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Mixed cryoglobulinemic glomerulonephritis and vasculitis in primary Sjögren's syndrome

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ABSTRACT

Introduction: Cryoglobulinemia is a condition where complexes of one or more different classes of immunoglobulins precipitate at low temperatures and become soluble again at higher temperatures. Cryoglobulins are typically categorized as types I to III, based on their immunoglobulin composition. Mixed cryoglobulinemia (type II and III) is most often associated with constitutional symptoms, such as fatigue, myalgia, arthralgia, sensory or motor changes (peripheral neuropathy) and palpable purpura (cutaneous vasculitis). Twenty to thirty percent of the affected patients suffer from membranoproliferative glomerulonephritis.

Case Presentaion: We discuss a case of a 45-year-old woman with a history of Sjögren's syndrome and mixed cryoglobulinemia who presented with acute renal failure, nephritic syndrome, vasculitis-like rash on the legs and non-healing skin ulcer. Further investigations confirmed type II mixed cryoglobulinemia associated with cutaneous leukocytoclastic vasculitis and membranoproliferative glomerulonephritis leading to end-stage renal disease (ESRD).

Conclusion: Mixed cryoglobulinemia secondary to primary Sjögren's syndrome (pSS) is rare and reported in 22.5% of cases of non-infectious cryoglobulinemic glomerulonephritis. Long-term renal prognosis is good with only 9% of these patients evolving to ESRD. Nevertheless, the long-term overall survival is poor with severe infections as the leading cause of death.

Case Report

Implication for health policy/practice/research/medical education:
We discuss the case of a 45-year old Caucasian woman with a history of Sjögren's syndrome and mixed cryoglobulinemia. Diagnostic tests for malignancy (lymphoproliferative or other) and hepatitis C infection were repeatedly negative. Cryoglobulins are most likely associated with Sjögren's syndrome. Kidney as well as skin biopsy samples showed presence of cryo-plugs and cryoglobulinemic glomerulonephritis and vasculitis respectively. We valued this case attributive as it features a juxtaposition of kidney and skin biopsies in a rare case of long-existing Sjögren's disease and secondary cryoglobulin-induced skin ulcer and fulminant glomerulonephritis leading to end-stage renal disease.

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Introduction

Cryoglobulinemia is a condition where complexes of one or more different classes of immunoglobulins precipitate at low temperatures and become soluble again at higher temperatures. Cryoglobulins are typically categorized as types I to III, based on their immunoglobulin composition as described by Brouet and colleagues (1). In type I, the cryoglobulin consists of a single monoclonal immunoglobulin class, usually generated by a lymphoproliferative malignancy (e.g. multiple myeloma). In type II cryoglobulinemia, the cryoglobulins are composed of at least two immunoglobulins, one of them a monoclonal antibody directed against polyclonal immunoglobulin G (IgG). This is most commonly seen in combination with monoclonal immunoglobulin M (IgM) which possesses rheumatoid factor (RF) activity. Type II cryoglobulins are often associated with chronic viral infections, particularly hepatitis C virus (HCV) infection (2).

In type III cryoglobulinemia, both immunoglobulin

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components are polyclonal IgG and polyclonal IgM. These cases are often secondary to autoimmune disorders, but have also been associated with infections (i.e. chronic hepatitis B, bacterial endocarditis) or other immunologic disorders (i.e. post-infectious glomerulonephritis) (1-3).

Mixed cryoglobulinemia (type II and III) is most often associated with constitutional symptoms, such as fatigue, myalgia, arthralgia, sensory or motor changes due to peripheral neuropathy and palpable purpura as a result of cutaneous vasculitis (4). Twenty to thirty percent of the affected patients suffer from membranoproliferative glomerulonephritis (GN) (5).

Case Presentation

A 45-year-old Caucasian woman presented to the emergency department with weight gain of 10 kg in 4 days and bilateral swollen legs. She had a history of primary Sjögren's syndrome (pSS) and mixed cryoglobulinemia with no evidence for underlying viral infection in 2015. At that time, the arthralgia and rash responded well to colchicine. Her father had died of GN at the age of 50 in Uzbekistan.

