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Mixed cryoglobulinemia; a rare presentation of Waldenström macroglobulinemia

Catarina Isabel Ribeiro[1*], Clara Santos[1], Clara Almeida[1], Teresa Melo[2], David Tente[3], João Carlos Fernandes[1]

[1]Nephrology Department, Vila Nova de Gaia-Espinho Hospital Center, Vila Nova de Gaia, Porto, Portugal
[2]Clinical Hematology Department, Vila Nova de Gaia-Espinho Hospital Center, Vila Nova de Gaia, Porto, Portugal
[3]Pathologic Anatomy Department, Vila Nova de Gaia-Espinho Hospital Center, Vila Nova de Gaia, Porto, Portugal

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ABSTRACT

Type II mixed cryoglobulinemia is a systemic disease mediated by immune complexes. Renal involvement is present in almost one third of the cases and the membranoprolifer-ative pattern is the most common histological presentation. In turn, in Waldenström macroglobulinemia, renal impairment is rare, with few cases of associated cryoglobu-linemia being reported. The authors present the case of a patient with type II mixed cry-oglobulinemia associated with Waldenström macroglobulinemia diagnosis.

Case Report

Implication for health policy/practice/research/medical education:
Type II mixed cryoglobulinemia is a systemic disease mediated by immune complexes and renal involvement is present in almost one third of the cases. In turn, in Walden-ström Macroglobulinemia, renal impairment is rare, with few cases of associated cryo-globulinemia being reported. The authors present the case of a patient with type II mixed cryoglobulinemia associated with Waldenström Macroglobulinemia, and empha-size the idiosyncrasy of clinical presentation and the importance of a systematic and methodical approach in the etiological screening of cryoglobulinemia.

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Introduction

Type II mixed cryoglobulinemia is a systemic disease mediated by immune complexes. Renal involvement, present in about 20 to 30% of the cases, appears most often as the result of immune complex deposition, with membranoproliferative glomerulonephritis (MPGN) as the most common pattern of histological presentation (1).

MPGN represents 7% to 10% of all glomerular diseases confirmed by renal biopsy and is characterized by the presence of mesangial hypercellularity and endocapillary proliferation with thickening of capillary loops, sometimes producing a double contour appearance (2). Its new classification, proposed by Sethi et al in 2011 is based on both pathophysiological mechanisms and immunofluorescence, suggesting the categorization of MPGN into three etiologies, namely immune complex-mediated, complement-mediated and negative immunofluorescence (3). In immune complex-mediated MPGN, immune complex deposition may be due to; chronic infections driven by persistent antigenemia, secondary autoimmune disease, high levels of immune complexes and dysproteinemia associated with monoclonal gammopathy (4,5). All these etiologies can be associated with cryoglobulinemia (6).

Mixed cryoglobulinemia, is more common on females (3:1), and by itself, considered as a rare disease and its true prevalence remains unknown. Mixed cryoglobulinemia is probably a multifactorial and multistep process. Its' etiopathogenesis is not completely understood. Nevertheless, hepatitis C virus infection, together with the contribution of environmental and/or genetic factors, has been identified as some of the main causes. (7) In type

*Corresponding author: Catarina Isabel Correia Dias Ribeiro,
Email: catarina.isabel.ribeiro@gmail.com, catarina.dias.ribeiro@chvng.min-saude.pt

II mixed cryoglobulinemia, the cryoprecipitable immune complexes are composed of polyclonal IgGs, the auto-antigens, and monoclonal IgMs, the auto-antibodies. Clinical features include the involvement of kidneys, skin, lings, liver, endocrine glands and central nervous system. Diagnostic is based on clinical and laboratorial finding and relies on high clinical suspicion. Cutaneous symptoms such as purpura, mixed circulating cryoglobulins and C4 hypocomplementemia are some indicators of disease. (6,8)

Case Presentation

The authors present the case of a Caucasian female patient with 72 years old, referred to nephrology clinic due to proteinuria and kidney failure. Known pathological history included hypertension, osteoporosis and peripheral venous insufficiency. Patient was medicated with amlodipine, lisinopril, carvedilol, furosemide, cholecalciferol and bioflavonoids.

Six years ago, patient was diagnosed with rheumatoid arthritis following the investigation of arthralgias of the lower limbs and was medicated with methotrexate.

