JAMA Dermatology Clinicopathological Challenge

Painful Erythema and Edema of the Ears

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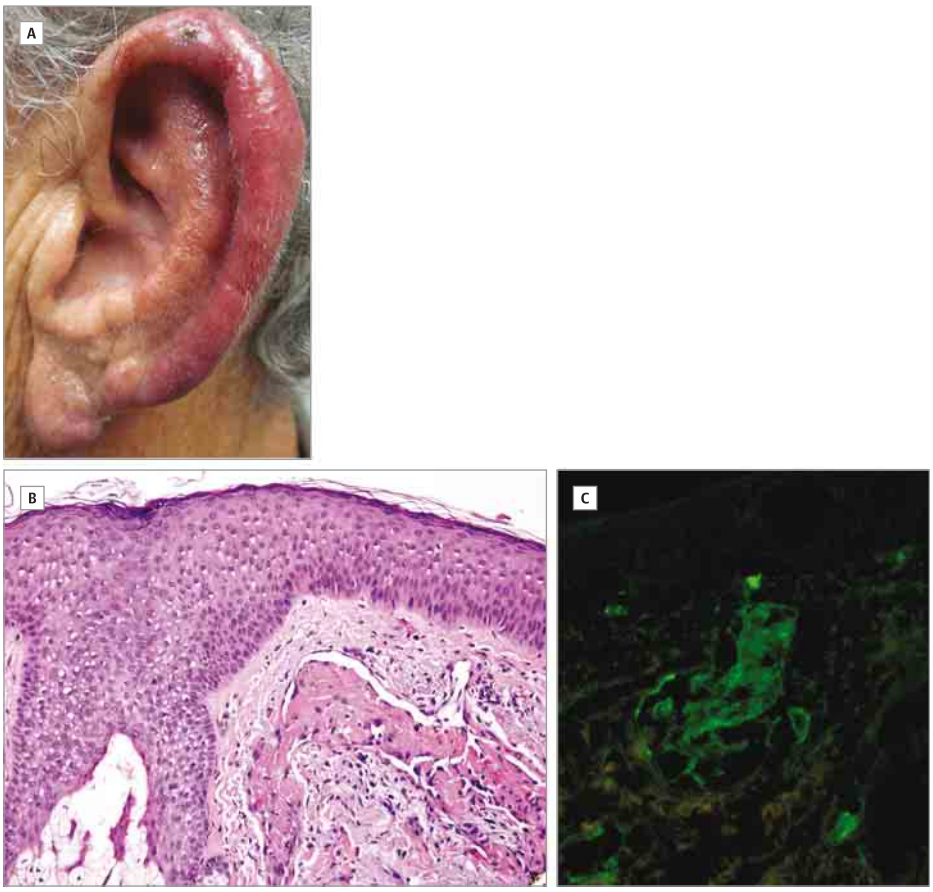

Figure. A, Clinically, the left ear demonstrates erythema, edema, and focal crusting. B, Biopsy specimen from the left ear reveals thrombi within engorged blood vessels but fails to reveal significant inflammation of blood vessel walls (hematoxylin-eosin, original magnification ×200). C, Biopsy specimen from the left ear under direct immunofluorescence and stained for anti-IgM highlights thrombi within vessels (original magnification ×200).

A man in his 70s presented with erythematous ears associated with a burning sensation. He reported that the lesions had begun 6 months previously and that they were most bothersome at the end of the day or when he was exposed to the cold and damp environment while out on his boat. He applied ice to alleviate the burning, but this worsened the condition. A heating pad provided some measure of relief, as did a brief course of systemic corticosteroids.

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Physical examination revealed that some papular lesions were associated with slight purpura and hemorrhagic crust (Figure, A). Histologic findings from biopsy specimens were also obtained by routine histologic analysis (Figure, B) and direct immunofluorescence examination (Figure, C).

WHAT IS YOUR DIAGNOSIS?

