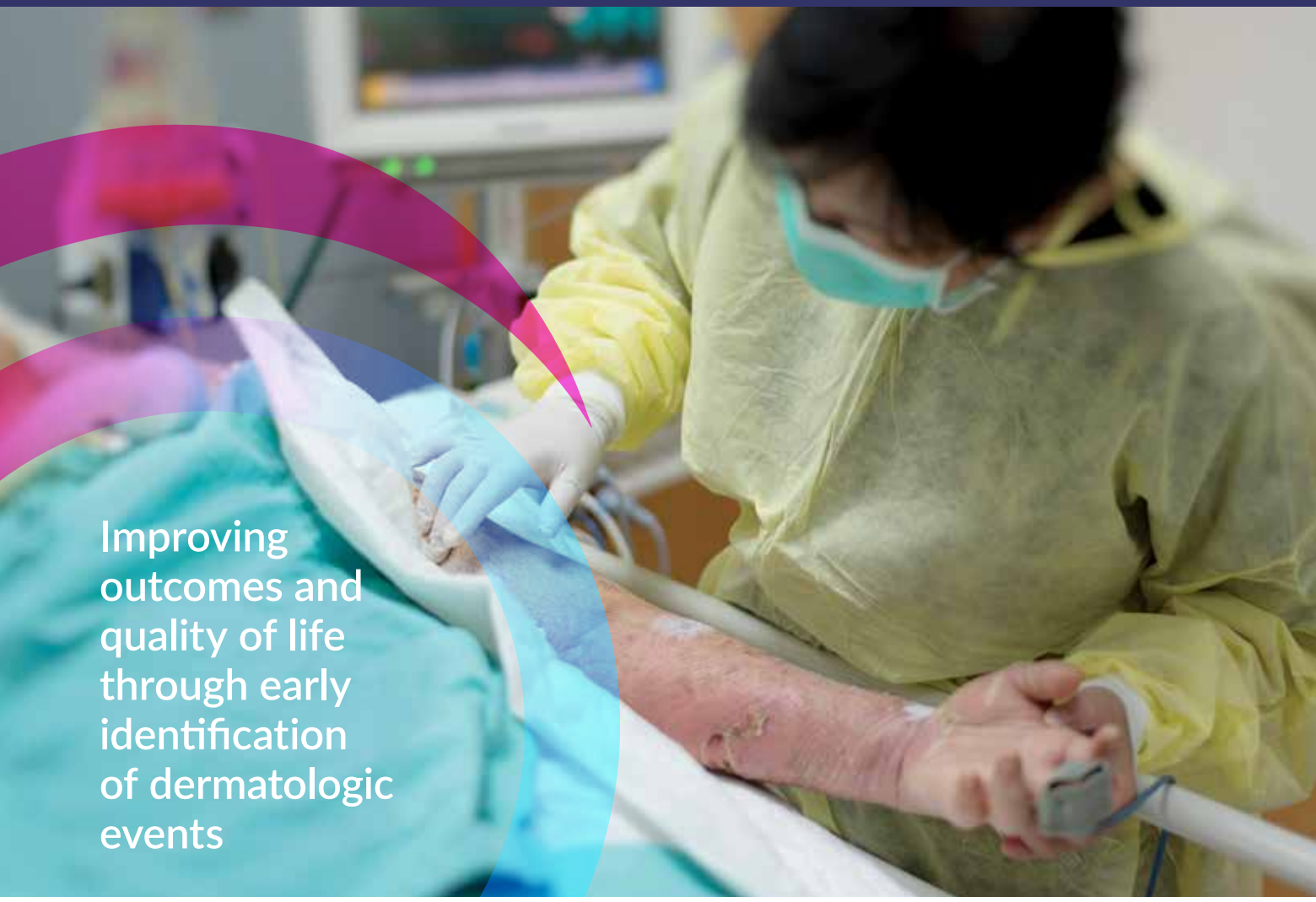
Dermatologic Issues Associated With Cancer and Cancer Therapy



Improving outcomes and quality of life through early identification of dermatologic events

APSHO
Advanced Practitioner Society for Hematology and Oncology

With funding support by

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Introduction

Dermatologic Issues Associated With Cancer and Cancer Therapy: Resources and Treatment

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THERAPEUTIC ADVANCES in oncology have paved the way for improved survival rates and better quality of life for patients across disease types. A number of these advances, however, have also led to increased incidence of dermatologic-based adverse events, which may be difficult to accurately diagnose in clinic due to nonspecific clinicopathologic features, especially when presenting in a patient who has overlapping pre-existing dermatologic conditions. Many centers, particularly in the community setting where access to dermatologists and oncodermatologists may be limited, lack comprehensive educational guidelines and resources for identifying, grading, and managing these toxicities. Even in those centers that do have diagnostic resources and treatment algorithms, the incidence of dermatologic toxicities from cancer therapy may be underreported simply because of inconsistent terminology used in electronic medical records (EMRs)—after all, there are seemingly endless ways to describe "rash."

Although patient complaints of cosmetic changes associated with nails, hair, and skin may not require intensive medical management, these can substantially affect quality of life. Skin toxicities may, in fact, be some of the most distressing adverse events for patients with cancer and can cause significant emotional turmoil.[1] Failure to prepare patients adequately prior to occurrence, late identification, and inconsistent management of dermatologic events all may lead to dose alterations and interruptions or discontinuation of therapy, which can influence a patient's overall outcomes.[2]

Advanced practitioners (APs) play a vital role in assessing symptoms of dermatologic toxicities, coordinating care with other subspecialties and providing proactive education about symptoms and management. For this reason, APSHO and its industry partners created an Educator Module and this corresponding resource to help APs become more familiar with the most commonly seen dermatologic conditions and their causative agents. Dermatologic emergencies and events related to radiation and stem cell therapies are also reviewed here. Although not comprehensive in scope, detailed information about presentation, diagnosis, and management is included, as well as tips for proactive patient education.

TYPES OF LESIONS & KEY TERMS

LESIONS

Lesions are breaks, wounds, or growths on the skin. There are numerous lesion types, but this list contains the most common types seen in conjunction with oncologic therapies. They can be characterized into primary and secondary types.

Primary Lesions

– **Macules** are usually < 10 mm in diameter, non-raised/depressed, and nonpalpable. Examples include freckles, port-wine stains, and even tattoos.

– **Papules** are elevated lesions such as lichen planus, warts, and some skin cancers.

