An interesting rash: leucocytoclastic vasculitis with type 2 cryoglobulinaemia

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Cryoglobulinaemia is exceedingly difficult to manage and an appreciation of its insidious presentation is key for diagnosis and early intervention.

Case history

A 56-year-old man presented with maculopapular erythematous rash bilaterally on his lower limbs.

The erythematous macules and purpuric papules over both his lower limbs had been present for several months and were made worse in cold conditions. He had joint arthralgia and weakness and had been hepatitis C positive for the past 25 years. He had three courses of interferon therapy (including pegylated interferon alfa) for his hepatitis C infection. During each course of interferon therapy, the eruption on his lower limbs became slightly better, however, the therapy was unable to clear the hepatitis C infection and so the erythematous markings on his lower limbs worsened. He also had Raynaud's phenomenon for one year prior to presentation.

The patient worked as a plumber and, hence, often had to go into cold environments and deal with cold water which exacerbated his condition subsequently straining his financial situation.

There were multiple erythematous macules and purpuric papules; each <5 mm in diameter on both lower limbs located on both the anterior thigh and shin regions.

On general systems examination, he showed no signs of peripheral or central neuropathy. Respiratory, GI and CVS examinations were unremarkable. Urine dipstick showed the presence of white blood cells.

Arthralgia, Raynaud's syndrome and the peculiar rash suggested the possibility of an autoimmune aetiology. Autoantibody investigations were ordered to exclude systemic lupus erythematosus and scleroderma.

Since his arthralgia was exacerbated in cold environments and due to the fact that he had hepatitis C, it was necessary to exclude the diagnosis of cryoglobulinaemia. The diagnosis of cryoglobulinaemia is made from serum immunological investigations. These are difficult investigations to organize and, hence, cryoglobulin testing is poorly exploited in clinical practice.[1] The chief difficulty lies in ensuring that the blood sample is maintained at a temperature of 37°C until the serum is separated.[2]

A full blood count (FBC), urea and electrolytes (U&E) rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR) were ordered. Urinanalysis was requested after urine dipstick showed the presence of white blood cells. The lack of neurological involvement on examination was significant since cryoglobulinaemia is associated with cerebral ischaemia, spinal cord and cranial nerve involvement. It was necessary to investigate the possibility of vasculitis causing his skin rash by ordering a skin biopsy of the affected areas.

His skin biopsy revealed extravasated red blood cells, a number of infiltrating neutrophils and nuclear fragments with superficial dermis fibrinoid vessel wall necrosis using haematoxylin-eosin stain. His serum electrophoresis confirmed the presence of cyroglobulinaemia. Although his FBC, U&E and ESR tests were normal, his serum contained high levels of rheumatoid factor.[3] His urinalysis revealed a urine white cell count of 15 uL which prompted a need for renal biopsy to explore the possibility of glomerulonephritis. The autoantibody screen was negative.

The patient was diagnosed with leucocytoclastic vasculitis with type 2 cryoglobulinaemia.

A multidisciplinary approach was adopted since this rare disease affects many organ systems. A consultation was set up to review this case. The team comprised a rheumatologist, dermatologist, nephrologist and clinical immunologist, who discussed his management plan.

Considering the patient failed to respond to hepatitis C therapy, immunosuppression was the next step. Rituximab was considered as it has been shown to be a safe and effective therapeutic option in alleviating symptoms in such patients, even as a first line therapy.[4–7] A more detailed description of possible treatments is mentioned in the Discussion section below.

Discussion

This was a very complex case. This section will describe some of the causes of type II cryoglobulinaemia in addition to the management options.

Cryoglobulinaemia has a prevalence of 1:100,000, reported from a study in the US.[8] It affects women three times more than men and usually occurs in middle age. It is more common in Southern Europe.[9]

Cryoglobulinaemia is an autoimmune disease in which exposure to temperatures below 37°C causes circulating immunoglobulins to precipitate in the serum.[2] Warmth causes them to dissolve once again. There are three types of cryoglobulinaemia and they can be differentiated by clinical presentation. The most common reported manifestations of the disease are cutaneous involvement, articular involvement and peripheral neuropathy. Renal involvement also occurs frequently.

