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JAAD Grand Rounds quiz*

Identification No. 810211

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Learning objectives: At the conclusion of this learning activity, physician participants should be able to assess their own diagnostic and patient management skills and use the results of this exercise to help determine personal learning needs that can be addressed through subsequent CME involvement. Instructions for claiming CME credit appear in the front advertising section. See last page of Contents for page number.

Instructions: In answering each question, refer to the specific directions provided. Because it is often necessary to provide information occurring later in a series that give away answers to earlier questions, please answer the questions in each series in sequence. (J Am Acad Dermatol 2010;63:918-23.)

Chronic urticarial eruption

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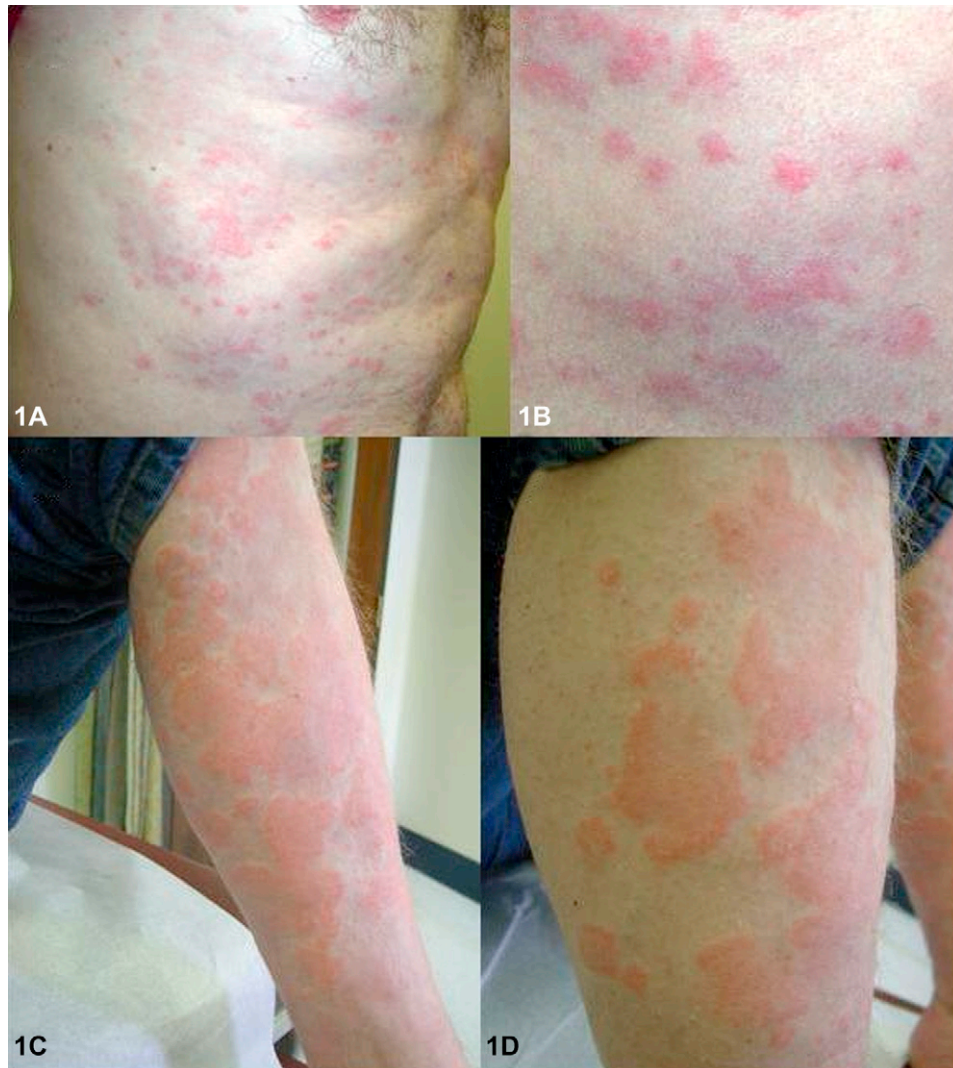
A 45-year-old man presented with an 18-month history of a recurrent urticarial eruption that preceded cyclical episodes of fever to 101°F (38.3°C), joint pain, headache, and increasing debilitation. The patient had tried numerous medications, including azathioprine, chloroquine, colchicine, hydroxychloroquine, methotrexate, nonsteroidal antiinflammatory drugs (NSAIDs), prednisone, and sulfasalazine, all without significant improvement. He denied pruritus, burning, lymphadenopathy, or respiratory symptoms. Review of systems was otherwise unremarkable. Diffusely distributed throughout the trunk, bilateral thighs, legs, and ventral forearms were multiple nontender, annular, indurated, erythematous, urticarial plaques, some with central clearing (Fig 1). A complete blood cell count with differential, chemistry panel, C-reactive protein, ferritin, iron panel, liver function tests, hepatitis panel, lactate dehydrogenase,

