IMAGES IN RHEUMATOLOGY

A rare association of cryoglobulinaemic vasculitis and granulomatosis with polyangiitis treated with a short course of glucocorticoids combined with cyclophosphamide and rituximab

Silva A[1*], Costa C[2*], Godinho I[2], Jorge S[2], Correia L[3], Boavida J[3], Vasconcelos P[4], Theias R[3], Janeiro J[5], Lopes JA[2], Romeu JC[7], Fonseca JE[7], Ponte C[7], Nogueira E[6]

BACKGROUND

Granulomatosis with Polyangiitis (GPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), related with the presence of proteinase 3 (PR3)-ANCA[1,2]. Cryoglobulinaemic vasculitis (CV) is caused by cryoglobulin immune-complex deposits that precipitate *in vivo* at temperatures of less than 37ºC[3]. Both diseases affect small- to medium-sized vessels and are characterized by inflammatory infiltrates and destruction of vessel walls.[1,3] Although GPA and CV have different pathogenesis, their association has been documented in very few case reports[3,4].

* Both authors contributed equally to this work

[1] Serviço de Reumatologia, Centro Hospitalar e Universitário Lisboa Norte - ORCID: https://orcid.org/0000-0003-4064-1198; [2] Serviço de Nefrologia e Transplantação Renal, Centro Hospitalar e Universitário Lisboa Norte - ORCID: ORCID: https://orcid.org/0000-0002-6468; [3] Serviço de Anatomia Patológica, Centro Hospitalar e Universitário Lisboa Norte; [4] Laboratório de Histopatologia Cutânea, Serviço de Dermatologia, Centro Hospitalar e Universitário Lisboa Norte; [5] Serviço de Imagiologia, Centro Hospitalar e Universitário Lisboa Norte; [6] Serviço de Nefrologia e Transplantação Renal, Centro Hospitalar e Universitário Lisboa Norte; [7] Serviço de Reumatologia, Centro Hospitalar e Universitário Lisboa Norte.

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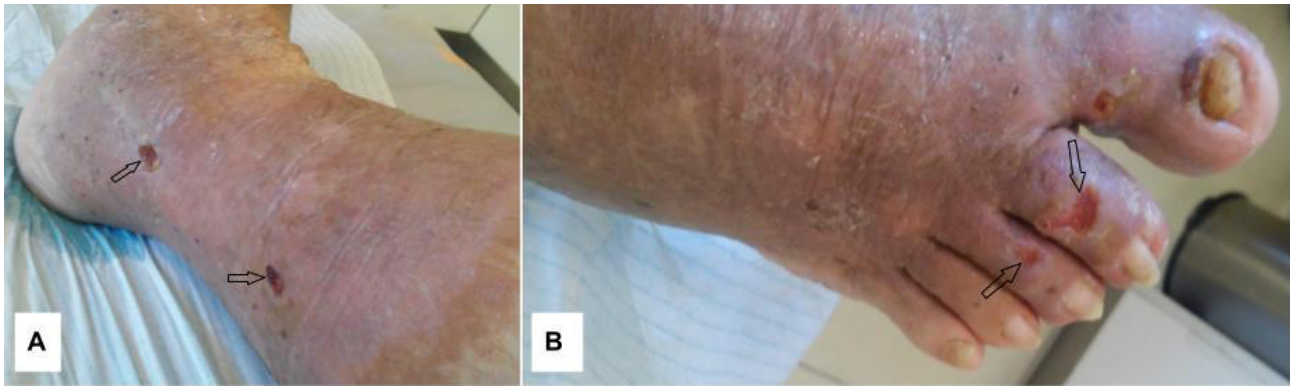
Correspondence to: Augusto José Serra Gaspar da Silva
E-mail: gusto.silva.83@gmail.com