Table 1 describes the distinguishing features of the three types of the condition. Types II and III are often collectively referred to as 'mixed' type. The patient in this case report was diagnosed by virtue of his immunoserology and his clinical presentation with palpable purpura and co-existent hepatitis C infection. His blood demonstrated polyclonal IgG with monoclonal IgM, thus using Table 1 his condition is classified as type II cryoglobulinaemia.

The main causes of cryoglobulinaemia include familial/genetic, autoimmune, rheumatoid and arthritis. Systemic lupus erythematosus (SLE) in addition to the characteristic SLE-associated vasculitis is also a cause of this condition. The patient in this case had a specific type of vasculitis known as leucocytoclastic vasculitis. Leucocytoclastic vasculitis is seen in cryoglobulinaemia, especially in patients with concomitant hepatitis C infection.

Infection is a very important cause of this disease and parasites (toxoplasmosis, malaria), bacteria (streptococcus, syphilis, Lyme disease) and fungi (coccidiomyocosis) have all been associated with

Table 1
The distinguishing features of the three main types of cryoglobulinaemia. Types II and III are often collectively called 'mixed type'

Cryoglobulinaemia type	*Immunoglobulin type*	*Clinical findings*	*Differential diagnosis*	*Frequency*[10]	*Associations*
Type I	Monoclonal IgM, (IgA and IgG less commonly)	Ischaemic necrosis, abdominal pain	Multiple myeloma, chronic lymphocustic leukaemia, waldenstrom macroglobu linaemia	25%	Lympho-proliferative disease
Type II	Polyclonal IgG with monoclonal IgM	Palpable purpura, membranoproliferative glomerulonephritis, arthralgias	Chronic liver disease, infections (chronic HCV infection, SLE, Sjögren syndrome)	25%	Hepatitis C infection, systemic lupus erythematosus, Sjögren syndrome
Type III	Polyclonal IgG with polyclonal IgM	Palpable purpura, livedoid vasculitis, arthralgias		50%	

this disease. Viruses such as cytomegalovirus (CMV), HIV, Epstein-Barr virus (EBV) and in particular; hepatitis A, B, and C[11] (or chronic liver disease) are also important causes.

This patient was hepatitis C positive hence this virus is most likely to be the major contributing factor. The purpose of this report is to ensure practitioners remain aware of the possibility of HCV infection in patients presenting with palpable purpura, livedo reticularis or urticaria.[12] This is especially pertinent considering studies have shown up to 8% of patients with a mixed cryoglobulinaemia and leukocytoclastic vasculitis have anti-HCV antibodies.[13]

Less direct causes of cryoglobulinaemia such as lymphoproliferative disorders and proliferative glomerulonephritis should not be ruled out, especially since there were white blood cells in this patient's urine. The characteristic initial symptoms of mixed cryoglobulinaemia are commonly referred to as 'Meltzer's triad' and consist of purpura, arthralgia and myalgia.[1,14,15] This triad in addition to renal involvement is more prevalent in type II cryoglobulinaemia.[16] Renal involvement initially presents as nephrotic syndrome with positive protein on urine dipstick, serum hypoalbuminaemia and oedema. This is promptly followed by hypertension.

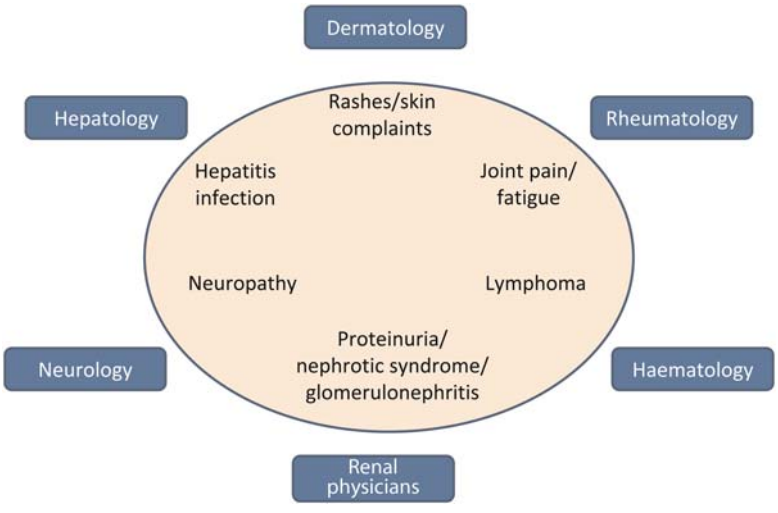
This patient's urinalysis did not show a nephrotic syndrome presentation but did reveal a urine white cell count of 15/uL. This is significant as over one-third of patients with cryoglobulinaemia develop membrane proliferative glomerulonephritis on long-term follow-up with half of these dying from renal insufficiency.[17] This risk is potentiated by relapsing cutaneous involvement, and a rising creatinine.[18]