A vasculitis-like rash on the lower extremities had developed anew over the last two months before presentation. Two weeks prior to admission, she developed an ulcer on the left ankle, which did not heal despite local treatment.

She reported diminished diuresis, one single episode of epistaxis, orthopnea, and cough with white-green sputa, nausea, xerostomia and xerophthalmia.

On admission, clinical examination showed signs of mild to moderate volume overload; pulmonary bibasal crepitations, elevated jugular venous pressure and bilateral ankle edema. There was a bilateral rash consisting of non-blanching petechiae. Arterial blood pressure was 166/99 mm Hg, pulse rate was 95 beats per min and oxygenation measured by pulse oximetry was 98% at ambient air room pressure. Laboratory results showed thrombopenia 34 × 10^3/µL, elevated serum creatinine (3.3 mg/dL [291.7 µmol/L]), and urea levels (167 mg/dL [27.8 mmol/L]), decreased bicarbonate level (11.1 mEq/L) and mild hypokalemia 3.1 mEq/L. Serum protein concentration was unchanged (7.9 mg/dL [79 g/L]). Protein electrophoresis on the serum showed hypogammaglobulinemia at the time of diagnosis. Earlier serum electrophoresis in 2015 showed a polyclonal increase in the gamma region. Blood analysis showed low complement levels with total hemolytic complement CH50 <10.0 U/mL [normal 31.6-57.6], C3 0.21 g/L [normal 0.90-1.80] and virtually undetectable C4 [<0.02 g/L; normal 0.10-0.40]. Urinalysis results showed a 24-hour proteinuria of 1.17 gram and an active urinary sediment with microscopic hematuria 365/µL and leukocyturia 68/µL. Auto-immune serology was positive for RF, anti-nuclear factor (ANF), anti-Sjögren's-syndrome-related antigen A (anti-SSA) and anti-Scl 70. Renal sonography finding was normal.

Further investigations confirmed mixed cryoglobulinemia with 2 clonal paraproteins IgM, one in the ß2 region and one in the γ-region (combined estimated at 1.2 g/L). HCV serology and polymerase chain reaction (PCR) analysis were negative. Lymphoproliferative or other malignancy were ruled out with bone marrow analysis (no clonal population; no myelodysplastic features) and positron emission tomography-computed tomography (PET-CT).

A renal biopsy was performed with evidence of membranoproliferative GN (Figure 1). Prior skin biopsy in the edge of the non-healing malleolar ulcer showed a cryoglobulinemic vasculitis (Figure 2).

Five days after admission therapy was initiated with rituximab (anti-CD20 antibody; 2 doses of 1 gram with 2 weeks interval) and high dose steroids (pulse doses of 500 mg methylprednisolone [equivalent to 625 mg

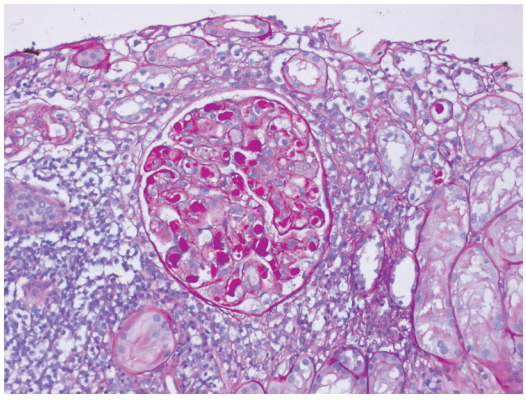

Figure 1. Renal biopsy, PAS with diastase, 200x magnification. Enlarged glomeruli with mild to moderate mesangial hypercellularity. PAS stain demonstrates PAS positive protein thrombi or "cryo plugs" which were IgG and IgM positive (IgG > IgM) on immunofluorescence studies (not shown).

