugs account for approximately two thirds of the cases attributed to drugs in large series in France, Germany and the United States. #This drug is no longer marketed. SOURCE: Roujeau JC, Stern R, Severe Adverse Cutaneous Reactions to Drugs. N Eng J Med 1994; 331:1272-1285.

mostly related to herpes while SJS was almost always related to drugs.²⁰

Less commonly, SJS is due to infection such as herpes simplex virus, Mycoplasma pneumoniae, influenza, lymphogranuloma venereum, histoplasmosis, Epstein-Barr virus, enterovirus, varicella²⁹ and cholera (Table 5). Other etiologies include malignancy and idiopathic. The SJS association with malignancy is usually due to post radiation therapy for underlying cancer⁶⁰ or methotrexate for underlying non-Hodgkin's lymphoma⁶¹. Very few reports of SJS after vaccination have been reported including measles immunization^{30,31} and small pox vaccinations³². Ball et al identified six probable cases of SJS/TEN after vaccination (hepatitis B (2), influenza (1), varicella (1), (Haemophilus influenzae type b/ measles, mumps and rubella vaccines) (1), (Diphtheria, tetanus, pertussis, H. influenza type b, rubella and oral polio vaccines) (1). However, it was stated that "a causal link between

SJS/TEN and vaccination cannot be established by this study."³³ The patient who received the influenza vaccine was 24 year old female developed SJS the same day she received the vaccine. Our patient received influenza vaccine and developed prodromal symptoms the same day. He had received yearly influenza vaccine for 7 years without any problems. However, it is very difficult to identify the causative factors of his SJS since he had been on other drugs that have been reported to cause SJS including Allopurinol, Amiodarone and Theophylline. However, Allopurinol was started 19 days prior to prodromal symptoms. Amiodarone was started 2 days prior to prodromal symptoms. The patient had been on Theophylline for about 5 years. In addition, for his fever, he received Levaquin six days after receiving immunization. Therefore, this complicated the clinical picture even more.

Our patient's SJS was most likely due to Amiodarone, Allopurinol or influenza

vaccine since they have been started less than three weeks prior to his prodromal symptoms. Levaquin was started after the onset of his oral lesions. Amiodarone is an efficacious antiarrhythmic drug that was given to the patient for his atrial fibrillation. Yung et al described a 71-yo female who developed TEN three months after commencing Amiodarone.⁵⁸ Other dermatological side effects of Amiodarone include photosensitivity, allergic rash and blue-gray discoloration. Allopurinol has been associated with SJS. Patients with chronic renal failure are susceptible to developing severe reactions from Allopurinol. Chan et al suggests that a lower dose of Allopurinol should be given to renally compromised patients.⁵⁹ Our patient also received an influenza vaccine less than 24 hours prior to his prodromal symptoms. Rechallenge may have resulted in a more rapid onset of SJS. However, a link between SJS and vaccines has not been established.

Pathogenesis:

The pathogenesis of SJS is unclear. There is evidence that SJS is immune complex-mediated. Adhesion molecules and HLA-DR antigens expressed by keratinocytes direct cytotoxic T cells in

Table 5. Other Causative Factors

INFECTIOUS:
Herpes Simplex Virus Type 1
Mycoplasma pneumoniae
Epstein-Barr Virus
Influenza
Histoplasmosis
Enterovirus
Cholera
VACCINE:*
Measles
Smallpox
Hepatitis B
Influenza
DTP
Hib
MMR
OPV
OTHER:
Malignancy
Idiopathic

DTP, diphtheria, tetanus, whole cell pertussis, Hib, Haemophilus influenzae type b; MMR, measles, mumps, rubella; OPV, oral polio vaccine.

