Case Report

Severe Cryoglobulinemic Vasculitis After Cytoreductive Therapy In Waldenström’s Macroglobulinemia And Hepatitis C-Virus: A Case Report

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Abstract

Cryoglobulinämia is characterized by the occurrence of serum proteins (mostly IgM or IgG) that reversibly precipitate in vitro at temperatures < 37 °C and redissolve at body temperature. These proteins are associated with infectious (e.g. viral, particularly hepatitis C), autoimmune/connective tissue diseases, or malignancies (especially lymphoproliferative diseases). Cryoglobulinemia is usually asymptomatic but can lead to cryoglobulinemic vasculitis (CV). CV is a type of small-vessel vasculitis and a rare extrahepatic HCV manifestation. The classical histopathologic finding of CV is leukocytoclastic vasculitis (LV). CV is usually treated by a combination of immunosuppressive therapy and treatment of the underlying disease (e.g. antiviral/cytoreductive therapy). Here we report the case of a 50-year-old HCV-infected woman, who developed a severe vasculitis boost after initiation of cytoreductive therapy in the context of Waldenström’s macroglobulinemia and HCV infection. While cryoglobulinemic vasculitis has been reported as one of the extrahepatic manifestations of HCV infection and in the context of lymphoma, a de novo onset of severe cryoglobulinemic vasculitis after initiation of cytoreductive therapy is a rare event.

Keywords: Cryoglobulinemic vasculitis; Mixed cryoglobulinemic vasculitis; Waldenström’s acroaglobulinemia; Hepatitis C; Viral vasculitis; Extrahepatic manifestation; Direct-acting antiviral

Case-Summary

We present the case report of a 50-year-old HCV-infected woman with M. Waldenström who developed a severe vasculitis boost two weeks after initiation of cytoreductive therapy. The patient presented first in November 2018 to the Emergency Room of the University Hospital of Düsseldorf, Germany with typical B symptoms (fever, night sweat, weight loss) and multiple (N>20) subcutaneous swellings (infraorbital, cervical, and thoracic; maximum 5cm diameter, indolent, movable). The left half of the face was swollen, consistent with a superior vena cava syndrome. There were pale brownish hyperpigmentations...
on both legs (pretibial and above the instep). A chronic, therapy-naive hepatitis C infection (genotype 1b) was first diagnosed in 2010 in her home country (Moldavia). She had no previous history of skin disease and no other comorbidities. The patient was admitted as an inpatient to the Department of Hematology/Oncology under the suspected diagnosis of lymphoproliferative disorder. The laboratory tests showed proteinuria (3,294 mg/L), hypochromic-microcytic anemia (hemoglobin concentration 8.2 g/dl), and iron deficiency. Other abnormal laboratory findings were: β2-microglobulin: 4.57 mg/dl, IgG: 312 mg/dl, IgA: 130 mg/dl, IgM: 1,613 mg/dl. The white blood cell count, platelet count, and renal function tests were in the normal range. We carried out a CT scan (cervical, thoracoabdominal) and a cranial MRI, which showed splenomegaly, generalized lymphadenopathy, and bilateral infiltration of the sphenoidal sinus and left parotid gland. The histopathology and cytological results of the bone marrow puncture showed 10% CD19+-cells with predominant FMC7 (97%) and partial CD5 (30%)/CD23 (49%) co-expression. A kappa-restricted expression of immunoglobulin light-chains of CD19+-cells indicated presence of a clonal B-cell population. We performed a lymph node extirpation (right axilla) revealing infiltration of lymphoplasmacytic Non-Hodgkin lymphoma (NHL) with a growth fraction of about 30%. In summary, these findings were compatible with a low-grade malignant B-NHL, subtype lymphoplasmacytic NHL with light-chain restriction type kappa/IgM, classifiable as Waldenström’s macroglobulinemia.

Virologic analyses revealed HCV viremia of 7 million U/ml, genotype 1b. Laboratory tests and ultrasonography/elastometry showed no signs of advanced/chronic liver injury. Liver enzymes were within normal range with the exception of an isolated, minimal GOT-elevation.