uric acid, urinalysis, rheumatoid factor, antinuclear antibody, SS-A, SS-B, antineutrophilic cytoplasmic antibody, anti-streptolysin O, rapid plasma reagin, hemolytic complement, C3, C4, direct immunofluorescence, *Helicobacter pylori* antibody, radioallergosorbent for latex, immunoglobulin E, antithyroid peroxidase antibody C1 esterase inhibitor function, and thiopurine methyltransferase were all within normal limits. The erythrocyte sedimentation rate was elevated at 47 and serum protein electrophoresis showed an IgM spike, which was revealed to be IgM kappa by immunoelectrophoresis. Serum IgM was elevated at 504 (upper limit of normal, 263). A computed tomographic scan of the sinus revealed a sphenoid sinus retention cyst but was otherwise unremarkable. A chest radiograph and abdominal ultrasound were within normal limits. A skin biopsy specimen revealed neutrophilic dermatosis (Fig 2).

1. Which of the following is required for definitive diagnosis of this condition?
 - a. Arthralgia
 - b. Elevated C-reactive protein
 - c. Leukocytosis
 - d. Monoclonal IgM
 - e. Suggestive radiographic bone evidence

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*The Self-Assessment Task Force of the American Academy of Dermatology is led by Erin E. Boh, MD.

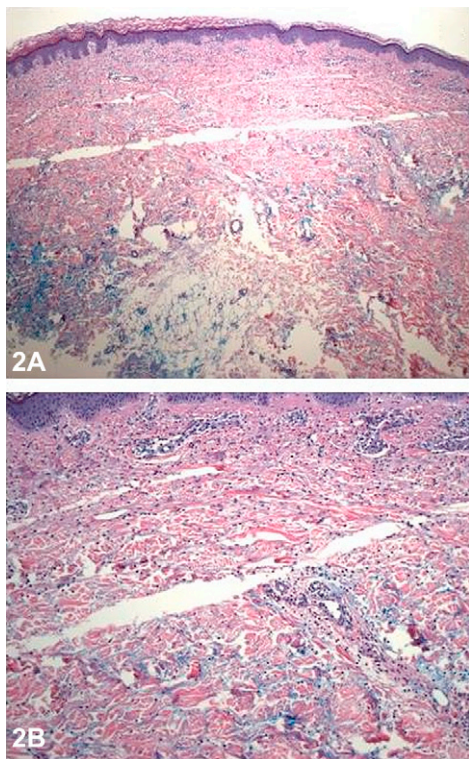


2. What is the most effective treatment modality?
 - a. Antihistamines
 - b. Dapsone
 - c. Interleukin-1 receptor antagonists
 - d. Intravenous immunoglobulin
 - e. Systemic corticosteroids
3. Complications of this disease include which of the following?
 - a. Acute myelogenous leukemia
 - b. Hepatitis C
 - c. Respiratory infections
 - d. Systemic lupus erythematosus
 - e. Waldenström macroglobulinemia