*** A causal link cannot be established.**

the destruction of keratinocytes.³⁴ Evidence also shows immune complex deposition, namely granular IgM and C3, on superficial cutaneous vasculature in EM.³⁵ Clinical manifestations of SJS mimic Kawasaki disease and toxic shock syndrome both of which are associated with high-titer antibodies directed against superantigens. It is then possible that SJS may at least partly, be mediated by

dysfunctional immune stimulation caused by superantigen production and therefore amenable to IVIG therapy.³⁶ However, it has been proposed that it may be linked to abnormal detoxification of the offending drug.³⁷ Associations with HLA-B12 also suggests genetic susceptibility.³⁸

Histopathology

Epidermal injury may present as satellite-cell necrosis. It may progress to eosinophilic necrosis of the basal and suprabasal layers. In TEN, there is evidence of full-thickness epidermal necrosis and subepidermal split above the basement membrane. There is scant amount of inflammation in the dermis.

Differential Diagnosis

The differential diagnosis includes generalized fixed drug eruption with its ill defined large erythematous patches, bullae or erosions, staphylococcal scalded skin syndrome especially in infants and pemphigus vulgaris with its oral lesions. Direct immunofluorescence can rule this out. Erythema multiforme can be ruled out by causative factors, typical target lesions and absence of internal organ involvement. Kawasaki disease with conjunctival injection and sloughing of hands and feet can mimic SJS. Acute onset paraneoplastic pemphigus, acute graft versus host disease, viral exanthems and exfoliative dermatitis are also good considerations.

Workup

Laboratory workup should include complete blood count since patients with SJS/TEN are usually lymphopenic and anemic. Neutropenia also suggests a poor prognosis. Electrolytes should be checked since epidermal fluid losses is common. Renal function should be monitored since prerenal azotemia is another common finding as seen in our patient. Bacterial colonization and sepsis need to be ruled out so cultures of blood, urine, wounds and sputum should be done.

Sequelae/Prognosis

Complications of SJS are numerous. Cutaneous complications include scarring, hyper/hypopigmentation and in severe cases and abnormal nail growth. Our patient had ill-defined hyperpigmented patches 5 months after his SJS episode. (Fig. 22) His palms and soles had no residual lesions. (Fig. 23) Our patient had evidence of transverse ridges on all his nails consistent with Beau's lines (Fig. 24)

The regrowth of the epidermis usually takes about three weeks. Interestingly, it is usually the typical length of the hospi-

talization for TEN in a burn unit.⁴⁰ Persistent erosions may occur in the oral mucosa resulting in chronic dysphagia.



Fig. 22- 5 months after IVIg treatment. Hyperpigmented patches on abdomen



Fig. 23 - 5 months after IVIg treatment. No residual lesions on palms.



Fig. 24 - 5 months after IVIg treatment. Beau's lines. Horizontal ridges on nails.

Our patient's oral mucosa completely resolved. Ocular complications of SJS include corneal ulceration and even blindness. Other mucosal complications include respiratory failure from tracheobronchial shedding, esophageal strictures, vaginal stenosis, and penile scarring.¹⁸ The most feared complication is sepsis, which is the most frequent cause of death. (Table 6) Septicemia is usually caused by *Pseudomonas*

aeruginosa, *Staphylococcus aureus* or *Candida albicans*. Fortunately, our patient did not develop sepsis. He was admitted back to the hospital 5 months later for cardiac problems.

The mortality rate of SJS is about 5-15%^{41,57} but about 30% for TEN.⁴¹ Factors that suggest poor prognosis include old age, increased BUN concentration, neutropenia and extensive cutaneous and visceral involvement. Our patient had all factors: 67yo, neutropenia, elevated BUN, extensive cutaneous involvement and visceral insult (tracheobronchial and alimentary tract). Interestingly, prognosis is not affected by the dose or type of the culprit drug.⁹ In addition, HIV infection does alter prognosis.

Management

Management of SJS is multidisciplinary. (Table 7). First, withdrawal of suspected drug(s) should be done. All drugs, especially those initiated within one month of reaction should be suspected.⁹ Because patients with SJS suffer from

Table 6. COMPLICATIONS OF SJS

CUTANEOUS:
Scarring
irregular pigmentation
eruptive nevi
abnormal nail regrowth
ORAL:
Persistent erosions
OCULAR:
Corneal ulceration
severe keratitis
anterior uveitis
blindness
ANOGENTITAL:
Phimosis
vaginal synechiae
SYSTEMIC:
Respiratory failure
esophageal strictures
sepsis
death

fluid and electrolyte imbalance, loss of skin barrier and hypermetabolic state, their hydration status should be closely monitored. The initiation of intravenous-fluid replacement is of prime importance. Patients may even need to be transferred to burn or intensive care unit.