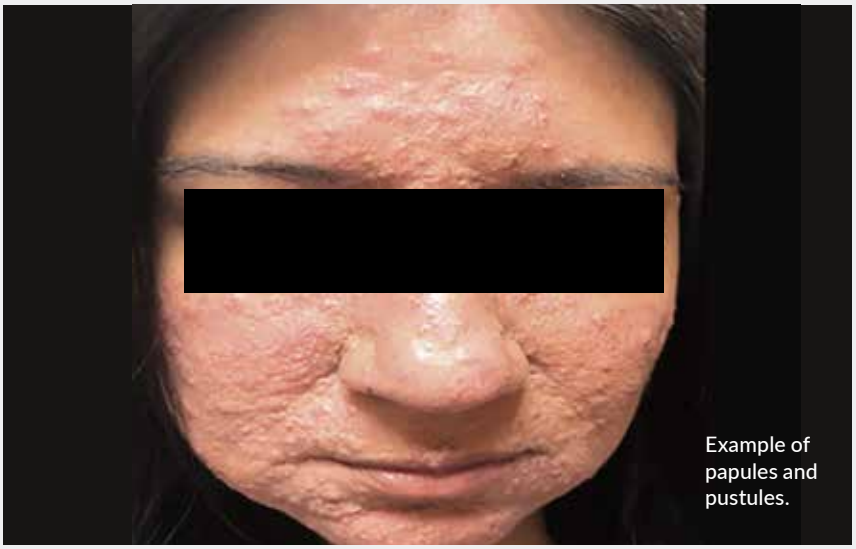
– **Plaques** are > 1 cm in diameter and are elevated or depressed on the skin surface. Examples include psoriasis plaque and granuloma annulare.

– **Nodules** are firm papules > 1.5 cm in diameter that extend into the dermis or subcutaneous tissue around the nodule. Examples inlcude cysts, lipomas, and fibromas.

– **Pustules** are elevated, well-circumscribed lesions containing purulent material, < 1 cm in diameter. Pustules are common in bacterial infections and some inflammatory disorders.

– **Urticaria,** also known as wheals or hives, are red, pruritic, elevated lesions caused by localized edema. Urticaria is a common display of hypersensitivity to certain drugs and can be induced by physical stimuli such as temperature, pressure, and sunlight. Urticaria generally tends to last < 24 hours.

– **Vesicles and bullae** are both elevated, well-circumscribed, fluid-containing lesions. Fluid is usually serous but can be hemorrhagic. Vesicles measure < 1 cm in diameter; bullae > 1 cm in diameter. Vesicles are often seen with herpes infections and acute allergic contact dermatitis, whereas bullae may be caused by drug reactions, as well as burns, irritant contact dermatitis, or allergic contact dermatitis.



Example of papules and pustules.

Secondary Lesions

– **Scale** is hyperkeratosis caused by a buildup of stratum corneum secondary to increased proliferation and/or delayed desquamation.

– **Crusts (scabs)** consist of dried serum, blood, or pus. Crusting can occur in inflammatory or infectious skin diseases.

KEY TERMS

– **Atrophy** is the thinning of the skin, giving it a tissue paper–like appearance. Although atrophy can be caused by aging and sun exposure, it is also common with some inflammatory conditions and neoplastic skin diseases, such as cutaneous T-cell lymphoma. Long-term use of topical corticosteroids can also cause atrophy.

– **Telangiectasia** are small, permanently dilated blood vessels commonly seen in prolonged high potent steroid use and chronic radiation dermatitis. They usually fade with pressure.

– **Petechiae** are pinpoint-sized red dots of bleeding under the skin. These can be seen with thrombocytopenia and other platelet disorders, vasculitis, and infections. These can also be caused by simple injury or straining, such as coughing or vomiting. Petechiae are commonly seen in patients with leukemia.

Visit the APSHO Educator Module to learn more.

Key Terms Regarding Nail Changes

• **Chromonychia** is an abnormality in the color of the nail plate or subungual tissue.

• **Subungual splinter hemorrhages** are longitudinal, thin, dark-red subungual lines, usually secondary to trauma.

• **Leukonychia** comprises white spots on the nail plate or a complete whitening of the nail plate.

– **Mees' lines** are horizontal white lines or bands that appear on the nail plates of the fingernails and toenails.

– **Muehrcke's lines** are double white lines that run horizontally across the fingernail plate.

– **Beau's lines** are grooves that run horizontally across the nail.

• **Melanonychia** is a change of pigmentation that causes a brown-black stripe vertically on the nail plate. It may involve single or multiple fingernails and/or toenails.

• **Onychodystrophy** refers to abnormalities of nails outside of changes in pigmentation. It is simply the abnormal appearance or deformity of the nails.

• **Onycholysis** is a separation of the nail from the nail bed.

• **Onychomadesis** is characterized by separation of the nail plate from the proximal side with subsequent shedding of the nail as a new nail grows in beneath the old loose one.

• **Onychorrhexis** causes vertical ridges on the fingernails.

• **Onychoschizia** refers to fragile, brittle nails that split horizontally across the nail plate.

• **Paronychia** is a common bacterial infection of the nail fold involving edema, pain, and often purulent drainage. It occurs in the proximal and lateral fingernail and toenail folds and includes the tissue that borders the root side of the nail. The acute phase lasts < 6 weeks, and the chronic phase lasts > 6 weeks.

• **Pyogenic granulomas** are rapidly growing, red friable papules, often pedunculated, common after trauma.

• **Digital gangrene** is a form of vascular injury in which tissue necrosis develops at the tips of the fingers and toes.

• **Raynaud's phenomenon,** also known as Raynaud syndrome, is a condition that causes decreased blood flow to the fingers, resulting in a red, white, and blue discoloration of the skin secondary to cold stimuli. In certain cases, it also decreases blood flow to the ears, toes, nipples, knees, or nose. Patients may complain of numbness or coldness in the affected areas.

Grading of Dermatologic Adverse Events

The Common Terminology Criteria for Adverse Events (CTCAE) was issued by the National Cancer Institute and is a standardized criteria for adverse event grading in hematology/oncology.[3] A portion of the latest version of the CTCAE is dedicated to dermatologic toxicities based on body surface area (BSA). The grading ranges between 1 and 5, with 1 being mild and 5 death. For example, alopecia, which isn't life-threatening, is only graded between 1 and 2, compared with bullous dermatitis, which can be life-threatening and is graded between 1 and 4. The guidelines grade bullous dermatitis at grade 1 as mild—blisters covering less than 10% of BSA—compared with grade 4, which presents with blisters covering more than 30% BSA and systemic symptoms. These recommendations are discoverable via Google as well as via a publicly available PDF and a free, searchable app, both of which help APs recognize and document a patient's symptoms, making therapeutic decision-making easier.

