CASE REPORT

It's not what it looks like: atypical rash in cryoglobulinaemic vasculitis

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Accepted 12 March 2017

SUMMARY

A 48-year-old man with a history of intravenous drug use and chronic, untreated hepatitis C presented to the emergency room with acute bilateral lower extremity swelling, erythema and maculopapular rash. Serum C4 levels were low, but dermatology felt the rash was due to venous stasis dermatitis. The patient was discharged with compression stockings, but returned to the hospital 5 days later with no improvement in his symptoms. A more extensive laboratory workup revealed hepatitis C viral load of 4 million, elevated serum cryoglobulins, and skin biopsy showing leukocytoclastic vasculitis. He was treated with oral prednisone, with complete resolution of his symptoms after 2 weeks. He was scheduled for follow-up in gastroenterology clinic for treatment of his hepatitis C for definitive cure of his mixed cryoglobulinaemia, but failed to get insurance authorisation to begin treatment with Harvoni. He presented to the hospital 4 months later with diffuse alveolar haemorrhage.

BACKGROUND

Mixed cryoglobulinaemia (MC) is a heterogeneous disease process with a variety of underlying infectious, autoimmune and malignant aetiologies. However, they share certain clinical and laboratory findings. In particular, the hallmarks are circulating mixed cryoglobulins, low serum complement (C4) levels, palpable purpura and leukocytoclastic vasculitis pathology on skin biopsy. Notably, up to 90% of patients with MC have circulating levels of hepatitis C viral RNA (HCV-RNA). A classic clinical manifestation of cryoglobulinaemic vasculitis is a palpable purpuric rash in the lower extremities. Arthralgias are also common and renal or pulmonary involvement may be seen in more advanced stages of the disease and signify a poor prognosis. However, atypical presentations of the classic skin lesions can make the diagnosis difficult at times. We here present a case of a man with history of hepatitis C who had an atypical vasculitic rash which required multiple hospital visits before the correct diagnosis was made and confirmed by biopsy. We also provide a brief discussion of the barriers, social and structural, to successful treatment of the patient's underlying hepatitis C.

CASE PRESENTATION

A 48-year-old man with past medical history of remote intravenous drug use (IVDU) and a 5-year history of untreated hepatitis C presented with a painful, bilateral lower extremity rash and swelling for the past 2 weeks. He denied any fever, chills,

joint pains or other symptoms. He quit IVDU 3 years ago and was on methadone maintenance. He was previously referred to gastroenterology for evaluation of his hepatitis C and to discuss treatment options, but was fired from the practice after frequent missed appointments. Physical examination showed a bilateral, erythematous, confluent maculopapular rash on the lower legs with scattered flat, non-palpable, non-blanching papules on the upper thigh, sparing the genital and inguinal region (figure 1). There was significant warmth and swelling in the lower extremities bilaterally. The rash was exquisitely painful. Distal pulses and sensation were intact. While there were scattered palpable purpura on the upper legs that were consistent with a vasculitic process, the rash on the lower legs was confluent and erythematous without any palpable purpura and appeared more like a venous stasis dermatitis. The primary team felt vasculitis was the more likely diagnosis, and felt that venous stasis dermatitis was a possibility given the appearance of the lower legs. We also considered the possibility that both processes may have been occurring simultaneously. A consult was placed to dermatology for a second opinion and an initial workup for vasculitis began.

INVESTIGATIONS

Laboratory workup found C4 complement level was <1.7 mg/dL (normal: 12–38 mg/dL), C3 complement level was 69.7 mg/dL (normal: 59.0–152.0 mg/dL), C reactive protein (CRP) was 0.39 mg/dL (normal: <1.00 mg/dL) and erythrocyte sedimentation rate (ESR) was 10 mm/hr (normal: 0–15 mm/hr). Anti-neutrophilic antibody titre was negative at 1:40 and anti-proteinase 3 and anti-myeloperoxidase antibodies were undetectable. Urine studies, complete blood count (CBC) and basic metabolic panel (BMP) were all within normal limits.

Figure 1 Patient's lower extremity at time of initial presentation.

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To cite: Gleason T, Ghimire S, Paladugu S. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2017-219468

Dermatologists came to evaluate the patient. They were adamant that the rash was not a vasculitic process and that venous stasis dermatitis can sometimes present with scattered petechial and/or purpuric lesions if the onset of leg oedema is rapid. Despite this input from the dermatology service, the primary team still felt that vasculitis was a more likely diagnosis given the low C4 levels and patient's underlying hepatitis C infection. A meeting was held between the patient, primary team and dermatology service. The option was presented to the patient to stay in the hospital for further workup of his rash or to go home with compression stockings and then return to dermatology clinic as an outpatient to see if the rash had improved or progressed. The patient ultimately elected to go home and follow-up as an outpatient. Members of the primary team felt uncomfortable with the final diagnosis, but ultimately deferred to the expertise of the dermatology service.