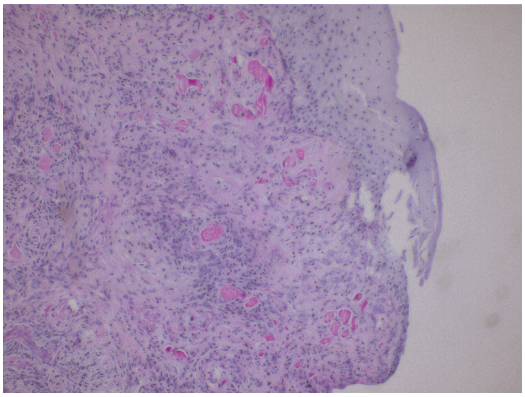

Figure 2. Skin biopsy, PAS with diastase, 50x magnification. Presence of intravascular PAS-positive protein thrombi or "cryo plugs" in the skin.

prednisolone] on 3 consecutive days, followed by 48 mg methylprednisolone [equivalent to 60mg prednisolone] daily), aiming to deplete the B-cells and consequently the production of cryoglobulins (6). Although renal biopsy showed only mild chronic damage, renal function did not recover under aforementioned therapy, despite negativation of cryoglobulins, depletion of B-lymphocytes in blood ($0.360 \times 10^3/mm^3$) and in bone marrow repeat (<1%). Renal replacement therapy was started 10 days after admission due to therapy resistant fluid overload and oligo-anuria.

The kidney function did not recuperate initially. A repeat renal biopsy four months after the first biopsy demonstrated acute tubulointerstitial nephritis (TIN) without evidence for residual cryoglobulinemic GN. The chronic interstitial damage was estimated to be 33%. The interstitial lymphocytic infiltrate consisted purely of CD3 positive T-cells (after rituximab treatment). Co-trimoxazole (trimethoprim-sulfamethoxazole), used in the secondary prevention of infections with high dose immunosuppressants, was discontinued upon receiving these results, suspecting co-trimoxazole toxicity might be causing the delay in the expected kidney function recuperation. Hereupon the serum creatinine slowly decreased, allowing to reduce hemodialysis sessions from thrice to twice weekly after four months and to discontinue hemodialysis entirely after 10 months (14 months after the onset and treatment of the cryoglobulinemic glomerulonephritis).

Discussion

We discussed the case of a 45-year-old Caucasian woman with a history of Sjögren's syndrome and mixed cryoglobulinemia. She presented with volume overload due to acute renal failure and a non-healing ulcer on the ankle, both as a result of cryoglobulinemia. Despite appropriate treatment, end-stage renal disease (ESRD) ensued and renal replacement therapy was initiated. Diagnostic tests for malignancy (lymphoproliferative or other) and hepatitis C infection were repeatedly negative. Cryoglobulins are most likely associated with Sjögren's syndrome.

Kidney as well as skin biopsy samples showed presence of cryo-plugs and cryoglobulinemic GN and vasculitis respectively.

In the early 1990's there were important advances in serologic diagnosis of HCV infection. This led to the discovery that 60% to 90% of mixed cryoglobulinemia cases were related to HCV infection. Since then, many series have investigated HCV-related mixed cryoglobulinemic disease. Noninfectious mixed cryoglobulinemic vasculitis on the other hand remains poorly studied with only small series documenting renal involvement.

Zaidan and colleagues retrospectively investigated 80 cases of mixed cryoglobulinemic GN that was not related to HCV infection. Mixed cryoglobulinemia was secondary to pSS alone in 22.5% of cases. The overall prevalence of pSS was 32.5% (7).

In the aforementioned case series, only 5.1% of cases required dialysis at presentation and 9% reached ESRD during follow-up (7). This case thus presents a rare fulminant course of cryoglobulinemic GN.

It is thought that the high concentrations of cryoglobulins and the consequent aggregates and circulating immune complexes overwhelm the normal phagocytic system activity. This then leads to accumulation of cryoglobulin complexes in the serum, which in turn leads to deposition of these immune complexes in target tissues where they induce disease (8).