Oral care is also critical. Benadryl/decadron (dexamethasone)/viscous lidocaine and Nystatin (mycostatin) mouthwash for symptomatic relief is usually helpful. If esophageal involvement is severe enough to interfere with eating, total parenteral nutrition may be war-

ranted. Aspiration pneumonia can be avoided by frequent, yet careful, suctioning of oropharyngeal secretions. When tracheobronchial sloughing is experienced, patients with SJS may undergo respiratory failure and require endotracheal intubation.

Due to common involvement of the conjunctiva, erythromycin ointment is beneficial. Ophthalmology is often involved to perform slit lamp examination and monitor corneal ulceration to prevent blindness.

Skin care is of great importance to prevent bacterial colonization and eventual sepsis. Topical care may include hydrocolloid or gauze dressings. Avoidance of sulfonamide-containing topical agents should be done. Debridement of necrotic skin should not be performed before disease activity ceases.¹²

Since patients with SJS usually complain of asthenia, pain control should be appropriately given. Avoidance of adhesive products and any trauma to skin should be considered.

Treatment with corticosteroids is at best controversial. Patterson et al³⁶ claim that early use of high-dose steroids may have a favorable influence. Others claim that corticosteroids contribute to increased mortality rates due to immunosuppression and secondary infection. Other anecdotal treatments for EM include thalidomide due to its anti-inflam-

Table 7. Management of STEVENS-JOHNSON SYNDROME

GENERAL:	*IV fluids, aseptic techniques *may need to be in intensive care/burn unit
ORAL:	*Suspensions with benzydol, viscous lidocaine, dexamethasone, mycostatin for symptomatic relief *gentle suctioning of secretions
OCULAR:	*erythromycin eye drops *may need ophthalmology for slit lamp examination
ANOGENITAL:	*Buttows wet socks or sitz bath for symptomatic relief
CUTANEOUS:	*may need pain medication for asthenia *Avoid adhesive and sulfonamide containing topical products *gentle cleansing of lesions followed by bacitracin ointment on erosions *hydrocolloid or gauze dressings
SYSTEMIC:	*monitor for pending respiratory and gastrointestinal compromise *supportive parenteral/peripheral nutrition if necessary

matory properties.⁴² Treatment with cyclosporine⁴³, cyclophosphamide⁴⁴ and plasmapheresis⁴⁵ have reported. Granulocyte colony stimulating factor has been reported for the treatment of SJS-TEN with neutropenia.⁴⁶ (Table 8)

Why use intravenous immunoglobulin?

The first reported use of intravenous immunoglobulin for SJS was in 1998. Most of the reported uses of IVIg treatment for SJS are in children. Morici et al used IVIg in 6 children and compared the

Table 8. Reported Systemic Treatment for STEVENS-JOHNSON SYNDROME

Corticosteroids
Intravenous immunoglobulin
Thalidomide
Cyclosporine
Cyclophosphamide
Plasmapheresis
Granulocyte colony stimulating factor

outcome with SJS patients treated with corticosteroids.⁵ A single infusion rate of 1.5-2 g/kg IVIg was used. The IVIg group

had a shorter duration of fever. Moudgil et al treated 2 children with IVIg with dramatic improvement.⁶ A 4 1/2 month old infant was treated with a single bolus of IVIg 400mg/kg with a 24 hour regression of cutaneous and mucosal lesions.⁴⁹ Amato et al treated a 22-month old girl with IVIg and steroids with improvement. Sanwo et al advocated for the use in patients with AIDS and Stevens-Johnson since IVIg has a potent anti-inflammatory activity without the risk of further immunosuppression.⁴⁷ Brett et al reported a beneficial role of IVIg in the treatment of SJS in an

immunocompetent patient using 1g/kg for the first dose then 60g for the second dose.³ (Table 9)