CASE-REPORT

A 34-year-old male, Caucasian, presented to our Rheumatology outpatient clinic with a three-year history of erythematous-purpuric rash on both legs with recent worsening and development of ulcers on his toes (Figure 1). He was previously evaluated in the Dermatology outpatient clinic and underwent skin biopsy, which revealed leukocytoclastic vasculitis of the superficial dermal plexus without eosinophils (Figure 2). He had a background history of intraventricular fibrillary astrocytoma with leptomeningeal dissemination treated with surgery and in remission for more than 18 years, right lobectomy due to bronchopneumonia 15 years ago and severe osteoporosis due to hypogonadism and prolonged immobilization. Laboratory tests revealed normocytic normochromic anaemia (Hb 9.2 g/dL), leucocytes of 4300 cells/mm^3 without eosinophilia, rapidly progressive renal insufficiency (SCr 0,9 mg/dl to 1,7 mg/dL), active urinary sediment, proteinuria of 1873.1 mg/24h, erythrocyte sedimentation rate (ESR) of 119 mm/h, C-reactive protein (CRP) of 7.5 mg/dL, hypergammaglobulinemia (1600 mg/dL), complement consumption (C3: 35 mg/dL, C4: 7 mg/dL, CH50 <13.5 U), positive PR3-ANCA (631.7 UQ), negative myeloperoxidase-ANCA and presence of cryoglobulins with a polyclonal pattern and monoclonal tendency



Figures 1A and 1B. Ulcers on the patient's toes and leg (arrows).

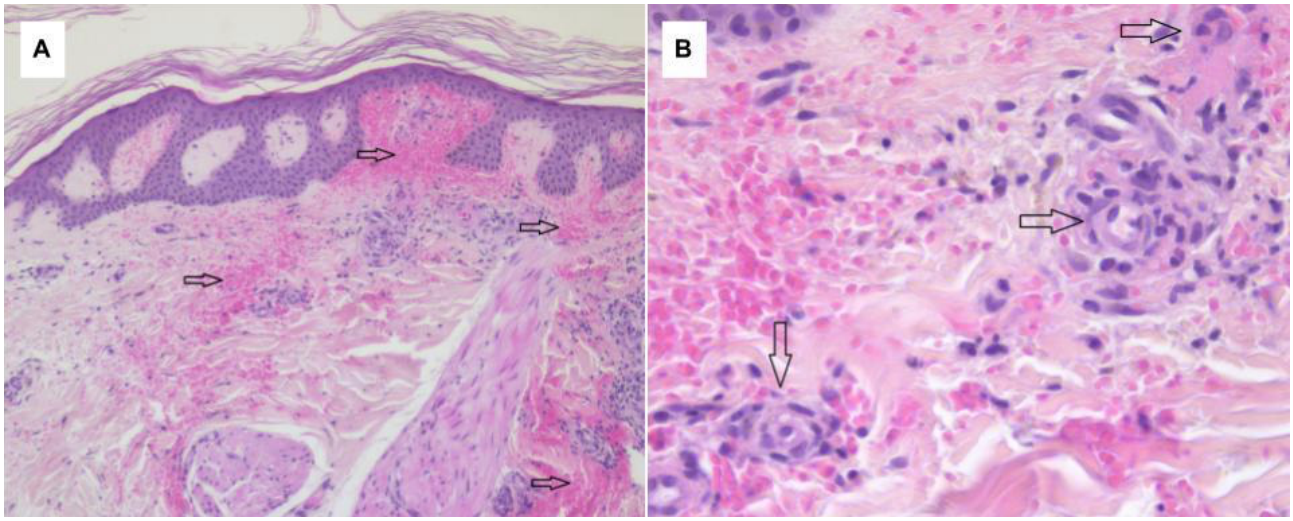


Figure 2A and 2B. (A) Skin biopsy from left leg (x100, HE): moderate edema of the papillary and medium dermis with abundant extravasated erythrocytes (arrows); superficial perivascular inflammatory infiltrate composed of lymphocytes, histiocytes and neutrophils with no eosinophils. (B) Skin biopsy from left leg (x400, HE): fibrin deposits on the vessel walls of the superficial dermis, with surrounding inflammatory infiltrate rich in neutrophils, representing the typical features of leukocytoclastic vasculitis (arrows).