> "Something doesn't have to be life-threatening to dramatically impact a patient's quality of life. Grading for dermatologic events is crucial, but not the end-all, be-all. Clinical experience and clinical confidence should also play a big part here.
>
> **— Krista Rubin, CNP,** Focus Group Member

Topical Corticosteroid Vehicles

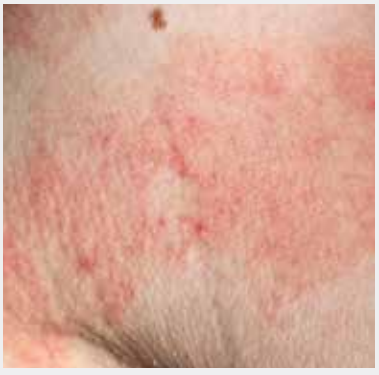
There are a number of vehicles for topical corticosteroid delivery.[4,5] Therapy should be prescribed based on the area being treated, type of rash/lesion, and patient's demographic characteristics and history.

Vehicles for Topical Corticosteroid Delivery

VEHICLE TYPE	SITES OF APPLICATION	PROS	CONS
OINTMENT (water suspended in oil)	• Palms, soles • Thickened, lichenified skin	• Occlusive effect • Emollient properties • Water resistant	• Greasy • Difficult to wash off • Harder to spread • Unsuitable for application to large body areas or hairy areas
CREAM (20%-50% oil in water)	• Dry, exudative skin • Infected/exudative plaques • Good on all body areas	• Moistening properties • Soothing • Easy to spread • More compliance	• Less hydrating • Less occlusive
GEL	• Hairy and oily areas such as scalp and face	• Easy to apply and wash off • Dries greaseless	• Not an emollient • Some contain alcohol, which can dry skin out
LOTION (suspensions or solutions of medication in water, alcohol, or other liquids)	• Exudative • Hairy areas	• Cooling effect • Easy to apply and spread	• Less occlusive
SOLUTION	• All areas	• Easy to spread • Good alternative to add to spray bottle when sprays are not covered by insurance	• Messy application • Most have high alcohol content (irritates skin)
FOAM (pressurized collections of gaseous bubbles in a matrix of liquid foam)	• Hairy, oily areas • Great for large surface areas of skin	• Easy to spread • Increased absorption	• Minimal hydration • Costly (many insurances don't cover)
SPRAY	• All areas • Avoid high-potency sprays on areas of thinner skin	• Large areas of skin • Easy to apply • Only need a thin layer	• May cause stinging/burning on application

Common Pre-Existing or Concurrent Dermatologic Conditions

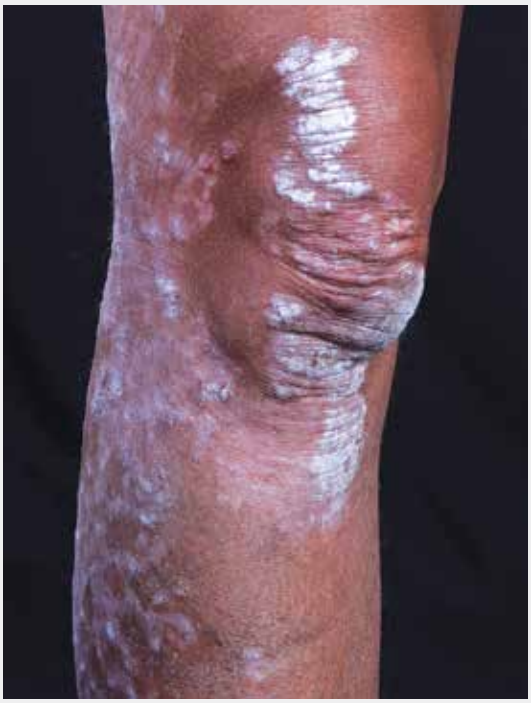
Atopic dermatitis (eczema) causes dry, itchy, scaly, and inflamed skin. Eczema can present as redness for people with lighter skin but may look brown, purple, gray, or ashen on people with darker skin. People with eczema may experience long periods of dormancy followed by flares, which can be caused by changes in diet or lifestyle. People with eczema also are at greater risk for developing food allergies, hay fever, and asthma.



Eczema is not a histamine-mediated rash, so Benadryl or other antihistamines are not effective management choices, but they can be useful in the management of pruritus associated with it. Used to treat a variety of dermatologic conditions that involve itching, redness, dryness, crusting, scaling, inflammation, and discomfort, clobetasol is a topical steroid used in the management of eczema.

Psoriasis is caused by an overactive immune system and results in

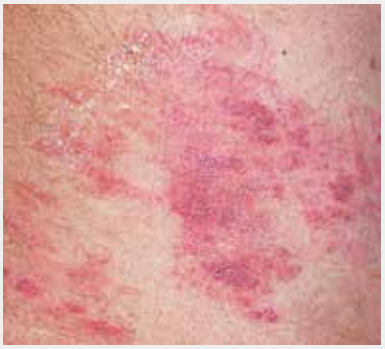
patches of skin becoming inflamed and scaly. Psoriasis is most often found on the scalp, elbows, and knees, but other parts of the body can be affected. Nails may appear thick and ridged or pitted. Like eczema, people with psoriasis can experience long periods of remission, interspersed by flares. Psoriasis can increase risk for certain cancers, Crohn's disease, diabetes, metabolic syndromes, obesity, osteoporosis, uveitis, and both liver and kidney disease. Clobetasol is a topical steroid used in the management of psoriasis.



Rosacea is a flushing or redness of the face. It is a long-term condition that involves flares brought on by medications or emotional triggers. Facial redness may evolve into pus-filled bumps and pimples resembling acne. Blood vessels may appear as thin red lines on the nose and cheeks, but this is a more severe symptom mostly found in men. Facial skin, especially on the nose, may thicken. Eyes may become red, sore, itchy, watery, or dry (ocular rosacea). Patients may report that their eyes feel gritty, and eyelids may swell and redden at the base of the eyelashes. Styes may develop. Rosacea tends to be underdiagnosed in patients with darker skin because darker skin may mask reddening.

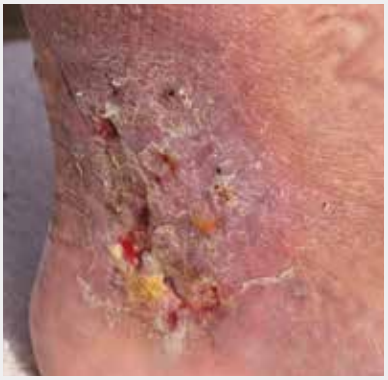
Common Infection-Related Events

The varicella-zoster virus is the same virus that causes chickenpox. When reactivated, it is known as herpes zoster (shingles). **Herpes zoster** displays as blister-like sores, usually



on one side of the body, face, and/or torso given that it follows a dermatomal pattern. Although usually a self-limiting rash, it is accompanied by pain and serious cases can lead to postherpetic neuralgia.

