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CASE STUDY

Mixed Cryoglobulinemia: An Unusual Presentation of Hepatitis C

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Abstract

A 50-year-old man with a history of hepatitis C presented with recurrent episodes of abdominal pain, arthralgia, and weakness. Although these symptoms seemed rather nonspecific, a purpuric rash of the lower extremities was the final clue to diagnosis. The diagnosis was then confirmed by histopathologic and serologic testing.

Introduction

More than 170 million people worldwide have chronic hepatitis C virus (HCV) infection, which results in considerable morbidity. HCV is also increasingly recognized for its extrahepatic manifestations. Although not well documented in primary care or emergency medicine literature, HCV is known to be a powerful B-cell stimulator that causes a serious lymphoproliferative disorder known as mixed cryoglobulinemia.

Mixed cryoglobulinemia is characterized by the clonal expansion of rheumatoid factor-expressing B cells in the liver, lymph nodes, and serum. The presence of cryoglobulins in the circulation (cryoglobulinemia) can lead to systematic vasculitis and damage of various end organs.

Case Report

A 50-year-old man with a history of hepatitis C presented to a community Emergency Department after 5 days of abdominal distention and generalized colicky abdominal pain that worsened with oral intake of fluids and solids. The patient reported multiple episodes of nonbloody diarrhea over the same period as well as subjective fevers, arthralgia, and a nonpruritic rash that was localized to his lower extremities (Figure 1).

The patient reported five episodes of identical symptoms over a previous nine-month period. Each episode lasted approximately one week and then spontaneously resolved. This was the first episode for which he sought medical attention.

On presentation, the patient was in moderate distress. Vital signs were unremarkable, except a low-grade temperature of 37.9°C. The patient was alert and oriented. His abdomen was soft, but diffusely tender without rebound or guarding. He had no fluid wave. Rectal examination found brown stool with trace-positive hemoccult results. Examination of the lower extremities revealed a palpable, purpuric rash from the distal thighs to the ankles. Pulse and capillary refill were intact. The patient was admitted to the hospital for pain control, hydration, and further assessment.

Initial laboratory testing revealed a white blood cell count of 8.5 × 10^3/mL, a hemoglobin level of 13.8 g/dL, and a platelet count of 60 × 10^9/L. Chemistries were unremarkable. Creatinine measured 1.7 mg/dL (normal < 1.1 mg/dL). Liver function tests revealed that his alanine aminotransferase level was 120 U/L (normal, 17-62 U/L), aspartate aminotransferase level was 112 U/L (normal <35 U/L), total bilirubin was 1.7 mg/dL (normal, 0.1-1.0 mg/dL), and international normalized ratio was 1.2 (normal = 0.8-1.2).

The history of hepatitis C and the constellation of recurrent abdominal pain, arthralgia, and lower-extremity rash suggested mixed cryoglobulinemia. A skin biopsy was performed during a dermatology consultation. Histologic sections revealed perivascular infiltration of lymphocytes and neutrophils, focal vascular damage, and positive immunofluorescent staining for IgM and C3. All of these findings were consistent with leukocytoclastic vasculitis, a hallmark of mixed cryoglobulinemia. Further serologic testing revealed depressed C3 and C4 levels and a positive result for cryoglobulin qualitative. Hepatology was consulted and the patient was discharged with ribavirin and pegylated interferon alpha-2a. At follow-up 1 month after hospitalization, his rash had resolved and he reported no further recurrence of generalized weakness, fever, or abdominal pain. Renal function had improved, with creatinine measuring 1.0 mg/dL.

Discussion

Cryoglobulins are single or mixed immunoglobulins that undergo reversible precipitation at low temperatures. Wintrobe and Buell first described cold-sensitive serum precipitates in 1933.[1] The term "cryoglobulins" was not introduced until 1947, by Lerner et al.[2] In 1966, Meltzer first described the correlation of cryoglobulinemia with the triad of purpura, arthralgia, and weakness.[3]

Cryoglobulins can be classified based on their components, as described by Brouet et al in 1974.[4] Type I comprises mono-