The patient returned to the hospital 5 days later with the same symptoms. Physical examination was unchanged from previous visit except for fever of 38.1°C. CRP had increased to 3.43 mg/dL and ESR was 24 mm/hr. Further laboratory workup revealed HCV load of 4 million international units/decilitre and positive serum cryoglobulins. Wedge biopsy of the skin was consistent with leukocytoclastic vasculitis.

DIFFERENTIAL DIAGNOSIS

In the absence of standardised diagnostic criteria for MC, diagnosis is based of clinical evaluation, laboratory values and pathology results.¹ The skin, kidneys and peripheral nerves are most commonly involved. Clinical findings may include skin purpura, skin ulcers, glomerulonephritis, non-erosive arthritis, acral ischaemia, cold-induced acrocyanosis and Raynaud's phenomenon. Laboratory abnormalities include elevated cryoglobulins, low complement levels (particularly C4), high rheumatoid factor titres, as well as other signs of hyperviscosity, such as platelet clumping or red blood cell (RBC) rouleaux formation. Finally, depending on tissue type for biopsy, histopathology may show leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, endoneural vasculitis or a non-specific necrotising vasculitis in small-medium-sized vessels.¹

However, there is significant heterogeneity in patient presentation, which can make diagnosis difficult. In addition, there is overlap with several other common autoimmune and lymphoproliferative conditions that may also be present concurrently with underlying hepatitis C infection. In particular, there is significant overlap with primary Sjögren's syndrome (SS), rheumatoid arthritis (RA) and B-cell non-Hodgkin's lymphoma (B-NHL).² A careful clinical and laboratory workup is needed to help differentiate between these conditions. MC typically involves the skin and visceral organs and has low C4 levels. Primary SS typically involves the salivary glands and will have positive autoantibodies (Anti-Ro/Sjögren's-syndrome-related antigen A (Anti-Ro/SSA) and/or Anti-La/Sjögren's-syndrome-related antigen B (Anti-La/SSB)) that are rarely seen in MC. RA more commonly involves erosive, symmetrical polyarthritis whereas the arthritis in MC is non-erosive. Also, anti-cyclic citrullinated peptide antibodies (anti-CCP) may be elevated in RA. Finally, MC and SS may be complicated by development of B-NHL. Careful clinical, serologic and radiologic monitoring, as well as biopsy of the bone marrow or any suspicious lymph nodes, will aid in diagnosing this dangerous complication.²

TREATMENT

The patient was discharged on an oral prednisone taper of 40 mg daily for 10 days, then 20 mg daily for 10 days, then

10 mg daily for 10 days. At 2-week follow-up appointment with gastroenterology, he had complete resolution of his rash and pain (figure 2). The patient underwent HCV genotyping, which revealed genotype 1a. He also underwent Fibrosure testing and ultrasound elastography, which revealed grade 1–2 and grade 2–3 fibrosis, respectively. Recommendation was made for 12 weeks of treatment with Harvoni, but insurance authorisation was needed before treatment could begin. Despite multiple efforts from the physician team and other support staff, the patient did not contact his insurance company and authorisation for treatment was never approved.

OUTCOME AND FOLLOW-UP

The patient returned to the hospital 4 months later with haemoptysis and shortness of breath. He had still not begun treatment for his hepatitis C. He was admitted to the intensive care unit (ICU) for acute respiratory failure. CT scan of the chest showed diffuse interstitial infiltrates bilaterally. He was given a diagnosis of diffuse alveolar haemorrhage and treated with high-dose intravenous methylprednisolone. His respiratory status improved over the next several days and he was discharged home on another oral prednisone taper, starting at 40 mg daily. Before discharge, the patient was again encouraged to contact his insurance company about authorisation for Harvoni. The patient was counselled that the pulmonary symptoms were likely related to his cryoglobulinaemic vasculitis and that involvement of the lungs was a sign that his condition was progressing and becoming more severe.

DISCUSSION

Cryoglobulins are a form of immunoglobulins that precipitate at temperatures below 37°C and come in three types (I–III). Type I involves a monoclonal IgG or IgM population of immunoglobulins. Type II and type III involve a mixture of monoclonal and polyclonal IgG and IgM immunoglobulins and are referred to as mixed cryoglobulinaemias.³ The term

Figure 2 Patient's lower extremity after 2-week course of oral prednisone.

cryoglobulinaemia was first coined in 1966 by Meltzer and Franklin⁴ in a case series of 29 patients with elevated cryoglobulins along with skin, joint and organ dysfunction. Cryoglobulinaemias can occur in a variety of infectious, autoimmune and malignant conditions, with the most prominent malignant aetiology being B-cell lymphomas.¹ Ferri *et al*⁵ discovered in 1991 that almost 90% of patients with mixed cryoglobulinaemia had circulating HCV-RNA.⁵ More recent research has found the prevalence of HCV-RNA in MC to be anywhere from 30% to 100%, with considerable geographic variation.¹ Conversely, circulating mixed cryoglobulins are present in over 50% of patients with HCV and cause overt symptoms of cryoglobulinaemia in around 5% of patients.² However, MC remains a relatively rare disease process and can be difficult to diagnose due to its heterogeneous presentation.

