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Cryoglobulinaemic vasculitis secondary to mantle cell lymphoma presenting with necrosis of fingers

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Abstract

We report a case of a male patient with mantle cell lymphoma (MCL) with secondary cryoglobulinaemic vasculitis without monoclonal protein. MCL was diagnosed during the diagnostics of necrosis of fingers, the first symptom of the underlying disease. The diagnosis was made after excluding other causes of cryoglobulinaemia, including infectious and autoimmune causes. The progression of necrosis was inhibited after the initiation of MCL treatment (rituximab, glucocorticoids) and symptomatic treatment (vasodilators).

This article describes the first MCL case associated with extensive necrosis of the fingers. Cryoglobulinaemic vasculitis without monoclonal protein due to malignancy is rare. An oncological aetiology must also be considered during the differential diagnosis of the causes of vasculitis, even if cancer symptoms are absent.

Key words: cryoglobulinaemic vasculitis; cryoglobuilinaemia; necrosis; mantle cell lymphoma

Introduction

Cryoglobulins are pathological immunoglobulins that precipitate at low temperatures (approximately 4°C) and redissolve when incubated at temperatures similar to those of the human body (approximately 37°C) [1].

These antibodies are usually classified into three groups. Type I are monoclonal immunoglobulins, which usually form due to haematological disorders. Type II are polyclonal IgG and monoclonal IgM, and type III are polyclonal IgG and IgM. Subtypes II and III are called mixed because they contain two different types of immunoglobulins. They occur most commonly in hepatitis C virus (HCV) infection. Less commonly, they are found in other diseases, including systemic lupus erythematosus, Sjögren's syndrome, lymphoproliferative disorders, and viral infections, such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) [1, 2].

Laboratory abnormalities that may indirectly indicate the presence of cryoglobulins include the following:

— decreased complement C3 levels, decreased total haemolytic complement (CH50) levels; found in most patients with mixed cryoglobulinaemia;

— monoclonal immunoglobulins in serum (type I);

— rheumatoid factor [1–4].

Cryoglobulins are detected in about 15–20% of patients with HIV-associated infections and may also occur in chronic bacterial and fungal infections. They are also found in 15–25% of patients with connective tissue diseases. Studies have found that these abnormal immunoglobulins can be detected in more than 50% of HCV-infected patients, with only 5% having symptoms associated with their presence.

A condition involving cryoglobulins in the patient's serum is referred to as cryoglobulinaemia. In clinical practice, it is a rare abnormality. Although asymptomatic in many people, the condition can also lead to vasculitis, accompanied by fatigue, arthralgia, petechiae on the skin and mucous membranes, peripheral neuropathy, ischaemic lesions and glomerulonephritis. Cryoglobulin-containing immune complexes are mainly localised in small to medium-sized vessels. The incidence of cryoglobulinaemia is approximately 1:100,000 people, with a three times higher prevalence in women [1]. Most cryoglobulinaemic vasculitis (CV) cases are secondary to HCV infection (80%), lymphoproliferative disorders (5%) and autoimmune diseases (6%, mainly Sjögren's syndrome). The remaining cases are associated with another infectious agent or have unspecified aetiology (idiopathy) [2].

This article presents a rare case of a patient with CV-induced finger ischaemia without monoclonal protein secondary to mantle cell lymphoma (MCL).

Case report

A 56-year-old man with suspected vasculitis was admitted to the Clinical Department of Rheumatology, Immunology and Internal Medicine at the University Hospital in Kraków for diagnosis and treatment of necrotic skin lesions of the distal phalanges of the hands. The patient had no history of chronic disease but smoked cigarettes (estimated at 60 pack-years). Before the described hospitalisation, the patient had been diagnosed in the district hospital's internal medicine department, where he presented with swelling of the lower extremities, increased Raynaud's phenomenon and a loss of 10 kg of body weight, which unfolded over several months. He underwent diagnostic evaluation, including high-resolution computed tomography (HRCT) and CT angiography (CTA) of the chest, CT of the abdomen and pelvis with contrast, gastroscopy, colonoscopy, ultrasound (US) of the lower limbs and bronchoscopy. Hepatosplenomegaly without lymphadenopathy and small focal lung lesions (inaccessible to bronchofiberoscopy) were found. The lesions were the summation of several smaller foci, in the pulmonologist's opinion, suggesting pulmonary tissue involvement in the course of systemic connective tissue disease. Laboratory tests for autoimmune disease did not reveal any anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibody (ANA) or anti-neutrophil cytoplasmic antibody (ANCA). A manual peripheral blood smear indicated the presence of young leucocytes at 35%. Their dynamic decrease was observed in follow-up studies, which is unusual for a haematological process. Due to the suspicion of vasculitis, 500 mg of intravenous methylprednisolone was administered over three consecutive days, with no clinical improvement. Physical examination on admission was notable for necrotic lesions of the skin of the distal phalanges II–V of the right hand and III of the left hand, palpable purpura of the skin of the extremities and focal necrotic lesions on the skin of both lower legs. The evolution of the necrotic lesions is shown in Figure 1.