Cellulitis is a common result of bacterial infections. It displays as red and swollen skin, and it is warm and painful to the touch. The skin may look pitted or be covered in blisters, and patients may have fever and chills. Cellulitis is most common on the feet and legs.



Systemic Treatment–Related Conditions

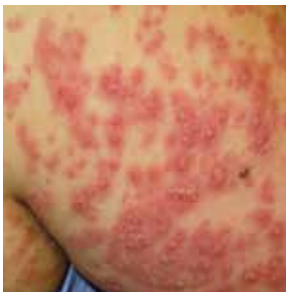
IMMUNOTHERAPY includes CTLA-4, PD-1, PD-L1, and LAG3 inhibitors, as well as bispecific agents, which include cytotoxic effector cell redirectors, tumor-targeted immunomodulators, and dual immunomodulators. Cutaneous immune-related adverse events are commonly associated with immunotherapeutic agents, with most being self-limiting and manageable. Patients receiving immunotherapy should be proactively educated about skin and sun protection.

TARGETED THERAPY including EGFR inhibitors, specific tyrosine kinase inhibitors, multikinase inhibitors, RAS-RAF-MEK-ERK pathway inhibitors, antiangiogenic agents, mTOR inhibitors, hedgehog signaling pathway (HhSP) inhibitors, and proteasome inhibitors are associated with a number of dermatologic toxicities, but perhaps the most common is rash.

CHEMOTHERAPY is cytotoxic therapy typically associated with alopecia and/or reversible hair loss. This toxicity may have tremendous impact on patients' quality of life. Patients should be informed up front regarding the potential for this toxicity so that they can have early access to wigs if desired. Rash can also occur from chemotherapeutic agents. Skin biopsy can help determine the severity and type of chemotherapy-associated rash.

Denotes conditions that **require immediate attention by a dermatologist**; consideration should be given for referral to the ED.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP): AGEP is a rare severe cutaneous adverse reaction that should be treated as a dermatologic emergency. AGEP presents as multiple non-follicular sterile pustules on a background of edematous erythematous skin, with fever and leukocytosis. Pustules may be concentrated in skin folds, and facial swelling may occur. The onset of this rash is usually 48 hours to 2 weeks after the initiation of the causative medication. Fever is usually a near-constant feature of this rash. Malaise may also be associated, but the patient usually feels otherwise well despite this being a potentially life-threatening condition. The diagnostic workup is a skin punch biopsy. If there is concern about a superinfection, a bacterial culture should be performed.[6]



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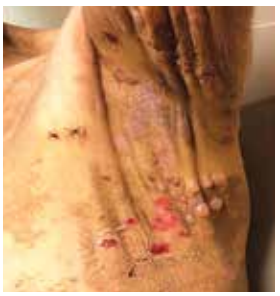
Low-grade disease may be treated with emollients, topical corticosteroids, and oral antihistamines, but AGEP typically leads to therapy discontinuation. Resolution is typically spontaneous around 1-2 weeks after onset and characterized by skin peeling and desquamation.

BULLOUS PEMPHIGOID: Characterized by large, fluid-filled blisters on skin that flexes, such as the lower abdomen, upper thighs, and armpits. This condition typically occurs 13 to 16 weeks after treatment initiation, but it is important to note that bullous pemphigoid may occur at any time during or after therapy. Lesions may persist long after therapeutic discontinuation, and this condition can be life threatening for patients in poorer health. Bullous pemphigoid requires a same-day referral to a dermatologist to do further testing, such as multiple biopsies and serologic testing. It is important to initiate treatment for bullous pemphigoid early. Topical or systemic corticosteroids may be used, in addition to omalizumab, dupilumab, and rituximab for more severe disease.[7]



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DRUG-INDUCED HYPERSENSITIVITY SYNDROME (DIHS, FORMERLY DRESS): Drug-induced hypersensitivity syndrome (DIHS) was formerly referred to as DRESS, or drug rash with eosinophilia and systemic symptoms. DIHS can have a

APSHO'S EXPERT-CREATED EDUCATION: A VISUAL RESOURCE FOR DAILY CLINIC

APSHO and its industry partners formed a Steering Committee of advanced practitioner (AP) experts in November 2023 in an effort to help APs become more knowledgeable about dermatologic toxicities associated with systemic therapies such as chemotherapy, immune checkpoint inhibitors (ICIs), and tyrosine kinase inhibitors (TKIs), as well as with radiation therapy and commonly used supportive agents. A larger focus group was convened in an effort to catalog commonly seen conditions and the questions associated with them. The resulting education—two live webinars and the APSHO Educator Module "Dermatologic Considerations During Cancer Therapy"—was created by Megan Bielawa, DMSc, MS, PA-C, and Cara Norelli, MS, AGNP-C, both of the Oncodermatology Department at Memorial Sloan Kettering Cancer Center.

The module provides visual examples of numerous treatment-related adverse events, including dermatologic emergencies such as drug-induced hypersensitivity syndrome and Stevens-Johnson syndrome, as well as more commonly seen issues such as lichenoid drug eruptions, mucositis, and a variety of nail changes. Recommendations for grading of dermatologic events and explanations of the pros and cons associated with the different therapeutic vehicles used in dermatology also are included, as is a helpful table of topical corticosteroid potency groupings and associated agents.

The slide-based Educator Module allows users to download slides, corresponding notes, and the video presentation separately or as a package to facilitate both self and group learning.