Diagnosis in this case was made difficult by the atypical skin manifestations of the patient's leukocytoclastic vasculitis. Namely, he presented with diffuse, painful erythema and swelling in the lower extremities bilaterally with only scattered palpable purpura on the upper legs, rather than the classic palpable, purpuric rash. The internal medicine team also erred in being overly deferential to the dermatology service. The laboratory results were indicating that the patient's rash was being driven by a vasculitic process, rather than being a simple case of venous stasis dermatitis. This deference led to mischaracterisation of the rash as due to venous stasis dermatitis and a delay in laboratory evaluation for cryoglobulinemia with subsequent definitive diagnosis by biopsy. Given the overwhelming association between MC and hepatitis C, any atypical skin findings in patients with known hepatitis C infection should be presumed to be a manifestation of MC until proven otherwise. Internal medicine physicians must be vigilant about this association and assertive in recognising cryoglobulinaemic vasculitis, as failure to promptly and accurately diagnose this condition can lead to unnecessary suffering and medical complications for patients.

First-line treatment for MC involves conventional immunosuppression with corticosteroids, either intravenous methylprednisolone followed by oral prednisone for severe cases or only oral prednisone for mild-moderate cases, followed by correction of the underlying cause of the MC. Cyclophosphamide, azathioprine or mycophenolate mofetil can be added as adjunctive agents for severe cases or cases that do not respond to steroids. Therapy with biologics is an ongoing area of research, with rituximab showing promise as a treatment agent in limited studies.¹ However, relapse rates are high unless the underlying cause of the MC is corrected. In the case of MC with underlying chronic HCV infection, this means treatment with antiviral agents for definitive cure.^{6,7}

This case illustrates some of the common barriers to treatment that are encountered in patients with cryoglobulinaemic vasculitis secondary to hepatitis C. There was some initial difficulty in making the correct diagnosis, but once the diagnosis was made, the appropriate treatment recommendations for the patient were relatively straightforward. However, our patient did not have easy access to resources that might help him arrange appropriate treatment. Owing to the high cost of Harvoni and similar treatments, patients are required to be highly compliant with appointments and physician instructions before beginning treatment. There are also hurdles to getting treatment approved by insurance companies, which requires patients to be advocates for their own care and sophisticated in navigating the complex world where healthcare and insurance intersect.

In the case of our patient, there were several missed opportunities to begin treatment before his condition became more

severe. After initial diagnosis of his hepatitis C, he was referred to gastroenterology for treatment, but missed several appointments and was fired from their practice. Once his cryoglobulinaemic vasculitis was diagnosed, he was again referred to gastroenterology and they agreed to readmit him to their practice because of his worsening symptoms. He was again evaluated and a treatment recommendation was made for Harvoni for 12 weeks. However, before treatment could begin the patient needed to contact his insurance company for authorisation. This never occurred and he was lost to follow-up until returning to the emergency room with diffuse alveolar haemorrhage, a poor prognostic factor that can be associated with mortality rates as high as 80%.¹ This is indeed a tragic case that illustrates some of the hurdles that patients face in obtaining treatment even after appropriate diagnosis of their medical conditions. We remain hopeful that the patient will be able to obtain treatment of his hepatitis C and are working with him to achieve that goal.

Patient's perspective

The patient was offered the opportunity to provide a written perspective, but declined at this time.

Learning points

- ▶ Mixed cryoglobulinemia (MC) is caused by deposition of circulating cryoglobulins that consist of monoclonal or polyclonal IgG and IgM into various tissues, with skin, joints and visceral organs most commonly involved.
- ▶ Hepatitis C RNA is detectable in 30–100% of patients with MC and 5% of patients with chronic hepatitis C will develop MC.
- ▶ Diagnosis can be complicated by heterogeneous disease presentation, but careful clinical, laboratory and histopathologic evaluation can help to make the correct diagnosis.
- ▶ Treatment for MC involves conventional immunosuppression with corticosteroids and correction of the underlying cause when possible, in the form of antiviral therapy in patients with chronic hepatitis C virus infection.
- ▶ Modern treatment for hepatitis C is incredibly expensive. There are often significant hurdles, social and institutional, to beginning appropriate treatment even after the correct diagnosis is made.

Contributors TG was the primary author of this manuscript. SG and SP also made substantial contributions to the writing, editing and revision of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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