A. Relapsing polychondritis

B. Granulomatosis with polyangiitis (Wegener granulomatosis)

C. Cold agglutinin disease

D. Chilblain

Diagnosis

C. Cold agglutinin disease

Microscopic Findings and Clinical Course

Laboratory studies revealed an elevated cold agglutinin titer of 1:160 (normal is undetectable). Microscopic examination revealed thrombi within blood vessels (Figure, B) but no significant inflammation in blood vessel walls. Direct immunofluorescence revealed IgM associated with thrombi (Figure, C). Treatment with cold avoidance and a short course of systemic corticosteroids was helpful.

Discussion

Cold agglutinin disease is a form of autoimmune hemolytic anemia in which exposure to cold precipitates the formation of thrombi. The ears and other acral sites may be affected. Pathogenic cold agglutinins lead to hemolysis and hemagglutination.[1] Most common are *V4-34* gene segment–encoded autoantibodies, usually directed at I and/or i carbohydrate antigens on the surface of erythrocytes.[1] Cold agglutinin disease is considered primary when no underlying systemic cause is identified and secondary when associated with infection (eg, infectious mononucleosis, influenza B, hepatitis, human immunodeficiency virus infection, mycoplasma pneumonia) or lymphoproliferative disease.[1-5] The *V4-34* encoded antibodies can be viewed as a subset of IgM antibodies showing cold agglutinin activity. Primary disease is typically attributable to a monoclonal cold-reacting autoantibody, whereas secondary cold agglutinin disease may be associated with either polyclonal or monoclonal autoantibodies. Cold agglutinin disease associated with low-grade lymphoproliferative disease typically involves a monoclonal antibody.[4] Affected individuals often present with anemia and Raynaud syndrome.

Several other disorders often involve the ear and may be associated with erythema and edema. Relapsing polychondritis, granulomatosis with polyangiitis, and chilblain may all be considered in the differential diagnosis. Acute relapsing polychondritis is associated with antibodies to type II collagen[6] and immunoreactant deposition at the fibrocartilaginous junction seen on direct immunofluorescence evaluation of lesional biopsy specimens. Type II collagen antibodies are not specific for relapsing polychondritis and can be seen in other conditions.

Erythema and edema of the ears are limited to areas associated with cartilage and may mimic the clinical findings in our patient, but these conditions are not exacerbated by exposure to cold. Arthralgias, scleritis, episcleritis, and airway involvement are all associated with relapsing polychondritis. Granulomatosis with polyangiitis (Wegener granulomatosis) may involve the ears but is not associated with worsening on cold exposure. Individuals with granulomatosis and polyangiitis often have a history of chronic sinusitis, rhinorrhea, and otitis media.[7] Laboratory studies reveal antineutrophil cytoplasmic antibodies in most patients. Biopsy of skin lesions of granulomatosis with polyangiitis reveals vasculitis, which was not encountered in our patient. Granulomas may be associated with vasculitis, although leukocytoclastic vasculitis without granuloma formation is a typical finding on skin biopsy.[7] Chilblain is associated with pain on sudden warming of body parts recently exposed to cold temperatures. The clinical course noted in our patient would be atypical because chilblain usually resolves over 1 to 3 weeks, although lesions have been noted to recur episodically for several years after an initial precipitating event. Biopsy of chilblain tissue often reveals necrotic keratinocytes, spongiosis, basal layer vasculopathy, and perieccrine inflammation.[8]

Skin biopsy is useful in differentiating all of the entities listed if the clinical presentation and laboratory studies have not allowed a firm diagnosis to be established. Biopsy of lesional skin in cold agglutinin disease reveals distended vessels filled with eosinophilic thrombi. Minimal inflammation is present, and leukocytoclasis is absent. Direct immunofluorescence may reveal IgM associated with thrombi. The detection of IgM corresponds to the presence of pathogenic anti I and/or i IgM autoantibodies responsible for erythrocyte agglutination.

Treatment for cold agglutinin disease may be difficult. Cold avoidance, systemic corticosteroids, cytotoxic agents, plasmapheresis, and rituximab may all be of benefit.[9] Fortunately, cold agglutinin disease may remit over time.

ARTICLE INFORMATION

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