The mechanism of action of IVIg is unclear. Its immunologic properties protect against excessive inflammation and immunologic destruction.⁴⁸ Proposed mechanisms of action of IVIg are as follows:

1. Inhibition of cytokine production and action and therefore downregulating cell surface molecules⁵⁰
2. Increased T-cell suppressor activity⁵¹
3. Prevention of C3 binding to target cells⁵²
4. Providing anti-idiotypic antibodies to autoantibodies⁵³
5. Fc receptor blockade of mononuclear phagocytes.⁵⁴

Successful reported dermatological uses of IVIg include idiopathic thrombocytopenic purpura, Kawasaki disease, Wegener's vasculitis, juvenile rheumatoid arthritis, dermatomyositis, bullous pemphigoid and pemphigus vulgaris, pemphigus foliaceus, herpes gestationis, graft vs. host disease, pyoderma gangrenosum, toxic epidermal necrolysis and Stevens-Johnson syndrome.(Table 10) The few indications licensed by the Food and Drug Administration for high dose IVIg are chronic lymphocytic leukemia, graft vs. host disease, post bone marrow transplantation, idiopathic thrombocytopenic purpura, pediatric human immunodeficiency virus and Kawasaki syndrome.⁵⁵ Intravenous immunoglobulin is prepared by cold ethanol fractionation from the pooled plasma of up to 20,000 donors per batch.⁵⁶

There are disadvantages to using IVIg, namely cost and adverse effects. The cost ranges from \$50/g to \$100/g. Reported doses of IVIg for the treatment of SJS include a single dose of 2 g/kg or 4 doses of 0.4-0.5 g/kg. (Table 11)

Intravenous immunoglobulin is also

Table 9. Reported uses of IVIg for SJS treatment

AUTHOR	AGE GROUP	IVIg DOSE
Morici et al	CHILDREN 6 children (4-13yo)	1.5-2 g/kg as single infusion
Moudgil et al	2 children	
Carzola et al	4 mo old infant	400mg/kg as a single bolus
Amato et al	22 mo. old female	
	ADULTS	
IMMUNOCOMPROMISED		
Sanwo et al	31yo male with AIDS 62 yo female with AIDS	400mg/kg/day x 4 days 400mg/kg/day x 4 days
IMMUNOCOMPETENT		
Brett et al	27yo female	1g/kg first dose 60g second dose
*All reported beneficial role of IVIg.		

associated with adverse effects. including fever, chills, lower back pain, nausea and vomiting. It is also associated with cardiac symptoms such as chest pain, tachycardia and hypotension and hypertension. Patients usually experience these symp-

Table 10 Dermatological uses of IVIg

Idiopathic thrombocytopenic purpura
Kawasaki disease
Dermatomyositis
Juvenile rheumatoid arthritis
Wegener's vasculitis
Bullous pemphigoid
Pemphigus vulgaris
Pemphigus foliaceus
Herpes gestationis
Graft versus host disease
Pyoderma gangrenosum

Table 10 Dermatological uses of IVIg

Single dose of 2 g/kg
Four doses 0.4-0.75 g/kg

toms within 30 to 60 minutes of infusion.⁵⁵ Fortunately, our patient did not have any of these adverse effects.

More serious but rare adverse effects include anaphylaxis, acute renal failure and aseptic meningitis. Anaphylaxis is more common in patients who are IgA deficient patients with anti-IgA antibodies. IgA deficient IVIg is available for such patients. There is a question of whether IVIg causes a prothrombotic tendency due to its high solute load.⁵⁵ Acute renal failure from IVIg is also believed to be caused by its high solute load inducing injury to the proximal tubule.⁵⁵ Fortunately, this is usually reversible. This was evident in our patient. His renal function returned to baseline with the usage of intravenous fluids without requiring hemodialysis. The etiology of his acute renal failure remains to be determined. In addition to IVIg, he was also on Solumedrol and total parenteral nutrition, both of which can cause renal adverse effects on an already renal compromised patient. Aseptic meningitis is usually seen from 10 hours to 7days after high dose IVIG therapy. Patients who suffer from this commonly recover.⁵⁵ (Table 12)

In summary, our patient had SJS-TEN overlap with severe mucosal involvement of three sites: oral, ocular and genital. The etiology remains to be determined. He was exposed to influenza vaccine and shortly thereafter experienced prodromal flu-like symptoms and subsequent SJS.