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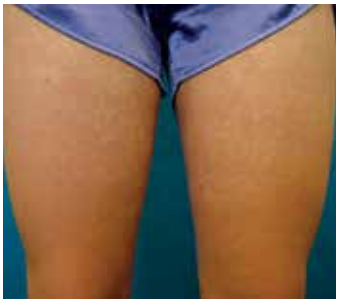

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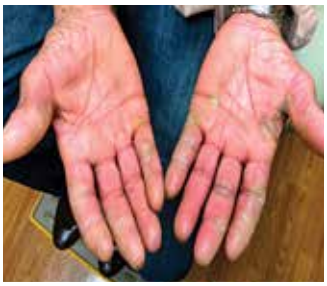
delayed onset from initiation of the causative medication—about 2 to 8 weeks. Because of this, it is important for patients to keep good, prolonged medication diaries and APs should carefully review history at presentation. The eruption may continue to flare despite discontinuation of the causative drug, so close follow-up with a dermatologist is key. The most common causes of DIHS are **anticonvulsants, sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs)**. DIHS presents as fever, malaise, and lymphadenopathy that precedes the rash by several days. Rash typically presents as a symmetric pruritic maculopapular eruption on the face, which then spreads downwards to the trunk and extremities; facial edema may be present. Visceral organ involvement, eosinophilia, and atypical lymphocytosis also may be present in these patients.[8]

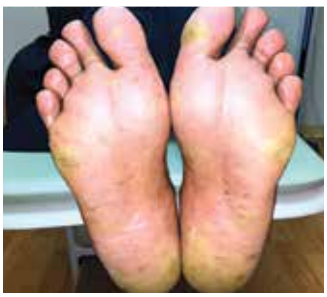
HAIR CHANGES: At around Week 8 of treatment, patients receiving **EGFR inhibitors** may experience changes to hair quality, texture, and growth pattern. Alopecia is rare, however. Thickening of the eyelashes (trichomegaly) and eyebrows also may be experienced. Eyelash trimming is recommended if inward curling is experienced, due to the risk for keratitis. **Multikinase inhibitors** may lead to brittle hair with kinking, depigmentation, and slower growth, all of which typically resolve after treatment cessation. Almost one-half of patients who receive sorafenib experience alopecia, which may be aided by topical minoxidil. **BRAF and Hedgehog pathway inhibitors, as well as radiation therapy,** stem cell transplant, and endocrine therapy, also are associated with alopecia.[7]

HAND-FOOT SKIN REACTION (HFSR): This reaction, which presents with diffuse painful edema and redness on the palms and soles of the feet, is the **most common cutaneous adverse event caused by tyrosine kinase inhibitors (TKIs)**. It is dose-dependent, and onset is 2 to 4 weeks after the initiation of treatment. It is associated with painful callus-like lesions, with associated erythema on areas of excessive pressure or friction, such as the heels and fingertips. The rash can progress to blisters and bullae. Paresthesia, such as tingling or burning, may or may not accompany this rash. Orthopedic shoes may help prevent foot issues, but treatments for low-grade disease are often required, such as emollients, keratolytic agents, topical corticosteroids

and/or anesthetics, and antiseptic soaks. Ultimately, if hand-foot skin reaction is severely impacting a patient's quality of life, dose reduction or therapy interruption may be necessary.[7,9]

HAND-FOOT SYNDROME: Also called palmar-plantar erythrodysesthesia, hand-foot syndrome has been found to occur in almost 30% of patients who receive bispecific therapy with **talquetamab** within the first month of treatment. It is also **heavily associated with cytotoxic chemotherapies**. Hand-foot syndrome presents as a burning/tingling sensation that then progresses to symmetric erythema, edema, and potentially blistering of the palms and soles. It occurs 1 to 3 weeks after the initiation of therapy, but it can occur sooner with capecitabine, and it usually resolves 2 to 4 weeks after discontinuation. Patients may use hand cooling during their treatments, which may reduce the incidence and severity of this rash. Keratolytics, such as urea cream, can also be used three times daily for prevention. Analgesics, such as lidocaine or even diclofenac, may be useful. Super high-potency topical steroids should be used for management.[7,10,11]





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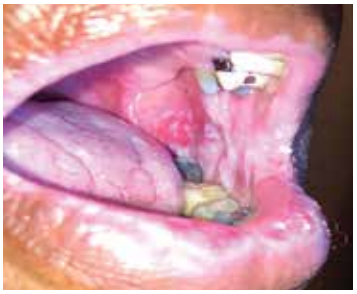
Taxanes such as paclitaxel and docetaxel are associated with a subtype of hand-foot syndrome that is accompanied by erythematous plaques on the dorsal surfaces of the hands and feet and is seen in up to 10% of patients treated with these agents. Plaques may also be seen on the Achilles tendon and malleoli. Cooling of the hands and feet directly before, during, and after infusion diminishes risk for this toxicity.[7]

LICHENOID REACTIONS: Lichenoid drug eruptions are one of the most difficult things to treat and one of the most frustrating rashes that APs may encounter. Commonly manifested as small, shiny, reddish-purple papules, lichenoid reactions are often intensely pruritic. Classic lichen planus, lichen planus pemphigoides, and lichen sclerosus atrophicus have all been reported as dermatologic events from **immunotherapies**. Interestingly, these rashes occur in approximately 25% of patients on immunotherapies so these will be something that most APs encounter in clinic. Lichenoid reactions occur about 6 to 12 weeks after the treatment is initiated. Topical steroids are given for low-grade disease, and oral steroids, acitretin, or phototherapy can be given for higher-grade disease.[7,12]



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MUCOSAL CHANGES/DISEASE: Chemotherapy-induced mucositis occurs in almost 50% of patients receiving **mTOR inhibitors**, but it is also seen in patients receiving **EGFR inhibitors** and those who have received **radiation therapy**. It presents as a thinned erythematous mucosa with associated pain, with or without ulcerative lesions, such as aphthous ulcers. Radiation-induced mucositis is very painful for patients and will affect their ability to eat and drink, which will strongly impact their quality of life. Patients with chronic inflammation should be monitored for secondary squamous cell carcinoma and for fungal superinfection. Lifestyle modifications are also important, such as avoidance of tobacco and spicy or acidic foods. Also, patients should use a soft toothbrush and floss daily. Dexamethasone swish and spit solution and lidocaine solution for spot treatment of focal ulcerations may decrease pain. Therapy interruption is necessary if the rash is grade 3 or higher.

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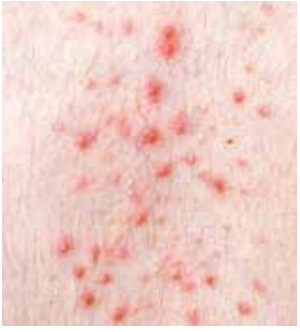
Stomatitis is the most high-grade toxicity seen with **mTOR inhibitors** and often results in dose modification or interruption. Almost one-half of patients on mTOR inhibitors experience a unique form of stomatitis that manifests as isolated discrete aphthae on nonkeratinizing epithelium and can result in pain, odynophagia, and dysphagia leading to severe dehydration and malnutrition. mTOR inhibitor-induced stomatitis can be managed with topical steroids, antiseptic washes, and anesthetics.

