Co-Ocurrence of Lymphomatoid Papulosis and Mycosis Fungoides in a Young Female: A Case Report

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Abstract

There have been reports of lymphomatoid papulosis (LyP) and mycosis fungoides (MF) presenting separately, simultaneously, and consecutively. LyP is a CD30+ lymphoproliferative disorder, and MF is the most common cutaneous T-cell lymphoma (CTCL). LyP most often presents with self-regressing, erythematous-to-brown papules or small nodules. Mycosis fungoides has a variety of clinical manifestations, but in early stages it commonly presents as an erythematous patch or plaque. Recognizing LyP is important due to its association with development of secondary malignancies, most commonly MF, Hodgkin’s disease, and anaplastic large-cell lymphoma (ALCL). We report a case of a 35-year-old woman with recurrent LyP lesions since childhood who went on to develop concurrent LyP and MF. We discuss the need to evaluate LyP patients for secondary lymphomas and provide a concise review of the literature focusing on clinical presentation, diagnosis, disease associations, and management.

Introduction

Lymphomatoid papulosis (LyP) is one of two CD30+ cutaneous lymphoproliferative disorders (the other being primary cutaneous anaplastic large-cell lymphoma [PC-ALCL]). LyP is slightly more common in males than females, with a male-to-female ratio of about 1.4, and occurs most frequently in the fifth decade of life. LyP lesions can, however, occur at any age. LyP commonly presents in a singular or multiple distribution with erythematous-to-brown papules and/or nodules on the trunk or extremities. Half of LyP patients develop asymptomatic lesions that self-regress in weeks to months; the rest develop pruritus, ulceration, and necrosis, with scarring and/or postinflammatory hyperpigmentation as lesions involute. The clinical hallmark of LyP is the waxing and waning of lesions, which helps differentiate it from ALCL and CD30+ MF tumors.

While the clinical picture for LyP is benign, careful microscopic examination often reveals a malignant-appearing histology. There are five recognized histopathological subtypes of LyP, of which type A is the most frequently encountered. Type A is characterized by a wedge-shaped lymphocytic infiltrate mixed with neutrophils, eosinophils, and histiocytes. Type B looks similar to MF, with small to medium lymphocytes with cerebriform nuclei and epidermotropism. Type C resembles ALCL, with sheets of large CD30+ lymphocytes. Type D has a predominantly CD8+ cytotoxic T-cell infiltrate, and type E is characterized by angiodestructive lymphocytic infiltrates that are both CD30+ and CD8+. Three other variants have been proposed, including type F, which involves a follicular LyP, and variants with γ/δ T-cell LyP phenotype and 6p25.3 rearrangement.

MF is the most common CTCL and frequently presents as a patch or plaque, usually without lymph-node or visceral involvement. Advanced-stage MF encompasses extracutaneous disease or advanced skin lesions, such as tumors. The classic MF presentation is erythematous, scaly patches that more frequently occur in sun-protected areas and may advance into raised plaques, nodules or tumors. There are also reports of MF presenting with erythroderma or pigment alteration. On histology, MF presents with atypical T-cells with cerebriform nuclei, epidermotropism, and a band-like dermal infiltrate of lymphocytes. Variable expression of CD30 can be seen at all stages of MF. It is important to recognize early MF, as one in 10 early-stage MF patients will progress to advanced disease stages.

Spontaneous self-regression of lesions is required for establishing a clinical diagnosis of LyP. Identifying LyP is of great importance, because 10% to 30% of patients will develop a secondary lymphoma. Mycosis fungoides (MF), along with cutaneous ALCL, are the two most common
secondary lymphomas associated with LyP. According to Wieser and Tetzlaff et al., MF should be considered in an LyP patient with erythematous patches or large, non-regressing lesions. The number and severity of LyP lesions do not predict the development of secondary malignancies, an important consideration in diagnosing and following LyP patients.