Three years after rheumatoid arthritis diagnosis, patient developed a skin rash, with purpuric painless and non-pruritic characteristics, with infracentimetric dimensions, especially on the upper limbs and face, spontaneously resolved after a few weeks. Analytical results showed normochromic normocytic anemia (hemoglobin 11.5 g/dL) with platelets, white blood cells and differential count within normal range. The erythrocyte sedimentation rate was 18 mm/H and C-reactive protein was less than 0.50 mg/dL. Renal function was normal, with serum creatinine 0.90 mg/dL and protein-creatinine ratio in sporadic urine sample of 0.80 g/g. Urine sediment did not show erythrocyturia or leukocyturia.

Further evaluation with immunological study identified a pronouncedly increased rheumatoid factor (1649 IU/mL), with negative results for anti-CCP, antinuclear antibodies including anti-SSA and anti-SSB, anti-dsDNA, anti-neutrophil cytoplasmatic antibodies, anti-cardiolipin and anti-beta-2 glycoprotein antibodies. Serum complement component 4 (C4) was diminished (8.7 mg/dL) and C3 was normal (89.1 mg/dL). Serum immunofixation identified an IgM kappa monoclonal gammopathy and immunofixation urine detected a monoclonal kappa light chain.

The study of hematological disease was carried out, excluding lymphoproliferative and plasmocytic diseases; bone marrow biopsy showed rare lymphocytes, with a slightly increased number of plasma cells (less than 5%); skeletal radiography excluded lytic lesions; and the thoraco-abdominopelvic computed tomography (CT) showed no evidence of adenopathy or organomegalies.

Three years later, the patient was referred to nephrology consultation due to nephrotic proteinuria and kidney failure. At first presentation, patient reported severe asthenia, anorexia, bilateral lower limb edema and purpuric lesions in lower limbs with painful ulcers in the right tibiotarsal region. She denied urinary, respiratory, gastrointestinal and musculoskeletal symptoms. There was no history of potential nephrotoxic drugs use. On physical examination, she was hypertensive (blood pressure 167/79 mm Hg), with bilateral lower limb edema up to the knee, purpuric rash in lower limbs with three necrotic ulcers in the right tibiotarsal region. Remaining examination was unremarkable.

Blood tests revealed worsening of anemia (hemoglobin 10.8 g/dL) and renal function (serum creatinine 1.29 mg/dL) and confirmed nephrotic proteinuria, with protein-creatinine ratio in sporadic urine sample of 4.60 g/g. Urine sediment showed 2-5 leukocytes/per field and 2-5 erythrocytes/per field. Further evaluation identified type II mixed cryoglobulins, with detection of polyclonal IgG and monoclonal IgM kappa. C4 remained low and C3 was normal. The remaining immunological study was normal. Serologies for HIV and hepatitis B and C were negative and PCR HCV was undetectable. Bladder-kidney ultrasound was normal. Histological study of necrotic skin ulcers showed perivascular lymphocytic inflammatory infiltrate, presence of polymorphonuclear cells, fibrinoid necrosis of the wall, in a single vessel and neutrophil karyorrhexis.

Percutaneous renal biopsy was performed and light microscopy revealed the presence of two ischemic glomeruli and ten lobulated glomeruli with proliferation and global endocapillary hypercellularity, thickening of capillary loop walls and double membrane; no spikes or holes and no evidence of atrophy or findings compatible with of acute tubular necrosis; no signs of interstitial fibrosis or inflammatory infiltrate; vessels without morphological changes; negative for Congo red (Figure 1 A,B). Direct immunofluorescence showed weak positivity (1+) for anti-kappa and lambda light chain antibodies and for the anti-C3 antibody in the loops and mesangial space; positivity (2+) for anti-fibrinogen and anti-IgM antibodies and (3+) for the granular, global and diffuse anti-IgG antibody, present in the glomerular capillary walls and in the mesangium; negative result for anti-albumin and anti-IgA antibodies.

Electron microscopy documented diffuse fusion of podocyte pedicels, mesangial and endocapillary proliferation with mesangial interposition and duplication of the basement membrane of the capillary loops; it also showed subendothelial immune-type deposits.