Figure 1. Evolution of necrotic lesions of the hands. **A.** Early lesions; **BC.** Advanced necrotic lesions before treatment; **DE**. Dry necrosis after the initiation of immunosuppressive and vasodilatory treatment.

In addition, a confluent fine-spotted rash was present mainly on the skin of the lower legs and in the area of the knee and ankle joints. There were no other clinical features typical of systemic connective tissue diseases, such as photosensitivity, arthralgia and arthritis, skin induration, muscle weakness or Sjögren's syndrome. Laboratory tests revealed leucocytosis

(25 x 10^3/uL) with the possible presence of abnormal leucocytes (11 prolymphocytes), rheumatoid factor and elevated C-reactive protein (CRP) levels (37 mg/l). The diagnosis was also extended to immunophenotyping of white blood cells. In the peripheral blood examined, a 36% population of monoclonal cells of the B lymphocyte lineage was isolated, with an antigenic pattern suggestive of MCL. In addition, during the differential diagnosis of potential causes of vasculitis (e.g. CV or polyarteritis nodosa), HBV, HCV, and HIV infections were excluded, and no anti-cardiolipin, anti-β2-glycoprotein, anti-myeloperoxidase (anti-MPO), or anti-proteinase 3 (anti-PR3) antibodies were found. ANAs were present in the serum at a titre of 1:160, determined by immunofluorescence, with a granular luminescence pattern, but antigenic specificity was not identified. The complement C3 concentration was within the normal range, while a reduced complement C4 concentration was detected (a finding that may indirectly indicate the presence of cryoglobulins). Further diagnostic tests for secondary causes of vasculitis revealed cryoglobulins in the patient's blood. Electrophoresis did not reveal monoclonal protein, ruling out the type I cryoglobulinaemia diagnosis. During hospitalisation, CTA of the chest and upper limbs was also performed, which did not indicate changes typical of polyarteritis nodosa but did reveal a suspicious focal lesion in the right lung with a diameter of 14 mm. After a pulmonology consultation, it was decided to refer the patient for a positron emission tomography–computed tomography (PET-CT) scan to exclude the neoplastic character of the pathology. The scans revealed lesions in the lung parenchyma with poor metabolic activation, interpreted as inflammation or lesions caused by the underlying disease. An ultrasound of the lower limbs showed atherosclerosis of the lower limb arteries without features of medium- and large-vessel vasculitis. Biopsy specimens were taken from the skin lesions on the lower limbs using a biopsy punch. Histological examination of the skin preparation revealed leucocytoclastic vasculitis. In the absence of lymphadenopathy, a bone marrow sample was collected. The histological preparation showed marrow involvement by MCL infiltration, and a t(11;14) translocation was present on cytogenetic examination. In view of the above findings, CV secondary to MCL was diagnosed. Due to the significant severity of finger necrosis, treatment with sildenafil, alprostadil via an infusion pump, pentoxifylline, low-molecular-weight heparin, acetylsalicylic acid, statin, and analgesic treatment with tramadol and oral paracetamol was implemented. In addition, due to rapidly progressing necrosis in the course of vasculitis, a second cycle of intravenous pulses of methylprednisolone (500 mg each over the next three days) was administered, followed by continued glucocorticoid therapy with prednisone at a gradually reduced dose of 1 mg/kg. After the treatment, the progression of

skin necrosis was stopped. An improvement in the vascularisation of the upper limbs was observed. After a haematological consultation, 700 mg of rituximab was administered with methylprednisolone, clemastine and paracetamol to initiate MCL treatment. The patient was then transferred to the haematology ward, where the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) was used to treat the underlying disease. No progression of necrosis or emergence of new vasculitis symptoms was observed after initiation of MCL treatment.

Discussion

To the best of our authors' knowledge, this article describes the first case of advanced necrosis of the fingers in the course of CV secondary to MCL. In addition, CV without monoclonal protein in the course of lymphoid malignancy is rare. In the available literature, one case of coexistence of MCL and CV with cyanosis of the nose, distal parts of the extremities, and their non-crippling skin necrosis has been described [5]. In the patient described, no monoclonal gammopathy was detected either [6].