Superior vena cava syndrome required immediate cytoreductive therapy and, considering the favourable prognostic impact of HCV therapy on the course of NHL, antiviral therapy with sofosbuvir/velpatasvir was initiated. After giving dexamethasone the first cycle of cytoreductive therapy was started with rituximab (375mg/m², 568mg absolute) and bendamustine (90mg/m²/d, d1-2). There was an increase of IgM (from 1.6 g/dl to 2.1g/dl) three days after rituximab administration. Two weeks after the first cycle of rituximab/bendamustine the patient developed fever, painful bilateral livid-erythematous maculae of the legs with bullae (Figure 1A and 1B), and Raynaud’s symptoms of the hands. We performed a biopsy (left lower leg) of one of the conspicuous lesions. Histopathologic findings proved a leukocytoclastic vasculitis with focal necrosis (Figure 1C). Laboratory findings showed a cryoprecipitate that completely resolved at 37°C. Further characterization of the cryoprecipitate demonstrated a proportion of 8.36 g/L IgM and 3.07 g/L IgG. The immune fixation proved a paraproteinemia type IgM with Bence-Jones (kappa) protein. The kappa/lambda quotient was 16.1. IgM was 1,103 mg/dl, IgG 349 mg/dl and IgA 126 mg/dl. Furthermore, there was hypocomplementemia (C3c: 64 mg/dl; C4: 6 mg/dl), and an elevated rheumatoid factor (164 IU/ml). A throat swab was positive for influenza A. Tests for HAV, HBV, tuberculosis, EBV, VZV, CMV, c-ANCA / p-ANCA, MPO and PR3 were negative. In summary, these findings were compatible with cryoglobulinemic vasculitis due to mixed cryoglobulinemia (MC).
**Figure 1.** Clinical and histological findings two weeks after the first cycle of Rituximab/Bendamustin.

(A) fluid-filled bullae on the medial left lower leg.
(B): bilateral livid-erythematous maculae with bursted bulla; notice the purple discoloration of dig. pedis IV and V (left foot), respectively III and IV (right foot)
(C): Spindle biopsy of a vasculitic lesion from the left lower leg, hematoxylin-eosin stain, light microscopy.

(1): Fibrin deposition perivascular; Furthermore: thrombosis of small vessels and destruction of the vessel wall in the upper parts of the corium (not shown).
(2): Pronounced inflammatory infiltrate perivascular (containing lymphocytes, histiocytes, neutrophil and eosinophil leukocytes) in the deep corium / subcutaneous fat tissue;
The vasculitic lesions showed serous and purulent secretion. Systemic antibiotic therapy (piperacillin/tazobactam), intensive topical ulcer treatment (with polihexanide, corticosteroids, and antibiotics), and surgical wound debridement were started. Long-term high-dose steroid therapy (100 mg prednisolone/d for four weeks) was initiated, with gradual tapering over 6 months. In parallel, antiviral therapy with sofosbuvir/velpatasvir was started and the second cycle of rituximab/bendamustine was administered. Initially, the vasculitic lesions and Raynaud’s symptoms improved, but after a short time, new vasculitic lesions appeared, accompanied by progressive ulceration (Figure 2A and Figure 2B) and a necrotic area of the

Figure 2
Left dig. ped. IV (Figure 2C). Additional prostavasin was given and plasmapheresis was performed (eleven times over a period of three weeks). After the second cycle of rituximab/bendamustine, a CT scan showed a good treatment response. We continued cytoreductive therapy (cycles 3-6 of rituximab/bendamustine, monthly intervals) and rituximab consolidation therapy (monthly). Sustained viral response was noted 12 weeks after termination of the antiviral therapy. Long-term wound care was necessary and improvement of the lesions and the necrotic area of the toe was observed, with continuing wound healing and dry gangrene of dig. pedis IV as the final result (Figure 2D, Figure 3A-C). 12 months after termination of the antiviral therapy there was no HCV-RNA detectable. Rituximab consolidation therapy was continued monthly for 2 years, and re-staging 24 months after therapy initiation showed sustained complete remission of the malignant lymphoma.

