Type II mixed cryoglobulinemia following influenza and pneumococcal vaccine administration

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INTRODUCTION

Influenza virus vaccine–induced cryoglobulinemia has been reported in only 1 patient,[1] whereas pneumococcal-induced cryoglobulinemia has never been described. Mixed cryoglobulinemia is a systemic inflammatory syndrome that is caused by the development of immunoglobulins that deposit at low temperatures affecting small and medium blood vessels and may manifest as either an inflammatory or noninflammatory vasculopathy.[2] Multiple organs including the skin are most commonly affected.[2] Mixed cryoglobulinemia has been regularly associated with Hepatitis C viral infection[2] and may persist even when the infection has been eradicated. Vasculitides have been associated with vaccination. We report on a patient without prior immunologic disease whose disease occurred shortly after vaccination with influenza and pneumococcal vaccines, and persisted.

Abbreviation used:

HCV: hepatitis C virus

REPORT

A 76-year-old man presented with flu-like symptoms and cyanosis of the toes and fingers 5 days after he received the trivalent influenza vaccine and pneumococcal vaccination. His medical history included coronary artery disease, bypass surgery, hypercholesterolemia, and gastroesophageal reflux disease. He had nonpalpable, purpuric lesions on his toes (Fig 1, *A*) and fingers (Fig 1, *B*) along with acral pain. He progressively had worsening purpura and digital ischemia along with livedo reticularis of both plantar surfaces. Within 4 weeks, he had anorexia, night sweats, myalgias, fatigue, and arthralgias. A biopsy was offered and discussed with the patient, but he refused initially.

Laboratory evaluation found a normal complete blood count, normal urinalysis, comprehensive metabolic panel, negative antinuclear antibodies, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, immunofixation electrophoresis, hepatitis A antibody, hepatitis B surface antigen, and hepatitis C antibody. The following test results were abnormal: rheumatoid factor, 24 (normal, <20 IU/mL); total hemolytic complement level [CH50], 28 (normal, 60-185); C3 level, 75.50 (normal, >78 mg/dL); C4 level, <1.67 (normal, >16 mg/dL); Westergren erythrocyte sedimentation rate, 48 (normal, <20 mm/h), high sensitive C-reactive protein, 5.24 (normal, <4.0 mg/dL); antiphosphatidylserine IgG, 19 (normal, <11); and antiphosphatidylserine IgM, 64 (normal, <25). A chest radiograph and Doppler studies of blood flow of the extremities were also normal. Initial testing for cryoglobulins was negative. Two weeks later, his rheumatoid factor was 54 IU/mL.

He was initially treated with oral prednisone, 20 mg daily, which was increased 2 weeks later to 40 mg daily. However, he continued to develop new acral purpuric lesions and had increasing acral pain. Therefore, 6 weeks into his course, intravenous rituximab, 375 mg/mm^2, was administered weekly for a total of 4 infusions. Because of limited clinical

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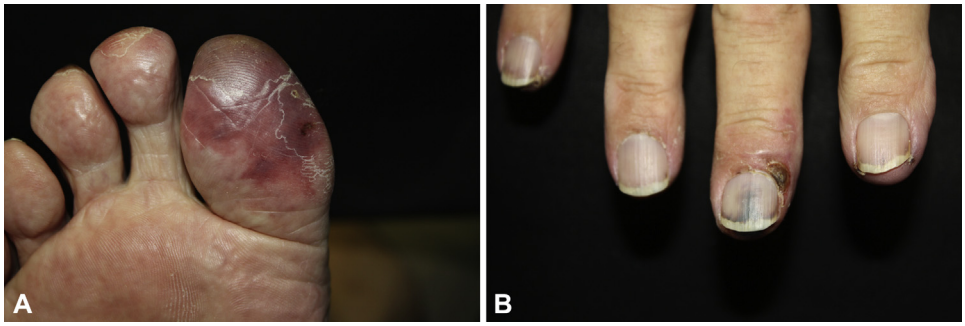

Fig 1. **A**, Purpuric lesions of the toes. **B**, Necrosis of the distal finger.

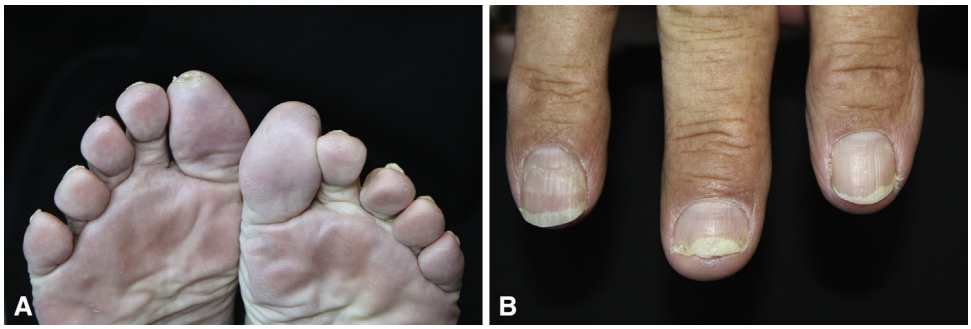

Fig 2. **A**, Healing of toes. **B**, Healing of fingers.