Hedgehog pathway inhibitors are associated with dysgeusia. Although there are no treatments, this resolves at treatment cessation.[1,12-14]

NAIL CHANGES: Nail changes such as melanonychia, onycholysis, paronychia, and onychomadesis are commonly seen with **chemotherapies (commonly taxanes) and some immunotherapies**. Nail changes are most likely to occur with taxanes. Although toxicity reversal is typically expected after treatment discontinuation, nail toxicities may be painful, especially under pressure, and may impact quality of life. Patients should be advised to keep their nails short as possible and to avoid mechanical stress. Local application of topical nail hardeners may help with nail breakage. Cooling of the hands and feet directly before, during, and after infusion diminishes risk for paronychia, which is an inflammation of proximal or lateral nail folds of all the nails on the hands and the feet. As secondary bacterial infections may occur, paronychia should be treated with daily antiseptic baths and creams. Systemic antibiotics may be warranted for extreme cases.[7, 15-17]

PRURITUS: Pruritus may occur independently or with a rash, as discussed later, and may have an impact on a patient's quality of life. Treatment can include Sarna anti-itch lotion, a dry skin care routine, pregabalin, or hydroxyzine if the pruritus is refractory. Pruritus and nonspecific maculopapular rash can evolve into bullous pemphigoid, which is a much more serious dermatologic event.

ACNEIFORM ERUPTIONS: Acneiform eruptions are associated with **EGFR inhibitors** and **MEK inhibitors.** All-grade acneiform eruptions occur in up to **90% of patients**. Onset is in the first 2 weeks to up to 2 months after treatment initiation. Patients present with folliculocentric, erythematous papules or pustules in sebaceous-rich areas (scalp, face, chest, and upper back), can have pruritus, burning, pain, and irritation. Prevention measures consist of a good dry skin care regimen and sunscreen use. Prophylaxis includes tetracycline antibiotics such as doxycycline or minocycline twice daily for 6 weeks in addition to a low-potency topical steroid applied twice daily to the face and chest. Prophylaxis should be started at the first treatment dose. Acneiform eruptions are mostly a clinical diagnosis, but if the rash if refractory or there is concern for superinfection, cultures should be obtained. This rash generally resolves 4 weeks after the causative agent is discontinued, although discontinuation is not always possible in patients with cancer who need to stay on their treatment. Topical steroids and topical antibiotics are the preferred agents for low-grade disease. For higher-grade disease, oral antibiotics such as tetracyclines, Bactrim DS, or cefadroxil should be utilized in addition to the aforementioned topical therapies. For severe or refractory disease, oral prednisone and isotretinoin can be used in addition to dose modification.[18]



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> "Even common supportive medications like allopurinol can cause rash.
>
> **— Dorothie Durosier Mertilus, PhD, DNP, APRN, AGNP-C,** Steering Committee Member

STEVENS-JOHNSON SYNDROME: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both severe, red-flag conditions that must be referred to the ED quickly. The onset is 1 week to 1 month after the initiation of the offending medication, with medications, such as **sulfonamides and anticonvulsants**, being the most common cause. In the setting of cancer care, however, immune checkpoint inhibitors are associated with a 4-fold increased risk of developing this rash. Discontinuation of the causative agent is paramount, and patients should be treated supportively in a hospital setting, such as a burn unit or an intensive care unit. Patients may be hospitalized for weeks to months, and they will require ongoing evaluations for electrolyte abnormalities, infection, and adequate pain control.

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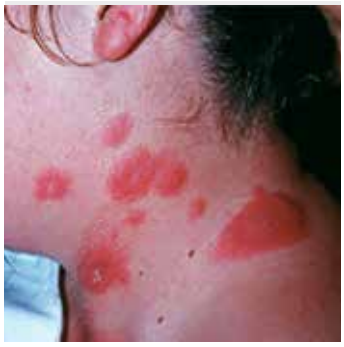
The main difference between SJS and TEN is BSA involvement. SJS involves less than 10% BSA, whereas TEN involves more than 30% BSA. A good way to clinically discern how much BSA is involved is to use your hand, which is approximately 1% BSA, to map out which body areas are involved and determine a total BSA.[19]

SWEET SYNDROME: As many as 15% to 20% of these cases are actually associated with malignancy, and presentation of Sweet syndrome can be a harbinger of malignancy, especially a hematologic malignancy. Incidence of Sweet syndrome can precede the diagnosis of cancer by several months. Sweet syndrome

presents as painful erythematous plaques, or papules, and nodules in an asymmetric distribution, plus fever or malaise. Headaches and ocular inflammation are also seen in these patients. Leukocytosis with neutrophilia is the most common lab abnormality associated with Sweet syndrome. Other labs (CBC, CMP, etc.) should be ordered to elucidate an underlying cause of the condition and narrow down the differential diagnosis. Patients should be referred to dermatology to obtain a skin punch biopsy and a tissue culture. For localized or mild disease, topical steroids, such as clobetasol, or intralesional corticosteroids, such as triamcinolone, should be used. For widespread or severe disease, a 4- to 6-week prednisone taper is the first-line treatment. Other treatment options include colchicine, dapsone, and potassium iodide, though these have a longer onset of action when compared to systemic steroids.[20]



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VITILIGO: Vitiligo is an immune disorder that causes loss of pigment in patches on any part of the body, including the hair and inside of the mouth, in a bilateral and symmetric pattern or, rarely, a segmented pattern. Vitiligo may be a pre-existing condition or may be a nonreversible adverse event associated with treatment, appearing months after initiation. Approximately 10% of patients receiving **anti-CTLA-4 agents** and 25% of patients receiving **anti-PD-1 therapies** develop vitiligo. In patients with advanced melanoma, vitiligo has been reported to be a positive prognositc factor for both treatment response and overall survival.[12,21] Topical JAK inhibitors (ruxolitinib), topical corticosteroids, topical calcineurin inhibitors, or phototherapy may be used to try to restore color to white patches.

Depigmentation may be recommended for patients who have vitiligo patches on more than half of their body. Although vitiligo is not painful, it may cause acute quality-of-life issues and social distress for patients.

XEROSIS/FISSURES: Xerosis occurs in up to 50% of patients receiving **EGFR inhibitors**, depending on dose. **Multikinase and BRAF inhibitors** are also associated with xerosis. Older age and history of eczema increase the risk for more severe development of skin dryness and fragility.