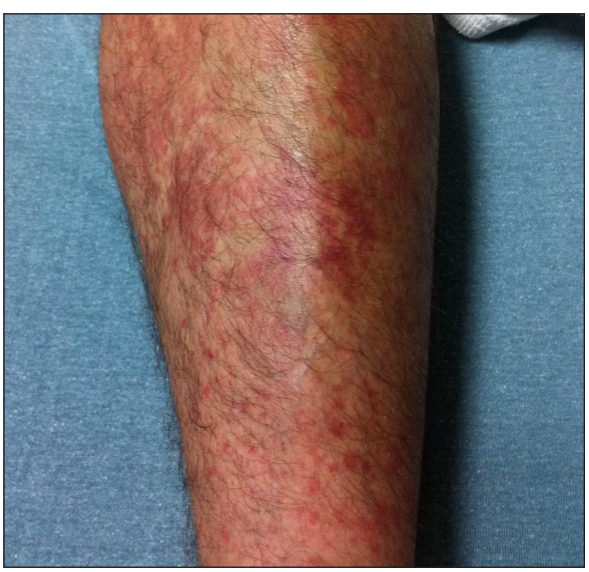

Figure 1. Image of purpuric rash of lower extremities.

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clonal immunoglobulins. Types II and III are immunocomplexes formed by monoclonal (type II) or polyclonal (type III) IgM that have rheumatoid factor activity and bind to polyclonal immunoglobulins. Type II and type III cryoglobulins are referred to as mixed cryoglobulins.[4]

The association between hepatitis C and mixed cryoglobulinemia was first recognized in the 1990s. It is now understood that the hepatitis C core protein creates an antigenic response and is bound by anticore IgG. This in turn binds to IgM with rheumatoid factor activity, forming the mixed cryoglobulin immune complex.

Estimates of the prevalence of mixed cryoglobulinemia in people with HCV infection vary widely. This is because of unfamiliarity with clinical symptoms, lead-time bias, and mishandling of specimens. For example, serum preparation must be performed at 37°C to prevent premature immune complex precipitation. The serum is stored at 4°C and then spun to obtain a measurement of cryoglobulins (cryocrit). A cryocrit > 2% indicates cryoglobulinemia.

Although the incidence of mixed cryoglobulinemia in vitro ranges from 20% to 56%, only 10% to 27% of these cases present with clinical symptoms.[5] Although it is known that mixed cryoglobulinemia is associated with increased duration of HCV infection, it is not clear why the virus induces mixed cryoglobulinemia in some patients but not in others.

These mixed cryoglobulins can precipitate and deposit on small-vessel and medium-vessel endothelium of all organ systems. Therefore, patients can present with a wide range of symptoms and findings (Table 1).

Our patient experienced Meltzer's triad of purpura, arthralgia, and weakness, the most common symptoms of mixed cryoglobulinemia. Abdominal pain is observed in 2% to 22% of patients. Acute renal failure is observed in 33% of patients with mixed cryoglobulinemia and is a major cause of morbidity.[6]

Table 1. Symptoms of mixed cryobulinemia

Organ system	Manifestations
Pulmonary	Dyspnea Cough Pleurisy Pleural effusions
Gastrointestinal	Abdominal pain Hemorrhage Hepatosplenomegaly
Renal	Membranoproliferative glomerulonephritis Hypertension Nephrotic syndrome
Musculoskeletal	Arthralgia Arthritis
Nervous	Sensorimotor neuropathy Visual disturbance Cerebral vascular accident
Cutaneous	Palpable purpura Ischemic necrosis Livedoid vasculitis Cold-induced urticaria Acrocyanosis

It is imperative to consider this diagnosis when evaluating patients with hepatitis C. Presenting symptoms can vary, and if untreated they can lead to significant vasculitic damage of end organs. Our patient's presenting symptoms initially led us to consider the diagnosis of Henoch-Schönlein purpura. Although this is a vasculitic disorder of children, adult cases have been documented. As with most cases of vasculitis, the management of Henoch-Schönlein purpura would have focused on supportive care and immunosuppression. This would have been inadequate treatment for our patient.

The cryoglobulin immune complex is an immunologic response to the hepatitis C core antigen. Therefore, definitive therapy for mixed cryoglobulinemia requires eradication of the hepatitis C virus. A hepatologist should be consulted early to guide the treatment plan. Although beyond the scope of this manuscript, current treatment recommendations include the combination of ribavirin and pegylated interferon alpha with or without a protease inhibitor such as telaprevir or boceprevir. In refractory cases, the addition of rituximab has been shown beneficial.[7-10] Duration of therapy ranges from 24 weeks to 48 weeks and is often influenced by the HCV genotype and response to treatment. Our patient was treated with a 24-week course of ribavirin and pegylated interferon alpha and has continued to be free of recurrent symptoms. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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