Series Editor: Camila K. Janniger, MD

Hodgkin Lymphoma Presenting as Generalized Pruritus in an Adolescent

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Pruritus is a common manifestation of Hodgkin lymphoma (HL), and given its high frequency, inclusion of itching as a B symptom of HL has been proposed. We present a 16-year-old adolescent boy with treatment-refractory eczema of 2 years' duration. Physical examination revealed a thin adolescent boy with widespread excoriations, but no eczematous or primary cutaneous lesions were identifiable. Lymph node examination revealed palpably enlarged nodes in the cervical and supraclavicular regions. Laboratory studies revealed leukocytosis and an elevated lactate dehydrogenase level. Diffuse lymphadenopathy was detected on a chest radiograph, and excisional lymph node biopsy revealed HL (nodular sclerosing subtype). The patient was classified as HL stage IIIB (Ann Arbor staging classification) after further evaluation. Chemotherapy was initiated followed by radiation therapy. The patient's pruritus markedly improved within 2 cycles of chemotherapy; however, his HL relapsed and additional salvage combination chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant were required. This case underscores the need for a complete history as well as a careful skin and systemic evaluation in patients presenting with long-term pruritus, including children and adolescents.

Cutis. 2011;87:169-172.

Pruritus in children and adolescents is a common presenting concern in dermatology clinics. Pruritus may be due to primary skin diseases such as atopic dermatitis, allergic contact dermatitis, infestations, infections, or other common cutaneous conditions; however, pruritus may be secondary to an underlying systemic process. In the latter scenario, primary skin lesions typically are not evident, making the systemic condition difficult to discern. Numerous systemic conditions have been associated with generalized pruritus. The more commonly associated conditions include chronic renal or hepatic disease, iron deficiency anemia, thyroid disease, and malignancies such as Hodgkin lymphoma (HL).[1] Because the overall incidence and prevalence of chronic systemic diseases is lower in children compared to adults, systemic causes of pruritus in children initially may be overlooked.

We report an adolescent boy with primary pruritus that went unrecognized for approximately 2 years. He was referred to our dermatology clinic for treatment-refractory eczema. Evaluation revealed generalized pruritus with secondary skin manifestations suggestive of neurodermatitis that prompted further evaluation, leading to a diagnosis of HL.

Case Report

Upon referral by his pediatrician, a 16-year-old adolescent boy presented to the dermatology department for further management of severe recalcitrant eczema. The patient reported itching of 2 years' duration. He had been prescribed multiple topical corticosteroids, oral antibiotics, and oral antihistamines over the last year with little improvement in his pruritus or skin lesions. At the time of presentation to our clinic he noted fatigue and a 7.5-kg weight loss. His medical history revealed bilateral congenital cataracts with no other clinical abnormalities at birth. The cataracts were surgically repaired at 4 years of age. At 15 years

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The authors report no conflict of interest.
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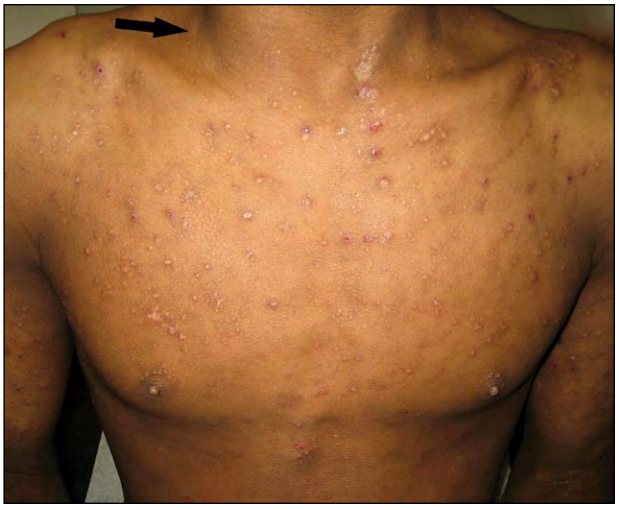

Figure 1. Multiple excoriations over the patient's trunk and extremities. No primary cutaneous lesions were present. Cervical fullness due to lymphadenopathy was observed in the right cervical region (arrow).