At the level of the kidney, this leads to membranoproliferative GN (as seen in 92.5% of cases in the aforementioned series) or less frequently to mesangial proliferative GN (seen in 7.5% of cases). Membranoproliferative GN is characterized by mesangial hypercellularity, capillary-wall remodeling with double contours and focal to diffuse endocapillary leukocyte infiltration. Intraluminal thrombi were observed in 47.8% of biopsy specimens, predominantly in patients with pSS. Interstitial fibrosis and tubular atrophy were reported in 61.2% of cases, but in less than 25% of cases classified as moderate to severe. Granular immune deposits were localized in the glomerular capillary wall and less frequently in the mesangium, staining mostly for IgG and IgM, and less frequently for IgA. C3 staining was observed in all cases, but was interestingly negative in the presented case. This demonstrates that C3 staining in subendothelial and capillary luminal cryoglobulins is frequent, but can be absent (7,9,10).

Patients with noninfectious mixed cryoglobulinemic GN have a poor long-term survival. Almost 25% of patients in the case series of Zaidan et al had died at last follow up (mean follow up ±SD) = 51 ± 54 months), and more than half did so during the first year after renal biopsy. Severe infections were the leading cause of death. During follow-up 8.9% of patients developed new-onset hematologic malignancy (B-cell non-Hodgkin lymphoma and Waldenström macroglobulinemia). Previous results suggest that essential mixed cryoglobulinemia may indicate a pre-B-cell lymphoma state, and thus should be closely monitored (e.g. complete blood count, serum electrophoresis, etc) (3,9,11-13).

The repeat biopsy demonstrated disappearance of the cryoglobulinemic GN but also the presence of acute TIN with an estimated 33% chronic interstitial damage. The interstitial lymphocytic infiltrate consisted purely of CD3 positive T-cells. Absence of B-cells in the infiltrate

is most likely explained by the previous treatment with rituximab and subsequent depletion of B-cells in bone-marrow, blood and kidney. Nevertheless, we found these findings quite surprising, as the patient was still receiving glucocorticoids (prednisone 10 mg daily; in the context of the tapering scheme after initial pulse dose) at the time of the second biopsy. Chronic TIN is the most common renal manifestation of Sjögren's syndrome, though patients rarely become overtly symptomatic (14). There are few data concerning the optimal treatment of interstitial nephritis in pSS. Seeing as the patient was already receiving glucocorticoids, other options should be explored (e.g. azathioprine or cyclophosphamide) (15). In this case, we opted to discontinue co-trimoxazole (used in secondary prevention of infections in the context of iatrogenic immunosuppression), to rule out drug related nephrotoxicity before exploring other immunosuppressive treatments. Hereupon the patient's kidney function recuperated slowly, but sufficiently enough to discontinue hemodialysis fourteen months after the initial presentation and treatment of the cryoglobulinemic glomerulonephritis.

Conclusion

We discussed the case of a 45-year old Caucasian woman with a history of Sjögren's syndrome and mixed cryoglobulinemia. She presented with volume overload due to acute renal failure and a non-healing ulcer on the ankle, both as a result of cryoglobulinemia. Despite appropriate treatment, ESRD ensued and renal replacement therapy was initiated.

Diagnostic tests for malignancy (lymphoproliferative or other) and hepatitis C infection were repeatedly negative. Cryoglobulins are most likely associated with Sjögren's syndrome.

Kidney as well as skin biopsy samples showed presence of cryo-plugs and cryoglobulinemic.GN and vasculitis respectively. We valued this case attributive as it features a juxtaposition of kidney and skin biopsies in a rare case of long-existing Sjögren's disease and secondary cryoglobulin-induced skin ulcer and fulminant GN leading to ESRD.

Authors' contribution

IVA and BM were the principal investigators of the study. IVA, TM, ES, IV and BM were included in preparing the concept and design. IV and ES performed essential technical investigations. BM and TM revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Written informed consent was obtained from the concerning patient after reading the case report manuscript.

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