

# A rare case of Waldenström's macroglobulinaemia-associated cryoglobulinaemia vasculitis

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## ABSTRACT

This case report presents a patient with vasculitis as a presenting symptom of type I cryoglobulinaemia due to lymphoproliferative disease. This is an uncommon cause of vasculitis, but important to recognise, as it influences treatment decisions. We discuss the differential diagnosis and extensive diagnostic approach of vasculitis. Above all, this case emphasizes that even a limited quantity of paraproteins can cause severe symptoms.

## KEYWORDS

Cryoglobulinaemia, paraproteinemia, vasculitis, Waldenström's macroglobulinaemia

## INTRODUCTION

Vasculitis has a varied and nonspecific clinical presentation and extensive differential diagnosis.<sup>1,2</sup> In this case report, we describe the diagnostic process from suspected vasculitis to established small vessel vasculitis based on monoclonal cryoglobulinaemia due to an underlying haematological disease. This case shows an uncommon cause of vasculitis and highlights that even a limited quantity of paraproteins can cause severe morbidity.

## CASE REPORT

A 78-year-old man was admitted to our hospital with malaise, night sweats, and weight loss. Six months before, he was evaluated by a neurologist because of axonal polyneuropathy. Work-up revealed an IgM-kappa

### What was known on this topic?

Vasculitis is a condition with a varied and nonspecific clinical presentation and extensive differential diagnosis. Clinical presentation depends on affected organs. The combination of constitutional symptoms and (multiple) organ dysfunction raises the suspicion of vasculitis. Cryoglobulinaemia is a phenomenon of precipitation of immunoglobulins with cold temperature. Monoclonal cryoglobulins are strongly associated with underlying haematological disease. Typically, clinical presentation is related to vaso-occlusion and occur in cold body parts. Rarely, small vessel vasculitis is described in these patients. Diagnostic approach and treatment aim to target the underlying condition.

### What does this add?

This case highlights that even a limited quantity of paraproteins can cause severe symptoms and require treatment. Furthermore, type I cryoglobulinaemia due to lymphoproliferative disease is an uncommon cause of vasculitis. We describe how the extensive diagnostic process of a suspected vasculitis can result in detection of a rare underlying cause with consequences for treatment.

paraproteinaemia of < 1 g/l. He did not suffer from B symptoms at that time and there were no signs of lymphadenopathy or bone marrow invasion. IgM antibodies against myelin-associated glycoprotein were not detected. His further medical history reported a coronary artery bypass graft and treated tuberculosis in childhood.

For the last two weeks, he reported malaise, night sweats, and weight loss. He felt progressive pain and stiffness in his legs during exercise, which was different from the previous neuropathic pain. Furthermore, he noticed a right-sided foot drop.

On physical examination there was no lymphadenopathy and examination of heart, lungs, and abdomen was unremarkable. We noticed livedo reticularis on both legs and bilateral pitting oedema. There were no signs of acrocyanosis or purpura. Peripheral pulsations were intact. Neurologic examination showed a paresis of the dorsiflexors of the right foot, suggestive for peroneus nerve damage. Initial laboratory tests showed mild normocytic anaemia, mild elevated C-reactive protein, and elevated creatinine kinase with normal liver and kidney function.

Because of the constitutional symptoms, livedo reticularis, and suspected myositis and mononeuritis multiplex, we considered a small vessel vasculitis (table 1). In order to identify the type of vasculitis and to consider the differential diagnosis of a malignancy or infection, additional laboratory tests (table 2) and a positron emission tomography/computed tomography (PET-CT) scan followed.<sup>3,4</sup> The PET-CT scan showed elevated uptake in the right upper

leg and an additional magnetic resonance imaging (MRI) scan was suggestive for inflammatory myopathy of the vastus lateralis muscle. Biopsy of skin, muscle, and fascia from the right quadriceps muscle showed perivascular infiltrates of predominantly lymphocytes with destruction of the small vessel walls. Together with fibrinoid degeneration, signs of leucocytoclasia, and thrombosis of the lumen, a leucocytoclastic vasculitis was diagnosed. Additional laboratory tests showed no evidence for an auto-immune aetiology or systemic rheumatic disease. Cryoglobulinaemic vasculitis was diagnosed due to the presence of cryoglobulins, which could be typed as type I (monoclonal IgM kappa). Bone marrow biopsy revealed