In addition, he was on Allopurinol, Amiodarone, Theophylline and Levaquin all of which have been known to cause SJS. All of the suspected culprit drugs were discontinued except for his systemic steroids and oxygen which he is

Table 12. Adverse effects of IVIg

Fever*	ONSET
Chills*	*within 30-60 minutes of infusion
Lower back pain*	
Nausea*	
Vomiting*	
Chest pain*	
Tachycardia*	
Hypertension*	
Hypotension*	
Anaphylaxis	
Acute renal failure	10hrs- 7 days of infusion
Aseptic meningitis	
Transient neutropenia	day 4-5
Eczema	
Alopecia	
Erythema multiforme	

dependent on for his chronic obstructive pulmonary disease. He was treated with four doses IVIg with improvement during the first 24 hours (Fig. 25) and with minimal sequela after 5 months (Fig. 26).

It is unclear if his response was solely due to IVIg treatment, IV solumedrol or merely the natural progression of his disease. However, he was started on IV solumedrol 48 hours before IVIg without improvement. Overall, he responded well to IVIg despite his adverse effect of reversible acute renal failure. Intravenous immunoglobulin should be further studied for the treatment of SJS-TEN and other dermatological diseases.



Fig.1 Pre-IVIg infusion



Fig. 25- 24 hrs. after 1st IVIg infusion



Fig. 26 – 5 months after IVIg infusion

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Disclosure:

Figure 20: This figure was obtained from *Dermochromes-Volume I, Dr. Kingsbury*. It is a cast model. It was published in 1914 by *Rebman Company* in New York, NY. I made numerous attempts to contact the company via letters, telephone and internet. Unfortunately, the company no longer exists. The publishing company that replaced *Rebman Company* is unknown. The duration of the copyright is also unknown. Due to the fact that this picture beautifully portrays the classic target lesion of erythema multiforme with its three concentric zones, its mention is valuable; even though I was not able to obtain consent.

Epidermotropic Metastatic Malignant Melanoma (EMMM) – a pathological variant of melanoma.

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Abstract

Epidermotropic metastatic malignant melanoma (EMMM) is a pathological variant of melanoma, which can histologically simulate a primary melanoma or melanocytic nevus. A 51 year old female presented 6 years ago with a 1.3mm, Clark level IV melanoma of the scalp. Since then, the patient presented with an almost identical histology in the areola, eyebrow, face, ear and scalp. The histology of these lesions showed atypical non-pigmented melanocytes in the epidermis and dermis with minimal lateral extension in the epidermis. Immunohistochemical analysis revealed HMB-45 expression superficially in the dermis with diminished expression deep in the dermal layers. Ki-67 staining was confined only to the superficial melanocytes. CD34 and Factor VIII showed staining around the capillaries without evidence of intravascular melanocytes. The histopathology of epidermotropic metastatic malignant melanoma may be problematic, simulating primary melanoma or a melanocytic nevus. However, clinical history coupled with melanocytic markers is helpful in distinguishing it from other melanocytic lesions.

Introduction

Epidermotropic metastatic malignant melanoma (EMMM) is a pathological variant of melanoma. The diagnosis of EMMM can be particularly problematic because the histopathological appearance can simulate primary melanoma or even a melanocytic nevus.¹ The metastases of malignant melanomas usually extend from the dermis to subcutaneous fat with sparing of the overlying epidermis. However, in rare instances metastatic melanomas can invade superficially and exhibit epidermotropism. In such cases, delineating a primary lesion from a metastatic lesion with epidermal involvement can be difficult.^{2,3} Epidermotropism has been seen in various types of cutaneous carcinomas (breast, neuroendocrine) including metastatic melanoma.^{4,5} Usually there is no host response but fibrosis or inflammatory infiltrates can be seen. The melanocytes comprising the tumors are often relatively

monomorphous. The lesions are usually well circumscribed and vertically oriented. Thinning of the epidermis by aggregates of atypical melanocytes and nests within the dermis may occur. Inward turning of the rete ridges at the periphery of the lesion can be seen. Considerable upward pagetoid extension of melanocytes, mitotic figures and both epidermal and dermal nests are characteristic of epidermotropism. There can be invasion of blood vessels and lymphatics.⁶