The delay in diagnosis of the patient's condition is not surprising considering the condition's polymorphism. This, too, is a pertinent aspect this report seeks to highlight. These patients often are referred to the specialty relating to the predominant symptoms (Figure 1).

With regards to management, focus can be directed to: (a) eradicate the HCV infection; (b) to suppress the B-cell clonal expansion and cryoglobulin production; or (c) to ameliorate symptoms depending on the individual case.[19] The most effective treatment for hepatitis C virus positive cyroglobulinaemia is eradication of the underlying HCV infection.[20]

Unfortunately, this patient failed to respond to the therapy for his hepatitis C infection. Hence suppression of the immune response is the next objective. Immunosuppressants (such as azathioprine and cyclophosphamide) may be used in this case,

Figure 1
Demonstrating the myriad of possible presentations of cryoglobulinaemia and the variety of sources of patient referral and investigation



however, they should be reserved until the renal biopsy is analysed for indications of renal disease.

Patients with similar presentations of arthralgia may receive benefit from non-steroidal anti-inflammatory drugs. However, if the condition continues to worsen, then plasmapheresis will be the logical treatment of choice. This should be followed by concomitant corticosteroid treatment. However, there have been no large multicentre randomized controlled trials carried out of plasma exchange versus placebo, or versus immunosuppressive therapy.[21] As mentioned previously, Rituximab has shown promise, and appears to be a safe and effective option.[4,6]

With regards to prognosis, cryoglobulins, arthralgia, and high levels of rheumatoid factor are risk factors for chronic cutaneous disease.[22] The overall prognosis is poorer in men with renal disease, widespread vasculitis liver failure, or lymphoproliferative disease.[23–25] Additionally, cryoglobulinaemia patients can develop congestive heart failure. There has been exciting new research that has shown high circulating levels NTproBNP (a marker for heart failure), in patients with mixed cryoglobulinaemia and chronic HCV infection. Routine screening of this marker in these patients may assist in identifying subclinical cardiac dysfunction.[26,27] The quantification of rheumatoid factor may enhance the clinical monitoring of cryoglobulinaemic vasculitis in HCV-infected patients such as the one in this case.[28]

The patient's social problems and concerns in this case report reflect the complex nature of the disease. It is common for patients to be referred between physicians for some time before the final diagnosis is reached and this is chiefly by virtue of the multisystem nature of the condition. A multidisciplinary team approach along with clear patient-centred education and support are vital in managing this difficult condition and in alleviating the patient's concerns and anxieties. The myriad of possible presentations make this rare condition very elusive to successfully diagnose. An awareness and low threshold for investigation will ensure an early diagnosis and timely commencement of treatment.

References

1 Shihabi ZK. Cryoglobulins: an important but neglected clinical test. *Ann Clin Lab Sci* 2006;**36**:395–408

2 Sargur R, White P, Egner W. Cryoglobulin evaluation: best practice? *Ann Clin Biochem* 2010;**47**:8–16

3 Abel G, Zhang QX, Agnello V. Hepatitis C virus infection in type II mixed cryoglobulinemia. *Arthritis Rheum* 1993;**36**:1341–9

4 Roccatello D, Baldovino S, Rossi D, *et al.* Rituximab as a therapeutic tool in severe mixed cryoglobulinemia. *Clin Rev Allergy Immunol* 2008;**34**:111–17

5 Zaja F, De Vita S, Mazzaro C, *et al.* Efficacy and safety of rituximab in type II mixed cryoglobulinemia. *Blood* 2003;**101**:3827–34

6 Gurcan HM, Keskin DB, Stern JN, *et al.* A review of the current use of rituximab in autoimmune diseases. *Int Immunopharmacol* 2009;**9**:10–25