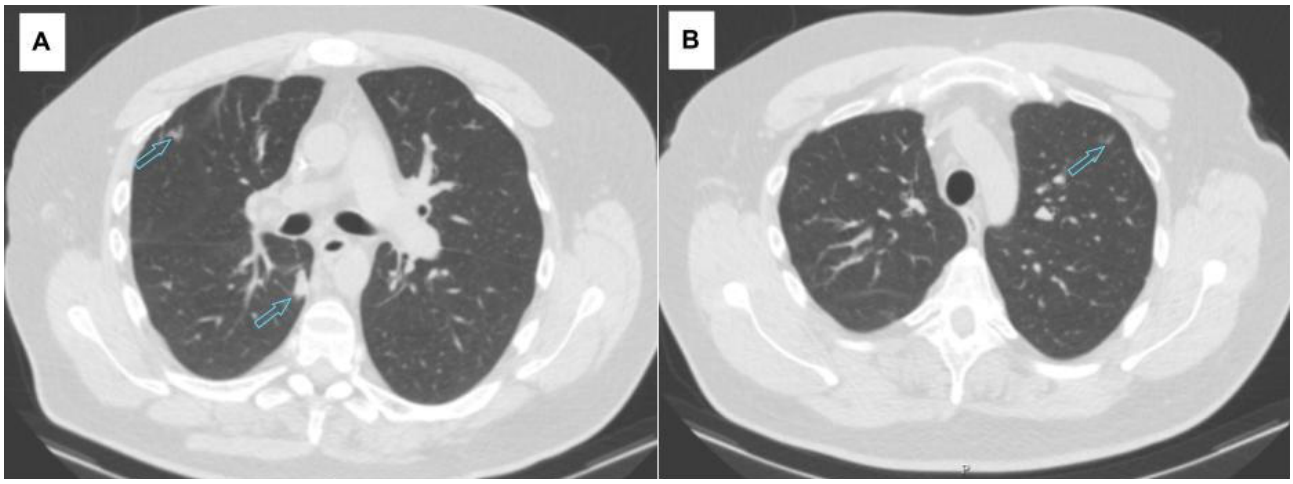


Figure 3A and 3B. Axial thoracic computed tomography with several pulmonary inflammatory infiltrates (blue arrows).

IgG (lambda). Free light chain assay, serum and urine immunofixation, and myelogram excluded monoclonal gammopathy. Thoracic computed tomography showed several nonspecific pulmonary inflammatory infiltrates in both lung fields (Figure 3). The patient was referred to the Nephrology team and underwent a renal biopsy, which revealed crescentic pauci-immune glomerulonephritis (Figure 4). Electronic microscopy showed rare subendothelial and luminal electron dense globules not well defined that could not exclude completely cryoglobulins (Figure 5). Diagnosis of GPA and CV was then assumed. Considering the severity of the renal lesions and the need to preserve fertility and avoid GC toxicity, the patient was started on rituximab (RTX, two pulses of 1g 15 days apart), low-dose cyclophosphamide (CYC, five pulses of 500 mg every 15 days) and 60 mg of daily prednisolone with a rapid 2-weeks tapering scheme (SMARTVAS protocol[5]). A marked improvement was observed. After six months of follow-up there was full resolution of the skin lesions, renal function recovery (SCr 0.77 mg/dL), reduction of the inflammatory parameters (ESR: 17 mm/h, CRP: 3.4 mg/dL) and PR3-ANCA titers (149 UQ), cryoglobulins became negative and the complement normalized. Re-evaluation chest CT showed a total resolution of pulmonary infiltrates after 10 months of therapy. The patient is currently under maintenance treatment with RTX 1g every six months and no adverse events have been reported.