Discussion

Schnitzler syndrome, first described in 1974, is a rare disabling disorder characterized by a chronic urticarial rash and a monoclonal IgM gammopathy. The eruption is accompanied by at least two of the

following features: fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepatomegaly or splenomegaly, leukocytosis, elevated erythrocyte sedimentation rate, and hyperostosis on bone morphologic investigations. The cutaneous eruption is usually the first manifestation, and begins on the trunk and extremities, sparing the palms, soles, head, and neck. To date, fewer than 100 cases have been reported, the majority of which have been in Europe. There is a slight male predominance (1.6:1), and the average age of onset is in the sixth to seventh decade of life. The diagnosis is often delayed from months to decades after initial presentation. The differential diagnosis includes adult-onset Still disease, acquired C1 esterase deficiency, systemic lupus erythematosus, cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome, chronic infantile neurologic, cutaneous, and articular syndrome/neonatal onset multisystemic inflammatory



disease, and Muckle–Wells syndrome), POEMS syndrome (*poly*neuropathy, *organomegaly*, *endocrinopathy*, *monoclonal gammopathy*, and *skin changes*), hypocomplementic urticarial vasculitis, cryoglobulinemia, hyperimmunoglobulin D syndrome, Waldenström macroglobulinemia, lymphoma, multiple myeloma, monoclonal gammopathy of undetermined significance, hepatitis B or C, chronic meningococemia, idiopathic chronic urticaria, delayed pressure urticaria, cryoglobulinemia, Behçet's disease, and mastocytosis. Workup for Schnitzler syndrome therefore must be broad to exclude all of these diseases. The histopathologic features of skin biopsy specimens are variable. The most common finding is that of a superficial dermal and perivascular neutrophilic infiltrate. A superficial perivascular mononuclear infiltrate suggestive of chronic urticaria and lymphocytic inflammation may also be seen.

The pathophysiology of the Schnitzler syndrome is poorly understood. Multiple theories have been proposed. Deposits of IgM- κ antiskin autoantibodies have been shown along basement membranes or in capillary walls, which are thought to be responsible for the cutaneous manifestations via immune complex formation and complement activation. Another theory is that cytokines may play a direct role in the pathogenesis of Schnitzler syndrome. Increased levels of interleukin (IL)-6, granulocyte macrophage–colony

stimulating factor and granulocyte colony–stimulating factor have been identified in the serum of some patients, but the role of these cytokines is not clear. IL-1 is thought to be the key mediator of cutaneous inflammation. This is supported by the fact that multiple patients have gone into complete remission following administration of an IL-1 antagonist.

Treatment for Schnitzler syndrome is frustrating and often ineffective. Corticosteroids at high doses are able to decrease symptoms in most cases, but are limited in terms of long-term use because of side effect profiles. Other agents and treatment modalities including alkylating agents, antihistamines, azathioprine, chlorambucil, chloroquine, corticosteroids, cyclophosphamide, cyclooxygenase inhibitors, dapsone, high-dose intravenous immunoglobulin, immunosuppressants, nonsteroidal antiinflammatory drugs, psoralen plus ultraviolet A light phototherapy, and plasmapheresis have been used with limited symptomatic success. Anakinra, an IL-1 receptor antagonist, appears to be a promising agent, because it has been effective in inducing remission in multiple patients. Rituximab, an anti-B-cell chimeric monoclonal antibody against the protein CD20, and thalidomide have also been used, but the role of these agents remains to be determined.

Most patients with Schnitzler syndrome have a chronic benign course. However, periodic evaluation for lymphadenopathy and bone marrow involvement and monitoring of serum protein electrophoresis are recommended because 10% to 15% of patients subsequently develop a lymphoplasmic malignancy, such as Waldenström macroglobulinemia, lymphoplasmacytic lymphoma, or IgM myeloma.

For this series, the recommended choices are: 1, d; 2, c; 3, e.

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