**Table 1. Symptoms related to vasculitis**

Constitutional symptoms
Fever of unknown origin, fatigue, weight loss, decreased appetite, and/or night sweats
Signs of ischaemia
Multiple affected organs
Eyes: uveitis, optic neuritis
Skin: erythema nodosum, (sub)cutaneous nodules, ulcers, palpable purpura
Ears, nose, and throat: jaw claudication, sinusitis, chronic otitis media, polyposis
Lungs: parenchymal nodules, haemorrhage
Heart: aortic regurgitation, peri-/myocarditis, coronary artery vasculitis
Gastrointestinal: abdominal pain, diarrhoea, bleeding, symptoms related to ischaemia
Kidney: glomerulonephritis, symptoms related to stenosis of the renal artery
Peripheral nervous system: mononeuritis multiplex, polyneuropathy
Central nervous system: headache, cerebral vasculitis, stroke
This list is a summary of possible symptoms, for the complete list, see reference 8

**Table 2. Laboratory findings**

	Laboratory findings	Reference values
Haemoglobin (mmol/l)	7.0	8.5-10
MCV (fL)	89	80-100
Leukocytes (10 <sup>9</sup> /l)	7.7	4-10
Thrombocytes (10 <sup>9</sup> /l)	216	150-400
Erythrocyte sedimentation rate (mm/1 <sup>st</sup> h)	13	< 10
C-reactive protein (mmol/l)	70	< 3
Creatine kinase (U/l)	2534	< 200
Total IgM (g/l)	1.79	0.45-2.30
M-protein (g/l)	IgM-kappa: < 1	Not detectable
Free light chain ratio	5.47	0.26-1.65
Antinuclear antibodies	Negative	Negative
Anti-MPO antibodies (U/l)	Negative	Negative
Anti-PR3-antibodies (U/l)	< 5	< 5
Lupus anticoagulation	Negative	Negative
Cryoglobulin (serum)	IgM-kappa cryoglobulinaemia	Not detectable
Rheumatic factor (kIU/l)	< 10	< 10
Anti-CCP antibodies (U/l)	< 25	< 25
C3 (g/l)	0.69	0.90-1.80
C4 (g/l)	< 0.08	0.16-0.42
Serology for HIV, hepatitis C and B	Negative	Negative

The above, as well as total eosinophils, creatinine level, liver enzymes, and urinalysis are recommended if vasculitis is considered.<sup>2,8</sup> C3 = complement 3; C4 = complement 4; CCP = cyclic citrullinated peptide; IgM = immunoglobulin M; MCV = mean corpuscular volume; MPO = myeloperoxidase; PR3 = proteinase 3.

slight infiltration of small B-cell non-Hodgkin lymphoma with plasmacytoid differentiation.

Once the diagnosis of symptomatic Waldenström's macroglobulinaemia was confirmed, we started first-line therapy:<sup>5-7</sup> six courses of dexamethasone, rituximab (an anti-CD20 monoclonal antibody), and cyclophosphamide (chemotherapy). After six treatment courses, paraproteins and cryoglobulins were not detectable anymore and creatine kinases – as a marker of myositis – was normalised. His symptoms improved and he went for clinical revalidation to regain condition.

## DISCUSSION

### Vasculitis

Constitutional symptoms and suspected myositis and mononeuritis multiplex were the main symptoms leading to small vessel vasculitis in this case. When vasculitis is considered, a detailed patient history and careful physical examination is essential, with regard to possible manifestations. Initial laboratory testing should include all tests presented in table 2, as well as eosinophil count, creatinine level, liver enzyme levels, and urinalysis.<sup>1,8</sup> Depending on affected organs, specific tests such as electromyography or liquor tests can be

performed. Vascular imaging through ultrasound, PET, CT, or MRI can support the diagnosis of large and medium vessel vasculitis.<sup>9</sup> For small vessel vasculitis, histological examination is necessary to confirm diagnosis and can be best performed in an affected organ.<sup>8</sup> Neutrophilic infiltration surrounding and involving blood vessel walls and fibrinoid necrosis are typical. Leucocytoclasia, extravasation of erythrocytes, necrosis, and thrombi can also be seen. The performed serum tests (auto-immune serology, complement factors, eosinophils) are necessary to differentiate in specific aetiology of vasculitis (table 3). However, a normal biopsy does not exclude vasculitis, as the inflammation can be segmented.