A gentle skin care routine and topical emollients should be recommended to prevent or manage mild disease. For grades 1 and 2, the causative agent may be continued at the current dose and ammonium lactate should be added. Ammonium lactate cream is a keratolytic that helps break down scale. For grades 3 or higher, dose modification is necessary, and cultures should be obtained if there is concern for superinfection. A topical medium- to high-potency steroid can be added. Ointments are preferred over other formulations, as they are easier to apply and more moisturizing.[13]

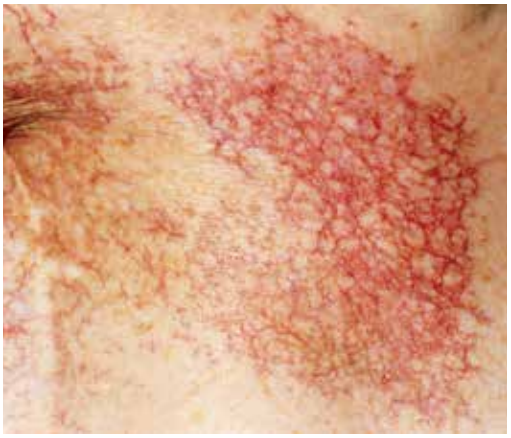
QUICK TIPS

Tips for Providers

- Know your vehicles for topical medications (see table on page 5) and understand your patient's preferences. Make sure the patient is going to use the medication prescribed to them. Even if they're given the best regimen in the world, if they're not going to use the treatment, it's not going to work.
- Incorrect application is a major impediment to compliance and adherence, so be sure to provide body maps for all dermatologic medications prescribed to these patients. Body maps help patients understand where (and when) they should be applying medications.
- Make sure that the patient and their family members are keeping detailed treatment diaries, so drug causality can be better assessed for these patients.
- Continuous topical therapies can become very expensive for patients, so be sure to enlist the support of pharmacists, who can help educate patients about substitutions.

Radiation Therapy–Related Conditions

RADIATION DERMATITIS, defined as skin injury due to radiation therapy (RT), can happen instantly or years after treatment. Risk factors include older age, darker skin, poor nutrition, smoking, compromised skin integrity, multiple exposures to radiation and higher cumulative radiation dose, higher body mass index, and concurrent systemic treatment with chemotherapy or targeted therapy, as well as pre-existing connective tissue disease and dermatologic conditions related to inflammation such as psoriasis, eczema, and acne. Radiation dermatitis is experienced by up to 90% of patients with breast cancer who receive RT and may appear as acute, chronic, or much more delayed, known as "radiation recall dermatitis." Acute radiation dermatitis can present within the first 90 days following RT, and chronic radiation dermatitis presents months to years following RT.



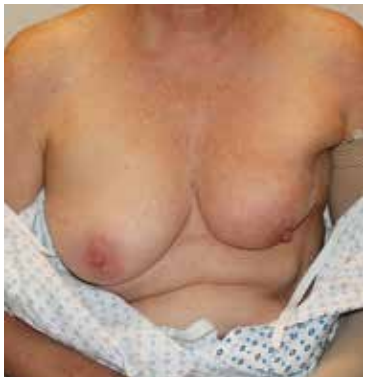
ACUTE RADIATION DERMATITIS: Typically, dry, erythematous patches localized to the RT field will present in Week 2 of RT, which may evolve into dry desquamation over the next few weeks of treatment. Other more symptomatic adverse effects include edema, pruritus, tenderness, moist desquamation, and ulceration. Rarely, radiation necrosis may occur as a late sequela. Most acute radiation dermatitis resolves with completion of therapy. Management includes good hygiene with perfume-free and dye-free skin-care products (use of antiperspirants and deodorants seem unrelated to risk or severity), and bland emollients or topical corticosteroids. Treatment consists of mid-potency topical steroids, such as triamcinolone cream twice daily. Nonadhesive dressings may be offered for open areas of skin, but bandages should not be used due to the risk of skin breakdown and allergic contact dermatitis. If there is concern for infection, mupirocin 2% ointment twice daily may be prescribed to use in conjunction with the topical steroid. For those patients with higher risk of radiation dermatitis, triamcinolone cream may be initiated before they start radiation therapy. This should be discussed with the radiation oncologist.[22,23]

CHRONIC RADIATION DERMATITIS: Chronic radiation dermatitis occurs months to years after radiation therapy. Patients will complain of hyperpigmentation or hypopigmentation. Atrophy is also a common complaint associated with chronic radiation dermatitis. In more severe cases, there may be chronic non-healing wounds, because the skin is so compromised, and fibrosis, which is a tightening of the skin. Referral for hyperbaric oxygen therapy can be a good option for nonhealing wounds. Treatment is aimed at symptomatic relief, and physical therapy may help with fibrosis.[22,23]

RADIATION RECALL DERMATITIS: Associated with a diverse range of antibiotics, chemotherapeutic and antineoplastic agents, and other medications, radiation recall is an acute inflammatory reaction localized to previously irradiated areas triggered by systemic therapy after RT. Radiation recall dermatitis can occur weeks to even years after radiation is finished. Skin reactions are rarely severe and are the most common manifestation of radiation recall. Presentation can range from mild rash, dry desquamation and/or pruritus to maculopapular and papular eruptions, ulceration, and skin necrosis—but only in the irradiated field.[22,24,25]

RADIATION-INDUCED MORPHEA: Radiation-induced morphea (RIM) can have a significant impact on a

patient's quality of life. Mostly occurring in patients with breast cancer, RIM is rare and often underrecognized. Autoimmune disorders, obesity, history of smoking, and breast implantation have been shown to be associated with more severe presentation of RIM. RIM is characterized by two distinct and sequential phases. In the **inflammatory phase**, RIM tends to present as a single round plaque that may extend beyond the radiation field.



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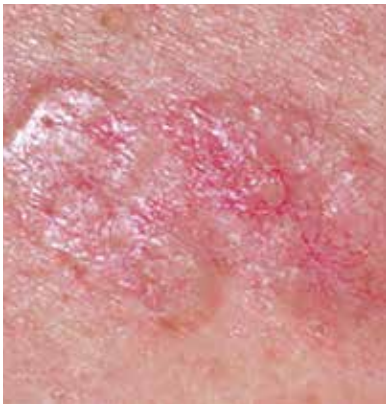
This phase may mimic cellulitis or radiation dermatitis, although radiation dermatitis is localized to the field area. The **burnout phase** is evidenced by decreased inflammation, development of fibrosis, and hyperpigmentation. Management is more effective in the inflammatory phase, as the burnout phase tends to result in irreversible fibrosis, and biopsy is essential to rule out other potential issues including metastatic breast cancer. Treatment is aimed at reducing inflammation, and topical ointments such as tacrolimus have been shown to be beneficial. Steroids, methotrexate, and cyclosporine can be prescribed for systemic inflammatory suppression.[22,24]

SECONDARY SKIN NEOPLASMS: Following RT, secondary skin neoplasms can occur within the radiated field. Some of these include basal cell carcinomas, squamous cell carcinomas and angiosarcomas. The median onset for these types of lesions are 6 years post-radiation. Atypical vascular lesions, although benign, are hard to distinguish from malignant neoplams so it is important for patients to have yearly skin checks with a licensed dermatologist.[24-26]



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• **Postradiation atypical vascular lesions** (AVLs) are also known as benign lymphangiomatous papules, lymphangiomas, and acquired lymphangiectasias. Presenting as well-circumscribed, papules or vesicles that are red to blue in color and usually < 5 mm in diameter, AVLs are typically seen 3-4 years after RT. Biopsy is needed to rule out other malignancies, as there is clinical and histologic overlap with malignant angiosarcomas. Treatment includes surgical removal, although it is not recommended since these lesions are indeed benign.