To date, cryoglobulinaemia in blood disorders has been described as secondary to Waldenström's macroglobulinaemia (WM) [7], chronic lymphocytic leukaemia [8], and indolent (slow-growing) B-cell lymphomas (which include MCL) [9]. However, the co-occurrence of MCL and cryoglobulinaemia has only been described twice so far [5, 6].

The literature also contains isolated case reports of vasculitis secondary to MCL, manifesting as acute glomerulonephritis with PR3-ANCA without necrosis, purpura, or cryoglobulinaemia [10, 11].

In addition to multiple CV symptoms, the patient also had pulmonary parenchymal lesions, splenomegaly and inconclusive test results detecting lymphoma cells in the peripheral blood, making the diagnosis of haematologic disease challenging. However, a correct diagnosis was made, enabling appropriate treatment. The halted progression of necrosis after treatment suggests that CV and its complications may have represented a paraneoplastic syndrome. Through a mechanism unknown to science, MCL induced secondary autoimmune disorders, leading to cryoglobulin production and secondary vasculitis.

Symptomatic cryoglobulinaemia is an indication to initiate therapy for low-grade lymphoma or WM [12, 13]. The presence of these abnormal proteins in a large retrospective study was considered an adverse prognostic factor for WM [14].

The mainstay of treatment for mild (arthralgia, myalgia, general symptoms) and moderate (purpura, arthritis) CV associated with HCV infection is causal treatment. In patients with

severe CV (renal involvement, nervous system involvement, skin necrosis/ulceration) associated with HCV infection, the addition of rituximab to antiviral therapy (four infusions of 375 mg/m^2 body surface area over four consecutive weeks) should be considered. Due to their unproven efficacy, other immunosuppressive drugs, such as corticosteroids, methotrexate, azathioprine, and cyclophosphamide, are not recommended for this group of patients. In other cases of CV with a known cause (e.g. HIV, HBV, malignancy), causal treatment is also recommended in the first line [2, 15].

Mild and moderate idiopathic CV require only symptomatic treatment (avoidance of low temperature, sparing lifestyle, NSAIDs), colchicine, dapsone or immunosuppressive drugs that can be used orally (methotrexate, azathioprine, low- or medium-dose corticosteroids). In more severe cases, aggressive therapy is required. Treatment is recommended as in small-vessel vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis). A combination of high-dose corticosteroids [oral prednisone at 1 mg/kg, with possible prior intravenous administration of methylprednisone at 7–15 mg/kg (maximum 1000 mg)] and oral cyclophosphamide (2 mg/kg per day; intravenous pulses 0.5–1.0 g/m^2 body surface area every four weeks for six months or according to the regimen recommended by the European Vasculitis Society (EUVAS): three intravenous pulses of 15 mg/kg (maximum 1.2 g) every two weeks, followed by 3–6 administrations every three weeks] or rituximab (four infusions of 375 mg/m^2 body surface area every week). In severe cases of CV, plasmapheresis may also be applicable [2, 15, 16].

A treatment regimen containing bortezomib may be effective in treating a patient with idiopathic CV [17]. Although bortezomib may be another effective drug in idiopathic and secondary CV, further studies on its efficacy and safety are required.

The case described in this paper presented a significant diagnostic challenge. MCL, whose main symptom was secondary CV with necrosis of the fingers, has never before been described in the literature. Moreover, the disease was not accompanied by symptoms typical of myeloproliferative disorders, such as lymphadenopathy, the constant presence of abnormal leucocytes in the blood count or monoclonal protein (typically accompanying cryoglobulinaemia caused by blood disorders). Given the rapidly progressive necrosis of the fingers, CT lesions that might suggest pulmonary involvement in vasculitis and the lack of evidence of viral infection, it was decided to initiate treatment to improve blood supply and immunosuppressive therapy. Subsequently, once the diagnosis of MCL was confirmed, lymphoma remission-inducing therapy was administered. The treatment administered led to inhibition of the progression of CV necrosis.

Conclusions

The case reported here not only presents the extremely rare clinical picture of CV secondary to MCL. It should also serve as a reminder that in cases of cryoglobulinaemic vasculitis, oncological vigilance should be maintained in the diagnostic process, in addition to considering infectious causes and primary autoimmunity.

Ethics statement

The patient consented to publishing the case report with photographs illustrating the course of the disease.

Author contributions

Authors' contributions: conception: J.B., W.J., M.K.; literature review: J.B., W.J.; data analysis: J.B.; writing of the manuscript: J.B., W.J., M.K.