In subsequent investigation, serum immunofixation was positive again for IgM kappa and urinary immunofixation was positive again for kappa light chain and a new

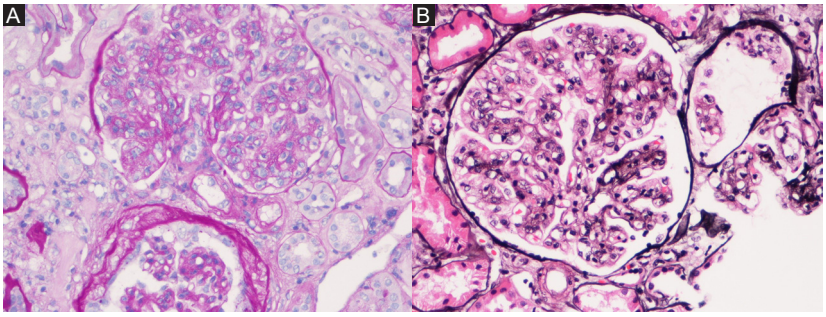

Figure 1. (**A**) Light microscopy, with periodic acid Schiff stain showing lobulated glomeruli with proliferation and global endocapillary hypercellularity (×200). (**B**) Light microscopy, with silver staining showing lobulated glomerulus, with global thickening of capillary loop walls and double membrane (×250)

IgM kappa. Free kappa/lambda ratio was 7.38 and the monoclonal component was 0.41 g/dL. Thoraco-abdominopelvic CT documented bilateral pleural effusion and small volume pericardial effusion, without adeno or organomegalies. Skeletal radiography did not show lytic lesions. She repeated bone biopsy showed a monoclonal B population. Therefore, the diagnosis of Waldenström macroglobulinemia (WM) was established and the patient completed immunosuppressive therapy with rituximab, cyclophosphamide and dexamethasone protocol.

The patient reached partial remission criteria, maintaining positive serum and urinary immunofixation but with a reduction of the monoclonal component by more than 50%. Two years after the end of treatment, the patient is clinically stable, asymptomatic, with hemoglobin 11.9 g/dL, serum creatinine 1.43 mg/dL and proteinuria of 161 mg/24 hours urine and a urinalysis with mild leukocyturia.

Discussion

WM is a malignant lymphoproliferative disorder that is characterized by bone marrow infiltration, with monoclonal production of IgM lymphocytes.

In the last decade, several authors have corroborated the association of monoclonal processes with the membrane-proliferative histological pattern. (9) Based on the 4th Edition of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, Ott et al documented that the hematological disorder most often associated with MPGN was monoclonal gammopathy of undetermined significance, followed by B-cell lymphoma, WM, chronic lymphocytic leukemia and multiple myeloma. (10) Given the emergence of an increasing number of cases, it was assumed that dysproteinemia may act as a mechanism that triggers the deregulation of the alternative complement pathway (9,11).

However, findings of an association of WM and a membrane-proliferative pattern described in type II mixed cryoglobulinemia remain scarce. Currently, it is known that in WM, renal involvement may occur in association with immune-mediated glomerulonephritis due to IgM deposition or associated with cryoglobulinemia. Although cryoglobulinemia is a rare manifestation of WM (described in 10% of cases), its possibility should not be overlooked. (12-14)

WM is characterized by a relatively indolent course. However, in some cases, the disease is more aggressive and is associated with a worse prognosis (9,12,15). Mixed cryoglobulinemia treatment depends on the treatment of the underlying pathology. Indications for early treatment in WM are mainly due to the presence of cytopenias, adeno or organomegaly, symptomatic hyperviscosity, neuropathy, amyloidosis and cryoglobulinemia; in these cases, some authors recommend combining cyclophosphamide with rituximab.

Conclusion

The authors describe a rare presentation of WM with hematological impairment, renal impairment, and with skin lesions. In the literature, the appearance of dermatological lesions is uncommon, reported in less than 3% of the cases at the beginning (9,16,17). This case is also illustrative of the usefulness of percutaneous renal biopsy in the diagnosis of early onset of hematological dysproteinemias. In addition, investigating the causes of cryoglobulinemia was of interest due to the visible impact on the therapeutic approach and subsequent prognosis. The authors emphasize the idiosyncrasy of clinical presentation and highlight the importance of a systematic and methodical approach in the etiological screening of cryoglobulinemia.

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Authors' contribution

CIR is the fist and main author; she prepared, wrote and reviewed the majority of this manuscript. CS is the second author; she participated in the clinical management of the patient reported and she collaborated too in review of this manuscript. CA, TM, DT and JCF participated in the clinical and anatomopathological approach and management of this case.