Figure 3

**Figure 3.** 11 months after the vasculitis boost. (A): left lower leg, nearly completed ulcer-healing, remaining small area of granulation tissue. (B): concluded wound healing of the right leg; note the brownish hyperpigmentation as a residuum of passed vasculitis (*). (C): final state of dry gangrene of dig. ped. IV left;
Discussion

We report a case of severe cryoglobulinemic vasculitis (CV) in a patient with Waldenström’s macroglobulinemia and long-term chronic HCV infection, developing after initiation of immunochemothepathy with rituximab and bendamustine. Chronic HCV infection is a common cause of mixed cryoglobulinemic vasculitis (MCV). In about 50% of patients with chronic HCV infection, circulating mixed cryoglobulins can be detected, but only a small proportion of these patients (10%) have clinically overt CV [1]. By inducing a state of activation of the immune system leading to an augmented proliferation of B-cell clones and the production of monoclonal IgM with rheumatoid factor activity and polyclonal IgG by directly modulating B- and T-cell function, HCV infection creates both a basis for lymphoproliferative disorders (~2.5 fold increased risk) as well as cryoglobulinemia [2-6]. The underlying immunological response in chronic HCV infection and MC/CV is complex and a topic of ongoing research. However, it is widely accepted that monoclonal IgM and polyclonal IgG bind together with HCV nucleocapsid and core antigens resulting in circulating immune complexes deposited in small-to-medium vessel walls, leading to complement activation, leukocyte recruitment, and vasculitis by micro-thrombosis and ischemic injury [7-9]. In line with this, higher concentrations of HCV-RNA have been detected in purpuric skin lesions associated with cryoglobulinemia than in normal skin [10], and elevated concentrations of HCV-RNA and anti-HCV-antibodies have also been detected in the cryoprecipitate compared to serum [11, 12]. It is important to mention that we did not perform direct histopathological detection of HCV-RNA or anti-HCV-antibodies. The predilection sites of CV are the lower extremities or areas exposed to pressure, due to stasis (lower pH) and lower temperature, which enhances cryoglobulin precipitation. The length of HCV infection seems to be directly related to the risk of developing MC and CV, which also could have played a role in our case with a long-term untreated HCV infection [13]. Altogether, it seems reasonable to strive for viral clearance as a main target in HCV-associated MC in order to down-regulate the B-cell triggered antibody production. Several studies of patients with HCV-associated CV have shown high rates of clinical vasculitis remission after DAA therapy [14-16]. International guidelines recommend HCV treatment to be started for patients with clinically significant extrahepatic manifestations, like cryoglobulinemic vasculitis [17]. Nevertheless, MC can persist, relapse, or reappear in some patients after sustained viral response (SVR) [18]. Recent reports showed that cryoglobulinemic organ manifestations (e.g. glomerulonephritis) could relapse despite SVR in the setting of HCV infection due to persistent disorder of memory B-cell clones, even after multiple immunosuppressive therapies, including rituximab [19]. In a long-term prospective study, 20% of patients still had positive test results for cryoglobulins two years after successful DAA treatment and 11% had relapse of vasculitis that included severe organ damage and death [20]. These findings may be explained by a delay in the clearance of cryoglobulins from the circulation and/or the persistence of the RF-producing memory B-cell clones independent of the viral trigger [20]. Rituximab (+/- plasmapheresis in fulminant cases) is used in patients with persistent or recurrent MCV after HCV eradication [21]. Another possible explanation for the persistence of cryoglobulins and CV despite viral clearance is more advanced liver damage with decreased ability to clear ICs [21]. Of note, MC is more frequent in older subjects, females, and patients with liver cirrhosis [22, 23]. In our case, there were no signs (clinical, imaging, or laboratory) of advanced chronic liver parenchymal damage. Some authors suggested that persistence of MC or CV despite viral clearance should trigger a search for a different underlying condition, especially unrecognized B-cell lymphoma [24].