**Case Report**
A 35-year-old female with a past medical history of recurrent LyP (diagnosed at age 10) and MF (diagnosed at age 28) presented with a painful red nodule on her right posterior neck and right buttock (Figure 1) and an erythematous, scaly patch on the left flank (Figure 2). In the past, the patient’s LyP lesions were treated with topical 0.05% clobetasol cream and triamcinolone acetonide injections, both with minimal improvement, and the MF lesions were treated with intermittent clobetasol. A workup in 2009 for systemic disease was negative and included bloodwork, chest X-ray, and CT scans of the chest and abdomen. A punch biopsy from the right posterior neck and left flank were collected. Both were fixed in 10% neutral buffered formalin and submitted for microscopic examination. The biopsy report of the neck lesion noted a focal necrotic epidermis above a wedge-shaped, perivascular and interstitial infiltrate of lymphocytes mixed with eosinophils and neutrophils (Figures 3, 4). Melanocytes demonstrated large, atypical nuclei. Additionally, occasional atypical mitotic figures were identified. Lymphocyte immunoreactivity demonstrated light positivity for CD8 and positivity for CD3, CD4, and CD30 (Figure 5). The biopsy report of the left flank revealed a psoriasiform acanthotic epidermis above a band-like infiltrate of lymphocytes (Figures 6, 7) with convoluted, or cerebriform nuclei consistent with MF. A band-like infiltrate of lymphocytes with positive immunoreactivity for CD30 and CD4 as well as negative immunoreactivity for CD8 and CD30. Lymphocytes were also present within the follicular adnexal epithelium.

Due to the recurring and self-limiting nature of LyP, we opted for symptomatic treatment only. The approach for MF will be treatment with mechlorethamine or possibly narrow-band UV-B, along with extensive workup for systemic disease, including complete blood count with differential, blood chemistry, lactate dehydrogenase, chest X-ray, and repeat CT scan of the abdomen and chest.

**Discussion**
The simultaneous occurrence of LyP and MF has been reported in multiple studies. In this instance, the co-occurrence of lesions at a young age, 35, made for a rare case. The patient had histopathological results consistent with type A LyP on the posterior neck and patch-stage MF with folliculotropism on the left flank. It is important to establish a diagnosis of LyP due to its association with cutaneous and extracutaneous malignancies, most notably MF, Hodgkin’s disease, and ALCL. When counseling patients, it is important to remember that the size and severity of LyP lesions do not correlate with development of secondary malignancies.

The patient in this case was female and presented with the most common type of LyP, type A. However, LyP is slightly more common in men (male-to-female ratio about 1:4), and a study by Wieser et al. concluded that male sex and histologic subtypes B and C were associated with a higher rate of secondary malignancy (type D was less frequently associated). This is reasonable, as MF histologically resembles type B LyP. Studies have conflicted, however, on that point; de la Garza Bravo et al. suggested type A LyP is most commonly associated with MF.

The etiologies of LyP and MF are unclear, but epidemiologic findings and biologic features of each disease point to the possibility of an infectious cause. Several studies have hypothesized a viral cause of LyP but failed to detect Epstein-Barr virus, human herpesviruses 6, 7, or 8, or human T-cell leukemia/lymphoma virus in LyP lesions. In regard to MF patients, some studies have found human T-lymphotropic virus type I in blood work and cutaneous lesions. An equal number, however, provide evidence against a role for human T-lymphotropic virus type I in blood work and cutaneous lesions.

The approach for MF will be treatment with intermittent clobetasol. A study by Gallardo et al. reported similar findings in two of three patients with LyP and MF. Chott et al. reported similar findings in two out of three patients with LyP and MF. Wood et al. detected identical TCR clones in two patients with LyP and MF. Zackheim et al. found identical TCR gene rearrangements in all seven of the patients with LyP and MF who had tissue available for clonality analysis.