Conflict of interest

The authors declare no conflict of interest.

References

1. Takada S, Shimizu T, Hadano Y, et al. Cryoglobulinemia (review). Mol Med Rep. 2012; 6(1): 3–8, doi: 10.3892/mmr.2012.861, indexed in Pubmed: 22484457.
2. Kur-Zalewska J. Cryoglobulinaemic vasculitis. Reumatologia/Rheumatology Supplements. 2016: 65–67.
3. Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. Curr Opin Rheumatol. 2013; 25(1): 10–18, doi: 10.1097/BOR.0b013e32835b15f7, indexed in Pubmed: 23196322.
4. De Vita S, Soldano F, Isola M, et al. Preliminary classification criteria for the cryoglobulinaemic vasculitis. Ann Rheum Dis. 2011; 70(7): 1183–1190, doi: 10.1136/ard.2011.150755, indexed in Pubmed: 21571735.
5. Pei S, Chen Ch, Lin S, et al. Mantle Cell Lymphoma Presented as Cryoglobulinemic Vasculitis. J Cancer Res Pract. 2020; 7(1): 41–44.
6. Andeen NK, Abdulameer S, Charu V, et al. A Diverse Spectrum of Immune Complex- and Complement-Mediated Kidney Diseases Is Associated With Mantle

Cell Lymphoma. Kidney Int Rep. 2022; 7(3): 568–579, doi: 10.1016/j.ekir.2021.12.020, indexed in Pubmed: 35257069.

7. Kyle RA, Ansell SM, Kapoor P. Prognostic factors and indications for treatment of Waldenström's Macroglobulinemia. Best Pract Res Clin Haematol. 2016; 29(2): 179–186, doi: 10.1016/j.beha.2016.08.014, indexed in Pubmed: 27825464.

8. Arora S, Levitan D, Regmi N, et al. Cryoglobulinemia in a patient with chronic lymphocytic leukemia - A case report and review of literature of renal involvement in CLL. Blood Cells Mol Dis. 2016; 60: 7–11, doi: 10.1016/j.bcmd.2016.05.009, indexed in Pubmed: 27519936.

9. Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood. 2017; 129(3): 289–298, doi: 10.1182/blood-2016-09-719773, indexed in Pubmed: 27799164.

10. Miyata KN, Siddiqi NA, Kiss LP, et al. Antineutrophil cytoplasmic antibody-positive pauci-immune glomerulonephritis associated with mantle cell lymphoma. Clin Nephrol Case Stud. 2017; 5: 9–15, doi: 10.5414/CNCS109036, indexed in Pubmed: 29043141.

11. Mhedhbi B, Chargui S, Harzallah A, et al. Proliferative glomerulonephritis and mantle cell lymphoma: a rare association. BMJ Case Rep. 2021; 14(2), doi: 10.1136/bcr-2020-238153, indexed in Pubmed: 33547121.

12. Kyle RA, Ansell SM, Kapoor P. Prognostic factors and indications for treatment of Waldenström's Macroglobulinemia. Best Pract Res Clin Haematol. 2016; 29(2): 179–186, doi: 10.1016/j.beha.2016.08.014, indexed in Pubmed: 27825464.

13. Arora S, Levitan D, Regmi N, et al. Cryoglobulinemia in a patient with chronic lymphocytic leukemia - A case report and review of literature of renal involvement in CLL. Blood Cells Mol Dis. 2016; 60: 7–11, doi: 10.1016/j.bcmd.2016.05.009, indexed in Pubmed: 27519936.

14. Gobbi PG, Bettini R, Montecucco C, et al. Study of prognosis in Waldenström's macroglobulinemia: a proposal for a simple binary classification with clinical and investigational utility. Blood. 1994; 83(10): 2939–2945, indexed in Pubmed: 8180389.

15. Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. Curr Opin Rheumatol. 2013; 25(1): 10–18, doi: 10.1097/BOR.0b013e32835b15f7, indexed in Pubmed: 23196322.

16. Mukhtyar C, Guillevin L, Cid MC, et al. European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009; 68(3): 310–317, doi: 10.1136/ard.2008.088096, indexed in Pubmed: 18413444.

17. Liu XH, Liu MX, Jin F, et al. Concomitant cryoglobulinemic vasculitis and cold agglutinin disease successfully treated with bortezomib: A case report. Medicine (Baltimore). 2019; 98(4): e14201, doi: 10.1097/MD.0000000000014201, indexed in Pubmed: 30681592.