Patients with EMMM characteristically present first with primary melanoma and subsequently develop multiple cutaneous metastases which can simulate primary lesions. They are often multiple, symmetric and less than 3 to 4mm in size and can occur from months to years after the primary lesion. Patients have often been described with multiple skin lesions, paradoxically without any other systemic involvement. While long survival times with skin involvement only, are not uncommon, metastasis to other organs usually indicates a poor prognosis. Epidermotropic metastases from internal malignancies are exceedingly rare, however, epidermotropic metastatic breast carcinoma, and intraepidermal involvement from metastasizing adenocarcinomas of the rectum, vagina, urethra, cervix and bladder have been reported.⁷

We report a 51 year old female with a history of a primary melanoma of the scalp who subsequently developed at least 14 regional skin metastases, of

which the majority were epidermotropic metastatic malignant melanomas. The patient had no early evidence of multi organ or systemic involvement despite very vigorous evaluation including CAT scan and lymph node dissection. After six years the patient was found to have developed pulmonary metastases.

Clinical History

A 51 year old female presented 6 years ago with a 1.3 mm, Clark level IV primary melanoma of the mid parietal scalp for which she underwent wide excision with margin evaluation. Over the ensuing years (3-6 years) the patient has

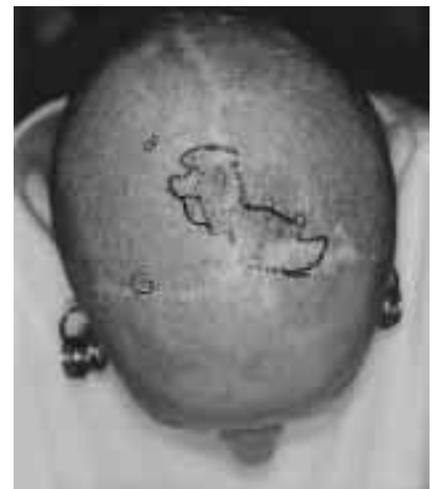


Figure 1. Excision of scalp lesion with multiple epidermotropic metastases.

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presented on follow up examination with multiple pigmented lesions, of almost identical histology in the areola, eyebrow, face, ear, with the scalp showing a predominance of these recurrent lesions. Generally these lesions were less than 4 mm in diameter and none of them arose in sites previously associated with preexisting melanocytic nevi. Most of the scalp lesions were located midline in the parietal scalp, extending across the mid-frontal scalp region adjacent to the initial excision (Figure 1). The clinical appearance of the lesions were macular and flesh colored. The lesions had irregular borders and focal areas of darker pigmentation. The biopsies showed distinctive atypical epithelioid non-pigmented melanocytes in the epidermis as well as the dermis and confirmed epidermotropic malignant melanoma. Multiple diagnostic evaluations including lymph node dissection and CAT scans were performed, and failed to reveal any evidence of systemic disease initially. Since the diagnosis of epidermotropic metastatic malignant melanoma had been established, all the lesions were excised. Multiple lesions on the scalp were treated with wide re-excision scalp reductions and skin grafts. Her only other known medical history included Waldenstrom's macroglobulinemia. There was no documented family history of melanoma or dysplastic nevus syndrome. After six years the patient was found to have developed pulmonary metastases.

Methods

All the biopsies taken from the patient were preserved in formalin fixed paraffin embedded blocks at the Mount Sinai histology laboratory. The blocks were collected and serial sections were obtained and stained with hematoxylin and eosin for light microscopic examination. All sections were evaluated with markers to confirm the nature of the melanoma. We studied each of the biopsies with antibodies against proliferation markers Ki-67, HMB-45 and vascular markers CD34 and Factor VIII. An avidin-biotin immunoperoxidase technique was used to stain the sections.