Conflicts of interest

The authors report no conflict of interest.

Ethical issues

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. Written informed consent was obtained from the patient for publication of this report.

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References

1. Beddhu S, Bastacky S, Johnson JP. The clinical and morphologic spectrum of renal cryoglobulinemia. Medicine (Baltimore) 2002;81:398. doi: 10.1097/00005792-200209000-00005.
2. Smith KD, Alpers CE. Pathogenic mechanisms in membranoproliferative glomerulonephritis. Curr Opin Nephrol Hypertens. 2005;14:396. doi: 10.1097/01.mnh.0000172729.60122.f9
3. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. Semin Nephrol. 2011;31:341. doi: 10.1016/j.semnephrol.2011.06.005
4. Fakhouri F. Clinical approach to primary membranoproliferative glomerulonephritis. Nephrol Ther. 2016;12 Suppl 1:S65-9. doi: 10.1016/j.nephro.2016.01.008
5. Zand L, Fervenza FC, Nasr SH, Sethi S. Membranoproliferative glomerulonephritis associated with autoimmune diseases. J Nephrol. 2014;27:165. doi: 10.1007/s40620-014-0049-0
6. Alpers CE, Smith KD. Cryoglobulinemia and renal disease. Curr Opin Nephrol Hypertens. 2008;17:243. doi: 10.1097/MNH.0b013e3282f8afe2.
7. Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. Lancet. 2012;379:348. doi: 10.1016/S0140-6736(11)60242-0.
8. Karras A. Renal involvement of cryoglobulinemia. Nephrol Ther. 2018;14(2):118-26. doi: 10.1016/j.nephro.2018.02.003.
9. Antón-Vázqueza V, Torrecillab IG, Gallegoc MG, Henaod VP. Waldenström macroglobulinemia presenting as cryoglobulinemic type II membranoproliferative glomerulonephritis. Nefrologia. 2018;38:439-41. doi: 10.1016/j.nefroe.2018.03.006.
10. Ott G, Balague-Ponz O, Leval L, Jong D, Hasserjian RP, Elenitoba-Johnson KS. Commentary on the WHO classification of tumors of lymphoid tissues: indolent B cell lymphomas. J Hematop. 2009;2(2):77-81. doi: 10.1007/s12308-009-0047-7.
11. Sethi S, Zand L, Leung N, Smith RJ, Jevremonic, D, Herrmann S, et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. Clin J Am Soc Nephrol. 2010;5:770-82. doi: 10.2215/CJN.06760909.
12. Kim YL, Gong SJ, Hwang YH, Joo JE, Cho YU, Lee JA, et al. Waldenstrom macroglobulinemia with CD5+ expression presented as cryoglobulinemic glomerulonephropathy: a case report. J Korean Med Sci 2011;26:824-8. doi: 10.1016/j.nefroe.2018.03.006.
13. Kratochvil D, Amann K, Bruck H, Buttner M. Membranoproliferative glomerulonephritis complicating Waldenström's macroglobulinemia. BMC Nephrol. 2012;13:172. doi: 10.1186/1471-2369-13-172.
14. Matignon M, Cacoub P, Colombat M, Saadoun D, Brocheriou I, Mougenot B, et al. Clinical and morphologic spectrum of renal involvement in patients with mixed cryoglobulinemia without evidence of hepatitis C virus infection. Medicine (Baltimore) 2009;88:341-8. doi: 10.1097/MD.0b013e3181c1750f.
15. Veltman GA, van Veen S, Kluin-Nelemans JC, Bruijn JA, van Es LA. Renal disease in Waldenstrom's macroglobulinaemia. Nephrol Dial Transplant 1997;12:1256. doi: 10.1093/ndt/12.6.1256.
16. Dimopoulos MA, Gertz MA, Kastritis E. Update on treatment recommendations from the fourth international workshop on Waldenström's macroglobulinemia. J Clin Oncol. 2009;27:120-6. doi: 10.1200/JCO.2008.17.7865
17. Gressier L, Hotz C, Lelièvre JD, Carlotti A, Buffet M, Wolkenstein P, et al. Cutaneous macroglobulinosis: a report of 2 cases. Arch Dermatol. 2010;146:165. doi: 10.1001/archdermatol.2009.359