change, an additional 2 infusions of rituximab were given monthly. Cryoglobulins were detected for the first time at the end of his fourth infusion of rituximab. His acral lesions healed roughly 3 months after his last rituximab infusion. Prednisone, 40 mg daily, was continued throughout the first 3 months of his course and then slowly tapered and stopped 4 months after his last infusion of rituximab (Fig 2, *A* and *B*). His cryoglobulin level continued to be detectable, and 18 months after his initial presentation, he had increasing acral ischemic symptoms, and an elevated IgM level and low C4 level led to plans for another 4 rituximab infusions. However, before the second set of infusions, palpable purpura developed on his legs (Fig 3). Biopsy at this time found leukocytoclastic vasculitis, and direct immunofluorescence microscopy found IgG in the vessel walls. At this time, he was treated by our service with oral prednisone, 40 mg daily, which was tapered and stopped over 3 weeks and his hematologist administered another 4 weekly infusions of intravenous rituximab. He was seen at Mayo Clinic Rochester (hematology), and a type II cryoglobulin was identified and characterized as IgM κ monoclonal cryoglobulinemia with polyclonal IgG cryoglobulinemia. A bone marrow biopsy finding was normal. Twenty months after his initial presentation, he began therapy with oral cyclophosphamide, 100 mg daily, and oral prednisone, 10 mg daily. His symptoms and clinical findings have been controlled with this regimen, and 3 years after his presentation, his doses have been decreased to cyclophosphamide, 50 mg every other day, and prednisone, 5 mg daily. Although his symptoms and physical findings have remained controlled, his low level of C4 has persisted.

DISCUSSION

We report the first, to our knowledge, English-language case of mixed cryoglobulinemia in a patient after receiving the trivalent influenza and pneumococcal vaccines, which were given 5 days before his initial clinical manifestations. Influenza vaccine–induced mixed cryoglobulinemia has been documented only once before,[1] but leukocytoclastic vasculitis following the influenza vaccination has been reported on multiple occasions.[3] In 1 case, small vessel vasculitis occurred on 2 occasions in a patient with a known paraproteinemia roughly 11 days after influenza vaccination on 2 separate occurrences.[4] Pneumococcal vaccine–induced cryoglobulinemia has not been reported previously. However, small vessel vasculitis development after the simultaneous administration of both vaccinations was previously seen.[5] The mechanisms of vasculitis and cryoglobulinemia induced by the influenza or pneumococcal vaccination remain unknown. It is not possible to ascertain which vaccine is

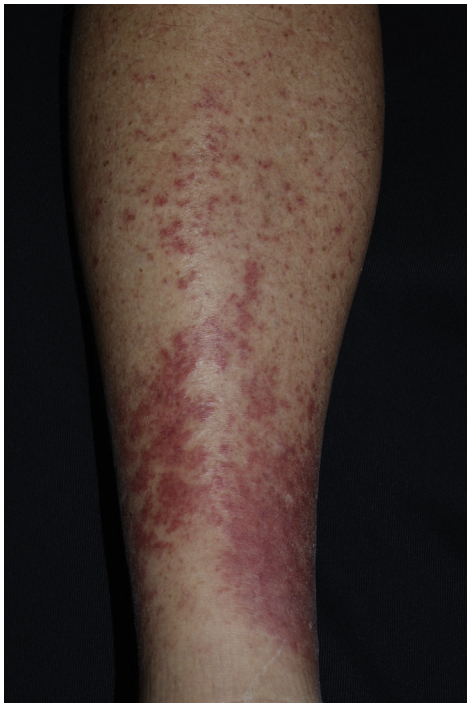

Fig 3. Palpable purpura on the legs.

responsible for this patient's disease, but it we propose that it is more likely caused by the viral vaccination.

Mixed cryoglobulinemia is commonly associated with viral infections including hepatitis C virus (HCV), hepatitis B virus, or Epstein-Barr virus.[2] The mechanism of viral-induced cryoglobulinemia is not completely understood but is postulated to be caused by cryoglobulin formation induced by cytokine or chemokine-mediated immune response to the HCV infection.[6] It is not clear why cryoglobulins are produced as a response to a viral antigen triggered in response to a vaccination. Studies have shown that mixed cryoglobulinemia can persist or recur after successful treatment of HCV without detectable HCV RNA in the serum yet detectable in the cryoprecipitate.[7]

Although a causal link with the influenza vaccination cannot be proved by our observation, we can speculate that based on the timing of the vaccination, constellation of symptoms, and positive laboratory results, influenza virus–induced cryoglobulinemia is the most probable cause of our patient's symptoms. Induction of cryoglobulin after viral stimulation may result in a prolonged disease. Early recognition and treatment can improve patients' long-term outcome. Further research is necessary to explore the possible immunopathogenic link due to the sequential nature of the disease following vaccinations.[3]

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