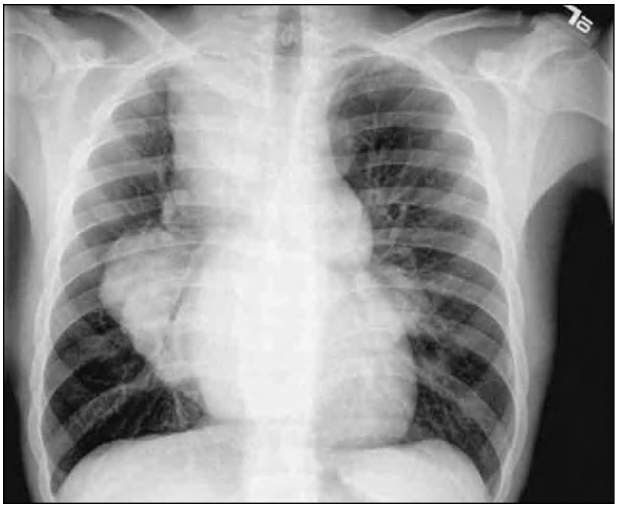

Figure 2. A chest radiograph revealed hilar and mediastinal masses compatible with lymph node enlargement.

of age, the patient sustained a spontaneous retinal detachment. He was otherwise in good health, with the exception of allergic rhinitis, until the development of lymphoma. The patient did not have any evidence of a known syndrome that would account for his ocular findings and lymphoma. He had no notable family history.

Physical examination revealed a thin adolescent boy with numerous excoriations over his trunk and extremities (Figure 1). No eczematous or primary cutaneous lesions were identifiable. Pathologically enlarged lymph nodes were detected in the right cervical and left supraclavicular regions.

Laboratory data revealed an elevated total white blood cell count (18,600/μL; reference range, 4500−12,500/μL) with elevated neutrophils (15,884/μL; reference range, 1800−7700/μL), monocytes (1302/μL; reference range, <801/μL), and eosinophils (558/μL; reference range, <451/μL), as well as decreased lymphocytes (775/μL; reference range, 1000−5000/μL). The lactate dehydrogenase level was elevated (477 U/L; reference range, 91−180 U/L). A chest radiograph revealed multiple mediastinal masses and diffuse hilar and paratracheal lymphadenopathy (Figure 2).

The patient was referred to the oncology department for further diagnostic workup and treatment. An excisional lymph node biopsy of the left supraclavicular lymph node revealed a nodular collection of lymphoid cells with a thickened fibrotic capsule and large, atypical, bilobed and multinucleated cells staining positive for CD30 (Figure 3). Flow cytometric immunophenotyping of the lymph node tissue failed

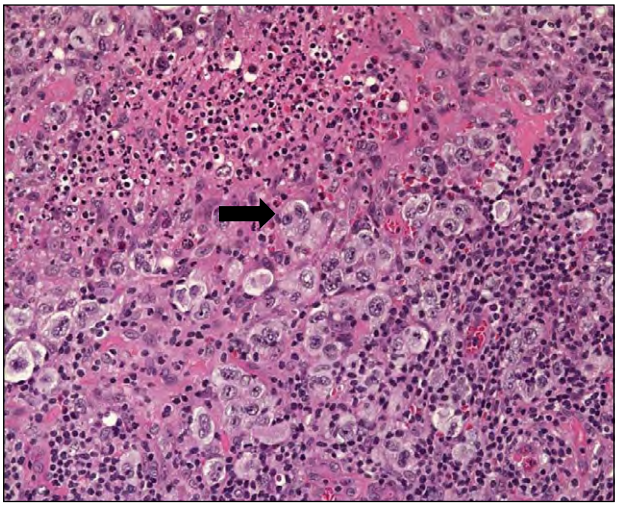

Figure 3. Biopsy of lymph node tissue demonstrated large, atypical, bilobed cells (Reed-Sternberg cells [arrow]) and multinucleated cells (H&E, original magnification ×20).

to identify any clonal B-cell populations. The histologic and flow cytometric findings were consistent with HL (nodular sclerosing subtype). Bone marrow aspiration and biopsies showed no morphologic evidence of HL. Computed tomography of the chest, abdomen, and pelvis demonstrated extensive mediastinal, hilar, bronchopulmonary, retroperitoneal, and inguinal adenopathy.