Histopathology

Most of the scalp lesions were located midline in the parietal scalp, extending across the mid-frontal scalp adjacent to the scar from prior resections. There was a 3x3 mm lesion proximal to the helix of the right ear. The other lesions were found on the areola, face and eyebrow. All skin biopsies of the patient were reviewed under light microscope to compare cytological architecture of the various sections obtained from this patient. Virtually all the biopsies showed

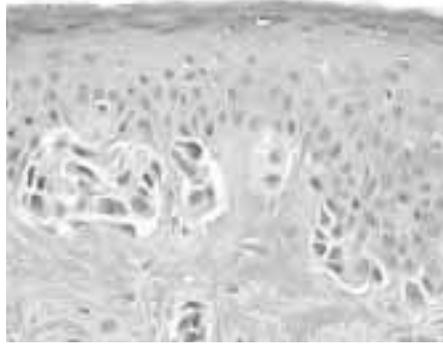


Figure 2



Figure 3. Atypical epithelioid and non-pigmented melanocytes invading epidermis and superficial dermis.

identical histopathology. There were atypical non-pigmented epithelioid melanocytes in the epidermis and dermis with areas of limited lateral extension in the epidermis (Figure 2). The lesions were asymmetrical and exhibited a pagetoid spread of atypical melanocytes in the epidermis as well as nests of melanocytes in the dermis (Figure 3). The nests in the dermis were irregular in shape and size. The nuclei of the cells were hyperchromatic or vesicular with small nucleoli. Sparse melanin was identified in a few cells. Occasional mitotic figures were found. Adnexal involvement by atypical melanocytes was also seen. No maturation of melanocytes was observed with descent in the dermis. There was no vascular involvement. Some of the lesions extended deep in the dermis. Many of the lesions were small and identical to a benign nevus.

Immunohistochemistry

The patient's biopsies were examined and demonstrated close correlation with the epidermal and dermal staining pattern often associated with a melanocytic nevus. HMB-45 was expressed superficially in the dermis with diminished expression in the deep dermal layers (Figure 4). Ki-67 staining was confined only to the superficial melanocytes (Figure 5). CD34 and Factor VIII staining was seen around the capillaries but did not

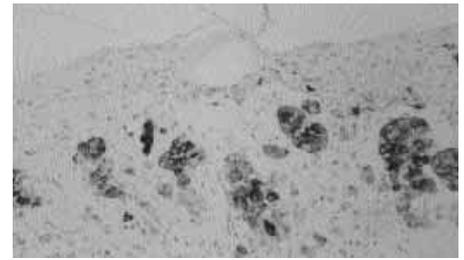


Figure 4.

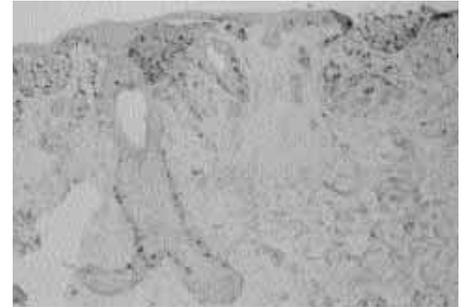


Figure 4 and 5. Immunohistochemistry of HMB-45 and Ki-67 in EMMM confining to superficial dermis. No intravascular involvement was seen.

demonstrate evidence of intravascular invasion by melanocytes.

Discussion

The pathological tenants of epidermotropic metastatic malignant melanoma have been well established over the years, yet definitive diagnosis remains a dauntingly difficult task. At the heart of this diagnostic dilemma lies the fact that epidermotropic metastatic malignant melanoma bears striking histologic resemblance to primary melanomas and melanocytic nevi. Historically, this distinction was rendered "clear cut" in 1953 by Allen and Spitz,⁸ who felt that the absence of junctional changes in the overlying epithelium was conclusive evidence for a dermal lesion to be considered metastatic or locally recurrent. Some twenty five years later, the Allen and Spitz theory was reexamined by Kornberg and Ackerman⁹. Kornberg et al. described four patients with multiple epidermotropic metastatic melanoma lesions that included the presence of junctional nests,¹⁰ which directly defied the initial theory of Allen and Spitz. Kornberg and Ackerman developed and discussed three specific histologic features that favored the diagnosis of EMMM. These three features included (1) thinning of the epidermis by aggregates of atypical melanocytes within the dermis often associated with widening of the dermal papillae and elongation of inward turning rete ridges at the periphery of the specimen; (2) atypical melanocytes within the intradermal endothelial-lined spaces, and (3) a zone of atypical melanocytes within