The diagnosis of LyP is dependent on histological examination demonstrating a recognized subtype and clinical observation of self-regressing or disseminated papulonodular skin lesions. All patients with LyP are recommended to have a punch biopsy from left flank with intraepidermal lymphocytes within the spinous zone. Some lymphocytes demonstrate a convoluted, or cerebriform, nuclei consistent with MF.
laboratory studies including a complete blood count with differential, blood chemistry, and lactate dehydrogenase. Patients with no signs of extracutaneous disease require no radiographic studies. When signs of extracutaneous disease are present, in either laboratory tests or diagnostic evaluation, a chest X-ray, computed tomography, lymph-node sonography, or positron-emission tomography should be performed.\textsuperscript{11,12}

The diagnosis of MF cannot be confirmed with a single test. The International Society for Cutaneous Lymphomas has developed a point-based algorithm that incorporates clinical, histopathologic, molecular, and immunopathologic findings.\textsuperscript{18} For the clinical and histopathologic categories, two points are given for basic criteria plus two additional criteria, and one point is given for basic criteria plus one additional criterion. The basic clinical criterion is persistent and/or progressive patches/plaques, and the additional criteria include non-sun exposed location, size/shape variation, and poikiloderma. The basic histopathologic criterion is superficial lymphoid infiltrate, and the additional criteria include epidermotropism without spongiosis and lymphoid atypia. For the molecular category, one point is given for the presence of a clonal TCR gene rearrangement. In the immunopathologic category, one point is given if any of the following is present: less than 50 percent of the T cells express CD2, CD3, or CD5; less than 10 percent of the T cells express CD7; or there is discordance of the epidermal and dermal cells regarding expression of CD2, CD3, CD5, or CD7.\textsuperscript{18}

The treatment for LyP and MF involves separately treating the lesions. Due to the chronic, recurring, and self-limiting nature of LyP, most patients receive treatment only if they’re symptomatic. Treatment involves a skin-directed or systemic approach. Topical corticosteroids and phototherapy (both psoralen and UVA and UVB) are skin-directed therapies used to provide symptomatic relief. Both treatment modalities may reduce the number of lesions but do not prevent recurrences.\textsuperscript{20} When treating children, the risk of developing skin cancers after phototherapy treatment should be assessed and weighed against the benefit of treatment. Methotrexate and brentuximab vedotin (a monoclonal antibody [cAC10] conjugated to monomethyl auristatin E, which targets CD30 receptors) are systemic forms of treatment for LyP. Both have shown good responses in terms of lesion regression. Weaning off methotrexate has been troublesome, however, so it is only recommended in highly symptomatic patients.\textsuperscript{20} To date, no LyP therapies significantly alter the disease or prevent development of an associated lymphoma. Further research involving randomized controlled trials are needed to determine the best treatments.\textsuperscript{14,20}

The treatment of MF is determined by the stage of the disease. Early-stage disease uses skin-targeted therapy such as topical corticosteroid, topical nitrogen mustard (mehlolethenamine hydrochloride), or ultraviolet-B therapy.\textsuperscript{14,18} Advanced stages can be treated with localized radiation to the tumor or systemic therapies such as total skin electron-beam therapy, a synthetic retinoid (bexarotene), histone deacetylase inhibitors (romidepsin or vorinostat), interferon alpha, a monoclonal antibody against the CD52 surface antigen on immune cells (alemtuzumab), combination chemotherapy, or allogenic stem-cell transplantation. Topical corticosteroids can be used as an adjunct to systemic treatments. Chemotherapy and allogenic stem-cell transplantation are reserved for rapidly progressive advanced MF, and the allogenic stem cells have curative potential.\textsuperscript{2,18} It is interesting to note that studies suggest patients with LyP and MF have a better prognosis than patients with MF alone.\textsuperscript{4,19}

**Conclusion**

Our patient had an initial diagnosis of LyP at a young age and subsequently developed LyP and MF lesions later in life. It is important to accurately diagnosis LyP and counsel patients on the possibility of developing a secondary malignancy.