Waldenström Macroglobulinemia (WM) is a malignant, low-grade B-cell clonal disorder characterized by lymphoplasmacytic bone marrow infiltration associated with the presence of monoclonal IgM. The overall risk of NHL in patients with HCV-associated MC is estimated to be 35 times higher than in the general population [25]. Accordingly, B-cell depletion therapy is considered as first-line therapy in the case of CV with HCV and lymphoproliferative diseases [26]. Rituximab, a B-cell depleting antibody directed against CD20, is a potentially effective agent in MC and showed better efficacy than conventional treatment (i.e. glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) in CV [27, 28]. Studies with HCV-positive patients showed that the addition of rituximab to pegIFN/ribavirin resulted in a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [29]. In summary, there seems to be a strong rationale for disease control with rituximab, with or without plasmapheresis, before initiation of antiviral therapy in patients with severe vasculitis (e.g. extensive skin disease, intestinal ischemia) [26]. In the present case, it remains unclear why the patient suffered a severe and de novo vasculitis after initiation of the cytoreductive/immunomodulatory therapy with rituximab/bendamustine. Due to the temporal link between rituximab/bendamustine therapy and the onset of vasculitis, the cytoreductive therapy suggests itself as a trigger. In HCV-associated CV, rituximab was identified to form a complex with RF-positive IgM, leading to accelerated cryoprecipitation with severe systemic reactions [30]. The authors identified high baseline levels of cryoglobulin, a high dosage of rituximab (1000 mg), and a high level of complement activation as independent risk factors. The authors suggested to use a low-dose rituximab therapy and plasma exchange before full-dose rituximab administration if there is low C4 (as a marker of complement activation) or high cryoglobulinemia. Our patient had a low baseline level of C4 (3 mg/dl). However, he received a low dose of rituximab (568 mg), which is usually considered safe. It should be noted that we did not perform quantification
or qualitative analyses of the cryoprecipitate before the onset of vasculitis. Rituximab is known to induce a transient paradoxical increase ("flare") in IgM serum levels (in 30-70% of patients with Waldenström’s macroglobulinemia, due to B-cell lysis [31]. In the present case, IgM increased from 1631 mg/dl to 2083 mg/dl after the first cycle of rituximab/bendamustine. Two weeks later, IgM dropped to 1418 mg/dl. It should be mentioned that rituximab also represents a high affinity binding partner for C1q and partially mediates its therapeutic effects by activating the classical pathway of complement [32], which is another potential trigger of CV in this case, but there are only three cases reported in the literature [35]. Considering the number of influenza cases per year, CV due to influenza seems to be a very rare event. Nevertheless, we cannot rule it out as a confounding variable in the present case.

In summary, several pathophysiological conditions (presence of IgM with RF-activity, initial IgM release after rituximab administration, persistence of HCV-antigen driven immunostimulation, complement activation via direct rituximab effects) may have contributed to the vasculitis flare after initiation of cytoreductive and antiviral therapy in the reported case.

Therefore, we would like to emphasize that in HCV-infected patients clinicians should actively search for signs of active or past vasculitis (e.g. hyperpigmentation of the lower body parts) and pay attention to the possible development of CV after therapy initiation, even if a low-dose rituximab regimen is chosen. Antiviral therapy (against various possible triggering antigens), immunomodulatory therapy (e.g. B-cell depletion, immunosuppressors, etc.), or combined treatment may have a pathophysiological rationale in individual cases.

Conclusion

This report highlights a rare case of severe cryoglobulinemic vasculitis after initiation of a rituximab-based cytoreductive therapy, probably due to a mixed underlying cause (HCV- and lymphoma-associated). Parallel employment of antiviral and cytoreductive therapy should be considered if there are signs of active or past CV, particularly in view of the multifactorial genesis of CV, the lack of precise knowledge of the leading disease pathobiology in the individual patient, and the good compatibility of commonly used pan-genotypic DAA-regimes with rituximab.

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