the dermis equal to or broader than that within the epidermis. While this classification remains very useful to date, it is limited in the sense that the literature supports other cases that may deviate slightly from these tenants. Heenan and Clay¹ described a case of epidermotropic metastatic malignant melanoma in a 51 year old male that demonstrated multiple areas of extensive epidermal involvement. Other authors have also postulated that the pathologic criteria of epidermotropic metastases does not always conform exactly to the classical stereotypic characterization offered by Kornberg and Ackerman. Abernathy et al.¹¹ reported two cases in which the patients not only had epidermotropic metastases resembling primary melanoma, but also many lesions that exhibited exclusive epidermal involvement consistent with a melanoma in situ presentation. There was no intravascular involvement. There are also documented cases of epidermotropic metastatic malignant melanoma arising directly from a diverse array of cutaneous pathologies including primary and junctional melanoma, benign, dysplastic, compound⁸ and congenital nevi.^{9,12,13,14} The biopsies in our patient revealed a pattern of histology similar to that as described by Kornberg and Ackerman. There were discrete nests of melanocytes overlying the epidermis with atypical melanocytic involvement in the dermis. There was no lateral extension in the epidermal component.

In attempting to distinguish between epidermotropic metastatic malignant melanoma and melanocytic nevi, histologic markers were helpful. We utilized HMB-45 and Ki-67. They are proliferation markers and their role is well established in the diagnosis of malignant melanomas. They are strongly expressed in melanomas and metastases and show insignificant superficial dermal staining in benign nevi.¹⁶ Although the extent of expression of Ki-67 and HMB-45 staining supported the diagnosis of melanoma, we also demonstrated a diminished expression of the markers deeper in the dermis.

This phenomenon has been described in nevi and as well in invasive melanomas with paradoxical maturation. It is difficult to speculate, but this pattern may be related to the indolent clinical course of these tumors in this patient. Epidermotropic metastatic malignant melanoma showing strong expression confined superficially to epidermal cells has been reported by other authors.^{10,11,15} Our results correlated closely with the literature showing this intense preferential expression characteristic of EMMM enabling us to distinguish the metastases from nevi. Ruhoy et al. touted this phenomenon of Ki-67 expression to be the most helpful feature in establishing the difference between EMMM lesions and benign nevi.¹⁵ Expression of CD34 and Factor VIII were assessed to determine the degree of vascular involvement. Bengoechea-Beeby et al showed deep invasion of the dermal capillaries in all of their reported epidermotropic metastatic skin lesions.⁶ Our case showed no intravascular involvement.

The melanocytic lesions in this patient, as well as the others aforementioned and discussed by their respective authors, are instructive for outlining the plethora of clinical and histopathological features salient to EMMM. One may still question the usefulness differentiating between primary melanomas and epidermotropic metastatic lesions, arguing that the nature of published data is sparse and case reports are inconclusive. One may even argue the point that a patient who has had primary malignant melanoma is at increased risk for having multiple primary melanomas.¹⁷ We conclude that the clinical history provides a compelling case that the subsequent lesions found in our patient were indeed true metastases as opposed to multiple primary lesions or benign nevi. The sheer number of lesions, size, location, and time course toward development make a strong case for metastases.¹¹ It is of utmost importance to accurately diagnose and differentiate between EMMM, melanocytic nevi, and primary malignant melanoma, the resultant therapeutic and prognostic

perils associated with misdiagnosis are clear. A good clinical history and conscientious follow up coupled with immunohistochemical evaluation of biomarkers and histopathological analysis is paramount in making an accurate diagnosis.

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