

Clinical Pearls

Peripheral T-cell lymphoma: a challenging mimicker of angioedema and urticaria



Although first described more than 130 years ago, the pathophysiology, origin, and management of several types of angioedema are not completely understood. Mimickers of angioedema further complicate the picture. Acquired angioedema has been associated with lymphoproliferative diseases, B-cell lymphomas, and monoclonal gammopathy of undetermined significance secondary to C1 inhibitor deficiencies,^{1–3} but there has been only 1 reported case of peripheral T-cell lymphoma (PTCL) presenting with angioedema, which was published in 1988.⁴

This report describes the case of a 56-year-old Hispanic man with hypertension who was admitted to the hospital with swelling of the face, rash, and shortness of breath of 1 month's duration. The skin complaint manifested as intermittent pruritus that initially appeared on the chest and gradually spread to the back and the face. This presentation was previously interpreted as chronic urticaria because the initial lesions manifested as fleeting cutaneous infiltrates, resolving within 24 to 48 hours of onset. At the time of presentation to the hospital, the lesions had become constant, progressing to fixed appearances within the skin that did not resolve at any one site of involvement. Skin lesions also became associated with swelling of the lips, tongue, and throat.

The patient's medical history disclosed that the onset of skin complaints and intermittent swelling of the lips, tongue, and throat occurred approximately 2 years previously. Previous investigations showed normal C3, C4, and CH50 levels; negative hepatitis B and C and human immunodeficiency virus serologies; myeloperoxidase antibodies; proteinase 3 antibodies; C- or P-antineutrophil cytoplasmic antibodies; HLA B27 antigen; rheumatoid factor; anticitrullinated protein antibody; and Sjögren syndrome type A and B antigen antibodies.

Previously, he had been treated with intravenous corticosteroids, antihistamine, and epinephrine, with minimal response. The patient did not report any fevers, night sweats, weight loss, flushing, wheezing, or gastrointestinal manifestations. There was no family history of angioedema.

Clinical examination showed fixed erythematous maculopapular lesions distributed over the anterior and posterior chest and face (Fig 1). Periorbital and upper and lower lip edema without tongue involvement was noted (Fig 2). Bedside laryngoscopy showed nonobstructive posterior pharyngeal edema. There was no palpable lymphadenopathy.

The full blood cell count showed a mildly elevated total white blood cell count ($11.8 \times 10^3/\mu\text{L}$), normal antinuclear antibody, and normal complement levels.

Acquired and hereditary causes of angioedema and urticaria were investigated and excluded. Normal C1q level (17.7 $\mu\text{g/mL}$, reference range 12–22 mg/dL) and normal C1 esterase inhibitor level (33 mg/dL, reference range 21–39 mg/dL) and function (104 mg/dL, normal >67 mg/dL) were found. Atopy was investigated and documented. In vitro specific IgE testing showed no evidence of atopy.

This patient lacked the major diagnostic criterion of hereditary angioedema: a deficiency (type I) or dysfunction (type II) of C1 inhibitor.⁵ The presence of erythematous plaques mimicking urticaria and lack of family history further excluded this diagnosis. Acquired C1 inhibitor deficiency also was an unlikely diagnosis. He was treated with intramuscular epinephrine, intravenous corticosteroids, and mycophenolate mofetil but the angioedema continued to worsen. Given the unusual presentation of skin lesions in this case and the high acuity of the patient, he was given a trial of 2 doses of icatibant while awaiting biopsy results. Although icatibant, a selective bradykinin β_2 -receptor antagonist, is approved for the symptomatic treatment of acute attacks of hereditary angioedema,^{6,7} thus warranting a trial in the present patient. Unfortunately, the urticarial-like lesions and nonobstructive posterior pharyngeal edema did not show improvement despite this therapy.

A tissue diagnosis was sought to further investigate differential diagnoses, such as cutaneous T-cell lymphomas, Sézary syndrome, and mycosis fungoides given the fixed skin lesions. Skin biopsy showed histopathology and immunophenotype compatible with the diagnosis of PTCL (Fig 3). Computed tomography of the neck depicted diffuse cervical and superior mediastinal lymphadenopathy.

The patient ultimately developed sepsis and multisystem organ failure. Owing to the advanced nature of the disease, he was not considered a candidate for chemotherapy and died on hospital day 25.

More common causes of angioedema and urticaria were entertained; however, ultimately the histopathologic picture of the skin biopsy examination confirmed the diagnosis of PTCL. Current medical literature describes PTCL as presenting with extranodal manifestations, including cutaneous involvement; however, to the authors' knowledge, this is a rare case of PTCL presenting with angioedema and cutaneous lesions initially mistaken for urticaria. In addition, this rarity resulted in a delay in diagnosis because the patient's underlying disease progressed without treatment.

Mycosis fungoides and Sézary syndrome are the most common types of cutaneous T-cell lymphoma⁸ and were important considerations in the differential diagnosis of this patient. Mycosis fungoides has a classically prolonged clinical course that

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The registry URL and assigned database number for clinical trial registrations.
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Figure 1. Fixed erythematous maculopapular lesions distributed over the anterior and posterior chest and face.

progresses over years through patch, plaque, and tumor stages, followed by lymph node and visceral involvement. It has classic histopathologic findings, including sparse intraepidermal and papillary dermal infiltrate of lymphocytes arrayed within a fibrotic papillary dermis below an epidermis that shows psoriasiform hyperplasia and lymphocytes distributed in a “string of pearls” pattern, seen in the patch stage of mycosis fungoides. The plaque stage of mycosis fungoides is characterized by a lichenoid psoriasiform pattern in addition to papillary dermal, superficial, and deep perivascular infiltrates of lymphocytes.⁹ Sézary syndrome is characterized by the triad of generalized erythroderma, lymphadenopathy, and presence of atypical T cells with cerebriform nuclei, or Sézary cells.¹⁰ Allergists should be suspicious of such disorders in patients presenting with urticarial-like lesions and eczema.

Unlike B-cell malignancies, the lymphoma-associated angioedema in this patient occurred without the activation of the complement cascade, suggesting the release of vasoactive molecules by T cells and, hence, the minimal response to corticosteroids,



Figure 2. Periorbital and upper and lower lip edema without tongue involvement.

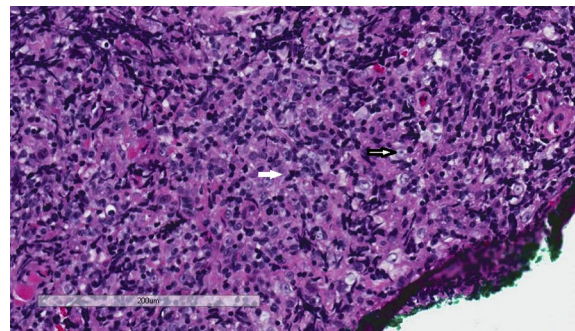


Figure 3. Skin biopsy examination shows dermal, atypical lymphoid infiltrates consisting of medium-sized lymphoid cells with round to irregular nuclear contours, dispersed to open chromatin, small nucleoli, and abundant cytoplasm (white arrow). There are scattered large lymphoid cells resembling immunoblasts or Hodgkin-like cells (black-outlined arrow). The epidermis is not involved, indicating epidermal or dermal discordance, which is suggestive of lymphoma.

antihistamine, and even mycophenolate and ica-tibant. Furthermore, it stresses the importance of always considering an underlying lymphoproliferative disorder in cases of angioedema and urticaria, which could allow for more prompt treatment.

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