### Cryoglobulinaemia

Cryoglobulinaemia is defined as the precipitation of immunoglobulins with cold temperature. Symptomatic cryoglobulinaemia is considered a rare disease in Europe,<sup>10</sup> although exact prevalence is unknown due to the heterogeneity in cause, clinical presentation, and geographical distribution.<sup>11</sup> After immunofixation, three subtypes can be identified.<sup>12</sup> Solely monoclonal immunoglobulins (paraproteins) are referred to as type I; type II comprises both monoclonal and polyclonal immunoglobulins, and type III only polyclonal immunoglobulins. Due to overlapping clinical presentation and pathophysiology, type II and III are also referred to as mixed cryoglobulinaemia; 5-25% of cryoglobulins are monoclonal.<sup>13,14</sup>

The cryoprecipitability of monoclonal immunoglobulins depends on intrinsic factors such as pH, temperature, and absence of sialic acid moieties.<sup>1</sup> The aggregated cryoglobulins seem to saturate the mononuclear phagocyte system activity, possibly by influencing Fc receptor function, resulting in accumulation and deposition of the cryoglobulins in specific organs.<sup>15</sup> Clinical presentation of cryoglobulinaemia is divergent, and in most cases even asymptomatic.<sup>16,17</sup> Symptoms are often secondary to hyperviscosity and vascular occlusion, such as Raynaud phenomenon, acrocyanosis, purpura, cold urticaria, ulcers, or skin necrosis.<sup>1</sup> Leucocytoclastic vasculitis due to type I cryoglobulinaemia is rarely described. A French nationwide study identified 64 patients between 1995 and 2010; before that, only case reports with few patients were published. None of these patients reported typical vaso-occlusive symptoms.<sup>14</sup>

In contrast, leucocytoclastic vasculitis is typically seen in mixed cryoglobulinaemia.<sup>1</sup> Immunoglobulins associate with rheumatoid factor (in contrast to monoclonal cryoglobulins), form immunocomplexes, and precipitate in small and medium-sized vessels. This leads through inflammation and complement activation to leucocytoclastic vasculitis. Mixed cryoglobulinaemia is related to chronic viral infections (particularly hepatitis

**Table 3.** Differential diagnosis of small vessel vasculitis<sup>1,3,4</sup>

<b>ANCA-associated small vessel vasculitis</b>
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Microscopic polyangiitis
<b>Immune complex-mediated vessel vasculitis</b>
IgA vasculitis
Cryoglobulinaemic vasculitis
Monoclonal cryoglobulinaemia, associated with lymphoproliferative disease
Mixed cryoglobulinaemia, associated with infectious and auto-immune disease
Cutaneous leucocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis (anti-C1q antibodies)
<b>Antibody-mediated small vessel vasculitis</b>
Anti-glomerular basement membrane disease
ANCA = anti-neutrophil cytoplasmic antibodies; IgA = immunoglobulin A

C, but also associated with hepatitis B and HIV), autoimmune diseases, and lymphoproliferative disorders.<sup>18</sup> Cryoglobulins could be detected in more than 50% of patients who were infected with chronic hepatitis C virus or HIV.<sup>19</sup>

The diagnostic approach of cryoglobulinaemia is focused on identifying involved organs and underlying disease, as this influences treatment decisions.<sup>1</sup> Renal and/or skin involvement can be diagnosed with urinary analysis, renal, or skin biopsy.<sup>2,8</sup> The type of cryoglobulinaemia has an important role in identifying underlying disease, and therefore quantity and type of immunoglobulin and presence of rheumatoid factor should be determined. Type I cryoglobulinaemia is strongly associated with underlying lymphoproliferative disorder, such as Waldenström's macroglobulinaemia or chronic lymphoid leukaemia.<sup>13</sup> Therefore, bone marrow examination is indicated.

#### Level of paraprotein and severity of symptoms

As our case demonstrates, even a limited quantity of paraprotein can cause cryoglobulinaemia with severe symptoms. A recent retrospective study among 64 patients with type I cryoglobulinaemia could not identify a correlation between paraprotein level and clinical severity.<sup>20</sup> Previous studies already demonstrated

that the concentration of paraprotein has little or no prognostic value.<sup>1,21</sup> Therefore, *starting* treatment against Waldenström's macroglobulinaemia is based on symptoms, regardless of the paraprotein level. In the majority of patients with type I cryoglobulinaemia, treatment of underlying disease leads to improvement or stabilisation of symptoms.<sup>13</sup>

#### CONCLUSION

Vasculitis can be a presenting symptom of type I cryoglobulinaemia due to lymphoproliferative disease, although rarely seen. Vasculitis should be considered in patients with constitutional symptoms and symptoms of multiple affected organs. An extensive diagnostic process is necessary to identify underlying cause. This case emphasises that even very limited quantity of paraproteins can lead to cryoglobulinaemia with severe symptoms.

#### DISCLOSURES

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