7 Ahmed MS, Wong CF. Should rituximab be the rescue therapy for refractory mixed cryoglobulinemia associated with hepatitis C? *J Nephrol* 2007;**20**:350–6

8 Gorevic PD, Kassab HJ, Levo Y, *et al.* Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. *Am J Med* 1980;**69**:287–308

9 Ferri C. Mixed cryoglobulinemia. *Orphanet J Rare Dis* 2008;**3**:25

10 Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* 1974;**57**:775–88

11 Pakula AS, Garden JM, Roth SI. Cryoglobulinemia and cutaneous leukocytoclastic vasculitis associated with hepatitis C virus infection. *J Am Acad Dermatol* 1993;**28**:850–3

12 Karlsberg PL, Lee WM, Casey DL, Cockerell CJ, Cruz PD Jr. Cutaneous vasculitis and rheumatoid factor positivity as presenting signs of hepatitis C virus-induced mixed cryoglobulinemia. *Arch Dermatol* 1995;**131**:1119–23

13 Gungor E, Cirit A, Alli N, Karakayali G, Gur G, Artuz F. Prevalence of hepatitis C virus antibodies and cryoglobulinemia in patients with leukocytoclastic vasculitis. *Dermatology* 1999;**198**:26–8

14 Monti G, Galli M, Invernizzi F, *et al.* Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. *QJM* 1995;**88**:115–26

15 Meltzer M, Franklin EC, Elias K, McCluskey RT, Cooper N. Cryoglobulinemia – a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. *Am J Med* 1966;**40**:837–56

16 Agnello V. Mixed cryogobulinemia and other extrahepatic manifestations of hepatitis C. *Hepatitis C* 2000;**2**:295–313

17 Invernizzi F, Galli M, Serino G, *et al.* Secondary and essential cryoglobulinemias. Frequency, nosological classification, and long-term follow-up. *Acta Haematol* 1983;**70**:73–82

18 Johnson RJ, Willson R, Yamabe H, *et al.* Renal manifestations of hepatitis C virus infection. *Kidney Int* 1994;**46**:1255–63

19 Iannuzzella F, Vaglio A, Garini G. Management of hepatitis C virus-related mixed cryoglobulinemia. *Am J Med* 2010;**123**:400–8

20 Charles ED, Dustin LB. Hepatitis C virus-induced cryoglobulinemia. *Kidney Int* 2009;**76**:818–24

21 Rockx MA, Clark WF. Plasma exchange for treating cryoglobulinemia: A descriptive analysis. *Transfus Apher Sci* 2010;**42**:247–51

22 Sais G, Vidaller A, Jucgla A, Servitje O, Condom E, Peyri J. Prognostic factors in leukocytoclastic vasculitis: a

clinicopathologic study of 160 patients. *Arch Dermatol* 1998;**134**:309–15
23 Della Rossa A, Tavoni A, D'Ascanio A, *et al.* Mortality rate and outcome factors in mixed cryoglobulinaemia: the impact of hepatitis C virus. *Scand J Rheumatol* 2010;**39**: 167–70
24 Saadoun D, Sellam J, Ghillani-Dalbin P, Crecel R, Piette JC, Cacoub P. Increased risks of lymphoma and death among patients with non-hepatitis C virus-related mixed cryoglobulinemia. *Arch Intern Med* 2006;**166**: 2101–8
25 Ferri C, Sebastiani M, Giuggioli D, *et al.* Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin Arthritis Rheum* 2004;**33**:355–74
26 Antonelli A, Ferri C, Ferrari SM, *et al.* High circulating levels of N-terminal pro-brain natriuretic peptide and interleukin 6 in patients with mixed cryoglobulinemia. *J Med Virol* 2010;**82**:297–303
27 Antonelli A, Ferri C, Ferrari SM, *et al.* High levels of circulating N-terminal pro-brain natriuretic peptide in patients with hepatitis C. *J Viral Hepat* (in press)
28 De Rosa FG, Agnello V. Observations on cryoglobulin testing: I. The association of cryoglobulins containing rheumatoid factors with manifestation of cryoglobulinemic vasculitis. *J Rheumatol* 2009;**36**:1953–5