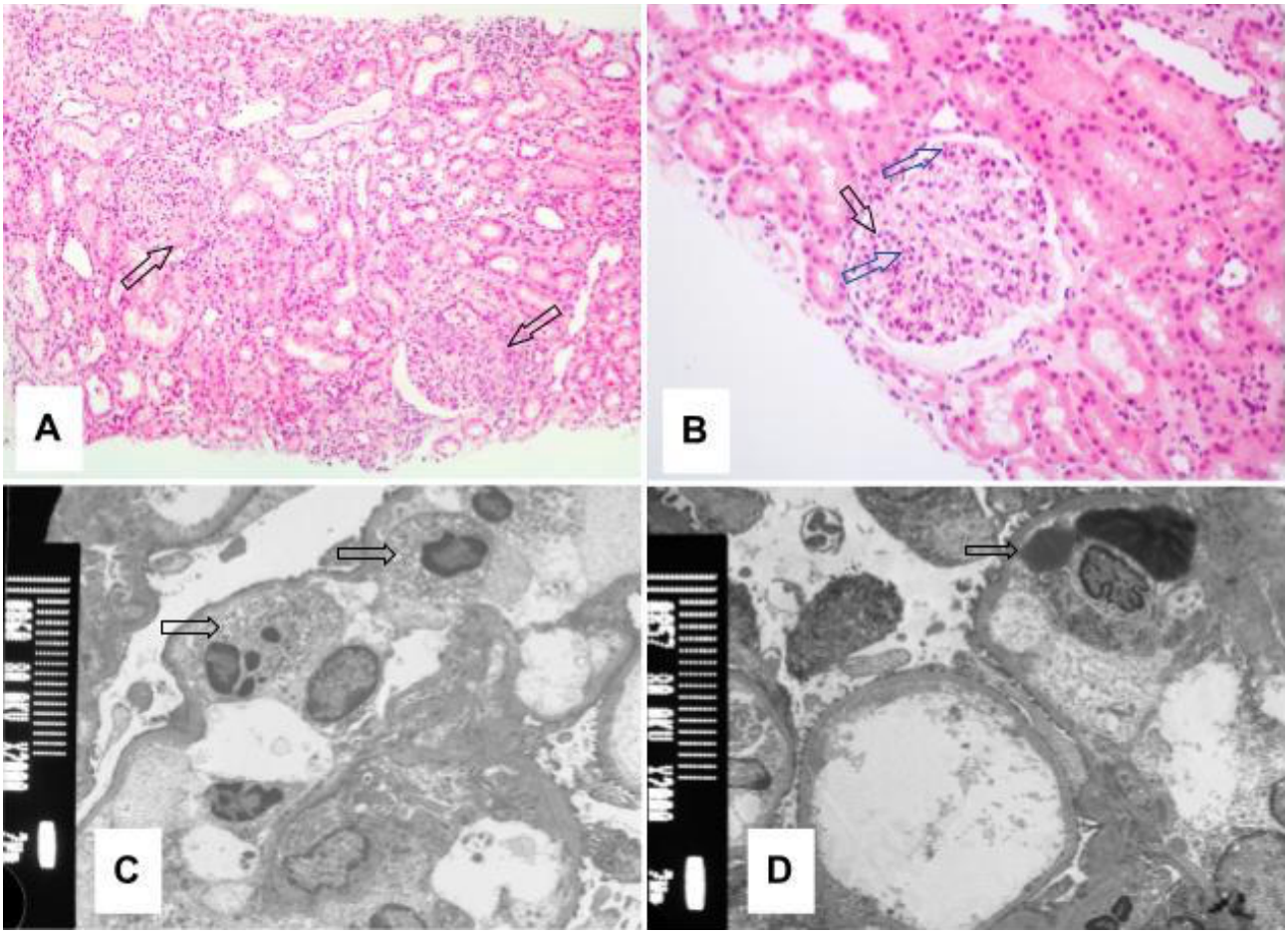


Figure 4A, 4B, 4C and 4D. (A) (Optical microscopy, H&E, 100x) - Photomicrograph of renal biopsy where two glomeruli with crescents are identifiable. (B) (optical microscopy, H&E, 200x) - Detail of glomerulus with cellular proliferation (black arrow) and presence of neutrophils in capillary lumens and mesangium (blue arrow). (C) (electron microscopy, 2000x) - Photomicrograph of renal biopsy showing a portion of a glomerular tuft with numerous neutrophils in the capillary lumen (arrow). No electrodense deposits were observed. (D) (electron microscopy, 2000x) - Photomicrograph of renal biopsy showing a portion of a glomerular tuft with a leucocyte and some ill-defined electrodense bodies in the capillary lumen (arrow). No electrodense deposits were observed

CONCLUSION

This case describes a rare presentation of both CV and GPA in a patient who showed a favorable response to an induction treatment with a combined RTX and CYC/GC-sparing regimen. The combination of very short courses of GCs with both RTX and CYC may offer a safe alternative to reduce GC toxicity and CYC-toxicity effects.

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