The patient was classified as HL stage IIIB (Ann Arbor staging classification) with lymph node involvement on both sides of the diaphragm,

presence of 1 or more B symptoms (ie, fever, night sweats, unintended weight loss), no lung or bone involvement, and no bone marrow involvement.[2] Chemotherapy was initiated with ABVE-PC (adriamycin [doxorubicin], bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide) protocol. Because there was only a partial response to chemotherapy, it was followed by radiation therapy. The patient's pruritus markedly improved within 2 cycles of chemotherapy; however, his HL relapsed 8 weeks after the end of radiation therapy. He was then treated with salvage combination chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant. He was asymptomatic (no skin and systemic symptoms present) at the time of HL relapse. At the time of this report (3 years after diagnosis), the patient is alive and well and in complete remission.

Comment

Hodgkin lymphoma accounts for approximately 15% of cancers in individuals aged 15 to 19 years. The disease commonly presents with firm, painless, enlarged cervical lymph nodes. Other manifestations may be seen as the disease progresses, including the B symptoms of fever, drenching night sweats, and weight loss (>10% total body weight over 3 months). The characteristic histologic feature of HL is the presence of Reed-Sternberg cells, large clonal cells with multilobed nuclei that arise from germinal center B cells.[3]

Both specific and nonspecific cutaneous manifestations may occur. Specific cutaneous lesions occur in a minority of patients (<5%), generally in late-stage disease, and are associated with a poor prognosis.[4] Proposed mechanisms of primary cutaneous involvement include retrograde lymphatic spread from involved lymph nodes (most common),[5] direct cutaneous extension from an underlying involved lymph node, and hematogenous spread.[4,6] Pruritus has long been associated with HL,[7] and severe pruritus is the most common nonspecific cutaneous manifestation, occurring in up to 30% of patients.[8] Pruritus of HL may manifest as prurigo nodularis[9]; nonspecific eczematous dermatitis[10]; generalized pruritus[11]; or generalized pruritus with widespread excoriations, as seen in our patient. Paraneoplastic pruritus has occurred with such high frequency that some researchers have even proposed that itch be considered a B symptom of HL.[8] Other researchers have suggested that severe itching in HL patients may be of prognostic significance, as these patients often experience more aggressive disease.[12] In fact, our patient experienced pruritus for 2 years before diagnosis and his HL was refractory to standard chemotherapy.

Despite its prevalence, the mechanism of pruritus in systemic disease, including HL, is still poorly understood. Unmyelinated C fiber terminal branches located in the skin are stimulated by various chemical mediators (pruritogens). Upon stimulation, impulses are transmitted to the ipsilateral dorsal root ganglia and then to the cerebral cortex via the spinothalamic tract.[13] In lymphoproliferative disorders, histamine has been proposed as a mediator of pruritus,[14] but other pruritogens, including serotonin, endogenous opioids, prostaglandins, neuropeptides, proteases, and cytokines, also may play a role. Cimetidine, a potent histamine H_2 receptor antagonist, has been reported as a successful treatment of pruritus associated with HL.[15] Eosinophilia associated with the pleomorphic infiltrate of HL and high serum levels of IgE may be contributing factors to histamine release and the pathogenesis of pruritus in HL.[16] Another proposed mechanism of itch in HL is the release of pruritogens such as leukocyte peptidases and bradykinins due to an autoimmune response to lymphoid cells.[17] Although systemically administered antihistamines may be partly effective in controlling pruritus, the mainstay of therapy for pruritus associated with HL is treatment of the lymphoma itself.

Our patient initially presented to his pediatrician and was diagnosed with severe eczema. He experienced little symptomatic relief with topical corticosteroids and oral antihistamines. Based on the recalcitrant nature of the patient's itching and examination findings suggestive of neurodermatitis with diffuse excoriations and no primary lesions, a search for an underlying cause of his pruritus was initiated. Further physical examination revealing lymphadenopathy allowed for identification of the cause of his primary pruritus.

This case underscores the need for a complete history and physical examination in patients presenting with long-term pruritus, including children and adolescents. If no primary skin lesions are identifiable, history should include a review of systems looking for evidence of B symptoms (ie, fever, night sweats, weight loss), and physical examination should include a search for lymphadenopathy. To determine an underlying cause of itch, appropriate laboratory studies should be pursued, especially if the patient is refractory to standard therapy. Suggested evaluations include complete blood cell count with peripheral smear, chemistry panel, and chest radiograph. Our patient is a powerful reminder of the importance of looking beyond the skin.

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