• **Secondary postirradiation angiosarcomas** are rare but can occur up to 6 years after RT. These present as red-purple plaques or nodules localized to the radiation field. These are larger than AVLs. In addition, increased Ki67 and MYC gene expression are markers for angiosarcomas and can help distinguish from AVLs, but diagnosis is reliant on a biopsy. Surgery can remove the main lesion, but there is a high rate of local recurrence, making them potentially difficult to diagnose.

• **Nonmelanoma skin cancers**—basal cell carcinoma and squamous cell carcinoma—tend to arise decades after the conclusion of RT for breast cancer, with higher cumulative doses of radiation, exposure of irradiated skin to ultraviolet light, and younger age at RT potentially associated with decreased time to incidence. Surgical excision is the recommended treatment. As RT increases a patient's risk for nonmelanoma skin cancers, dermatologic follow-up on

QUICK TIPS

Tips for Patients

- Make sure to reinforce a basic dry skin care regimen with all patients and caregivers. This includes good nail care and lifestyle modifications, such as wearing socks and gloves throughout the day, using nonperfumed products, and washing with cool or warm water versus hot.
- Patients should be sure to display body maps at home, so they can be sure that they're applying medications correctly.
- Patients and caregivers should be encouraged to have an open dialogue with their providers. They should understand how to contact the care team about the development of new or worsening skin issues, whether by phone or through the patient portal.
- It is critical for patients to keep a detailed medication and treatment diary so care providers can better assess which drugs are causing rashes and other dermatologic issues. Although patients and providers might assume a rash is from a cancer therapy, patients are often taking multiple medications that could also cause dermatologic side effects. Medication diaries are essential to determine the causative agent of the rash.

Stem Cell Transplant–Related Conditions

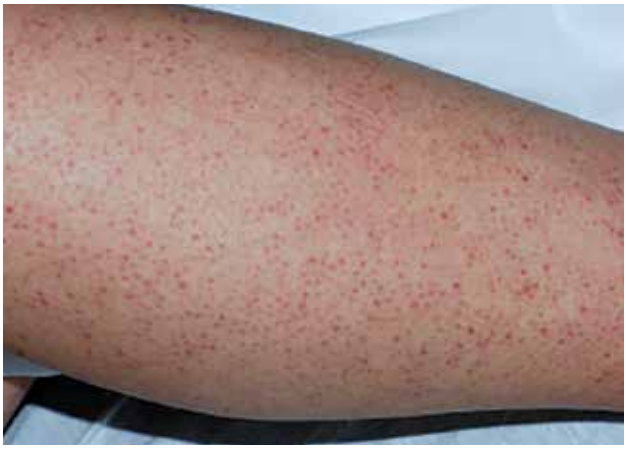
STEM CELL TRANSPLANT involves the use of systemic agents, such as chemotherapeutics and immunosuppressants for conditioning, and there is moderate to high risk for infections and graft-versus-host disease, depending on individual patient characteristics. All of these factors contribute to dermatologic manifestations of associated or consequential conditions, as well as to the development of independent dermatologic toxicities.

ENGRAFTMENT SYNDROME: Typically presenting within 7 to 14 days after hematopoietic stem cell transplant (HSCT), engraftment syndrome generally involves an erythematous rash on 25% of the body that presents concurrently with unexplained fever. This rash may include maculopapular erythema on the trunk and extremities, generalized erythroderma, and facial rash. Systemic symptoms, such as pulmonary edema, diarrhea, liver and renal dysfunction, and altered mental status, also may be present. Skin biopsy should be performed only if the rash is not responsive to corticosteroids after 48 hours. As there may be pulmonary involvement with engraftment syndrome, APs should monitor for hypoxemia, as well as liver and renal dysfunction. Engraftment syndrome may be difficult to distinguish from acute graft-versus-host disease, and incidence of acute graft-versus-host disease may be more common in patients with engraftment syndrome. Treatment requires an inpatient multidisciplinary approach. These patients should never be treated outpatient with just a dermatologist because the Bone Marrow Transplant (BMT) team must be involved.[27-29]

ERUPTION OF LYMPHOCYTE RECOVERY: This is a common rash occurring within the first month after conditioning therapy. On examination, this is seen as confluent red macules and papules that are itchy, and it is associated with fever. Rash typically self-resolves with desquamation over days to weeks, with no treatment required. Onset is 1 to 3 weeks post-chemotherapeutic regimen. If rash and fever do not self-resolve, APs should investigate other potential causes. Treatment is aimed at symptomatic relief. If a patient reports pruritus, a high-potency topical steroid or an over-the-counter cool antipruritic lotion can be given. If the patient is not symptomatic, topical steroids should not be prescribed.[27,28]

GRAFT-VERSUS-HOST DISEASE: A large percentage of patients who undergo allogeneic HCT will develop acute GVHD, which occurs within the first 100 days post-transplant and mainly involves the skin, gastrointestinal system, and liver. Skin involvement typically manifests as a maculopapular rash, which can be accompanied by persistent abdominal pain, diarrhea, and liver dysfunction. More severe cases may present with generalized erythroderma, bullae, and skin sloughing. Staging is based on the amount of rash as measured by BSA. Topical steroids and/or a topical calcineurin inhibitor are typically used for early-stage disease; management for more severe disease may include topical and systemic corticosteroids, aggressive wound care, and/or ruxolitinib.[30]

Acute GVHD is a risk factor for chronic GVHD, which occurs after the first 100 days post-transplant and involves 8 organ systems: skin/nails/scalp, eyes, mouth, gastrointestinal tract, genitalia, lungs, liver, and muscles/fascia/joints. NCCN Guidelines and consensus statement can help APs determine optimal management for chronic GVHD.[30]



Courtesy of *The ASCO Post*.

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