REVISTA BRASILEIRA DE REUMATOLOGIA

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Case report

ANCA associated vasculitis and chronic lymphocytic leukemia: a rare association☆

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ARTICLE INFO

Article history:
Received on 10 November 2011
Accepted on 14 May 2013

Keywords:
Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis
Leukemia, Lymphocytic, Chronic, B-Cell
Wegener's granulomatosis

ABSTRACT

The aim of the present work is to discuss the report of a patient who had simultaneous diagnosis of two rare diseases, vasculitis related to antineutrophil cytoplasmic antibodies and chronic lymphocytic leukemia. Both are diseases that may be multisystemic and thus cause diagnostic confusion. In this case, the patient had renal, pulmonary, hematological, and ocular symptoms, which could be secondary to vasculitis both as to leukemia. With the aid of imaging studies, pathological studies, immunohistochemistry and immunophenotyping, we conclude that it was a combination of the two diseases. There are other reports in literature of this association, however, with pANCA positive, this is the first report of chronic lymphocytic leukemia associated with cANCA positive vasculitis.

Vasculite associada à ANCA e leucemia linfocítica crônica: uma rara associação

Palavras-chave:
Vasculite Associada a Anticorpo Anticitoplasma de Neutrófilos
Leucemia Linfocítica Crônica de Células B
Granulomatose de Wegener

RESUMO

O presente trabalho tem por objetivo uma discussão acerca do relato de um doente que teve o diagnóstico simultâneo de duas doenças pouco frequentes, a vasculite relacionada ao anticorpo anticitoplasma de neutrófilos e a leucemia linfocítica crônica. Ambas são doenças que podem apresentar envolvimento multissistêmico e, assim, causar confusão diagnóstica. Neste caso, o doente apresentou comprometimento renal, pulmonar, hematológico e ocular, que poderiam ser secundários tanto à vasculite quanto à leucemia. Com auxílio de exames de imagem, estudos anátomopatológicos, imuno-histoquímica e imunofenotipagem concluímos tratar-se de uma associação das duas doenças. Há, na literatura, outros relatos desta associação, no entanto, com pANCA positivo; este é o primeiro relato de leucemia linfocítica crônica associada à vasculite com cANCA positivo.

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0482-5004/$ - see front matter.
http://dx.doi.org/10.1016/j.rbre.2014.02.008

Introduction

The group of vasculitides related to antineutrophil cytoplasmic antibodies (ANCA) is characterized by necrotizing inflammation of small vessels. The clinical manifestations of these vasculitides are diverse and multisystemic. Pertain to this group Wegener's granulomatosis (WG), microscopic polyangiitis and Churg-Strauss syndrome.

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disease; its etiology remains unclear, and is characterized by clonal proliferation of B lymphocytes. Often CLL is associated with autoimmune phenomena, mainly related to cells of the hematopoietic system, especially cytopenias.

Between ANCA associated vasculitides, WG is the most common and its annual incidence ranges from 1.3 to 14.4 per 1 million inhabitants.[1] CLL has a higher incidence, ranging from 3.5 to 13.7 per 100,000 inhabitants.[2]

The objective of this report is to show the association between two rare complex diseases, CLL and ANCA-related vasculitis, and this is the first report of this association with positive cANCA.

Case report

Man, 63 years old, black, driver (retired), hypertensive. After nine months of admission, edema, purpuric lesions and paresthesia in the lower limbs emerged, in association with malaise, weight loss (3 kg), daily fever and night sweats.

On physical examination, the patient was pale, emaciated and with lower limb edema +++/4, palpable purpura and decreased surface sensitivity.

Laboratory tests showed normochromic normocytic anemia (Hb 11.8 g/dL), leukocytosis (25,800/µL with 48% neutrophils and 46% lymphocytes), hypoalbuminemia (albumin, 3.0 mg/dL) and renal dysfunction (serum creatinine 13.4 mg/dL and urea, 175 mg/100 mL) with 24-hour hematuria and proteinuria = 1.04 g.

The possibility of infection was disregarded. Radiographies and CT scan were normal. Complement consumption was not verified. The search for cryoglobulins and cold agglutinin was negative. cANCA and anti-proteinase 3 were positive.

The electromyography confirmed a mixed sensory-motor polyneuropathy in lower limbs, with distal predominance.

The renal biopsy showed proliferative glomerulonephritis with diffuse endo- and extracapillary crescents. Immunofluorescence was positive for IgG and C3.

The skin biopsy of the lower limb was compatible with leukocytoclastic vasculitis. Immunophenotyping of peripheral blood was performed and showed positivity for: CD5, CD19, CD23, CD38, CD22, CD20 (weak), CD79b (weak) and CD11 (weak).

Then, the diagnosis of CLL associated with ANCA vasculitis was confirmed.

It was decided to start pulse therapy with 1 g/day methylprednisolone × 3 days and cyclophosphamide 500 mg monthly. CLL had no indication for treatment, just observation. The patient developed progressive clinical improvement. Six months after the onset of immunosuppression, the patient had a creatinine of 2.1 mg / dL.

After one year, the patient was being treated with azathioprine 200 mg/day in combination with prednisone 10 mg/day when he started presenting progressive leukopenia, intermittent fever and weight loss. Azathioprine was discontinued and the prednisone dose was escalated to 40 mg/day with a satisfactory response.

After two months the patient again presented fever, weakness, weight loss and, now, productive cough. Tomography was requested (Fig. 1), showing changes suggestive of WG: centrilobular pulmonary nodules, bronchiectasis, ground-glass opacities and pleural thickening. A transbronchial biopsy revealed chronic nonspecific peribronchial inflammation without granulomas and with negative immunophenotype for CLL. Thus, new immunosuppression induction with methylprednisolone and cyclophosphamide was performed.

On this same occasion the patient complained of pain and intense ocular hyperemia with progressive decrease in visual acuity. On ophthalmologic examination, the patient was diagnosed with anterior uveitis with epithelial precipitates, which also improved after immunosuppression.

Discussion

This report describes the case of a patient diagnosed with two relatively rare diseases in combination. This is probably the first case in the literature of CLL associated with cANCA-positive vasculitis.

During the entire follow-up period there was difficulty in differentiating the clinical manifestations presented by the patient, whether they were secondary to vasculitis or to CLL, since most of them were nonspecific but compatible with both diseases.

Initially , the patient had severe renal dysfunction secondary to pauci-immune crescentic glomerulonephritis (PICGN), with positivity for IgG and C3. The PICGN related to CLL has been described in rare reports. In the literature there are nine cases of this association and six of them were positive for p-ANCA.[3] ANCA has a direct implication in the pathogenesis of PICGN, and apparently this is reproduced in patients with CLL. The occurrence of ANCA in patients with CLL, however, is less than 2%.[4]

In WG, there is evidence of renal involvement in up to 80 % of patients, generally pauci-immune glomerulonephritides (immunohistochemistry with a higher frequency of IgM and C3), in which the characteristic lesion is a necrotizing glomer-

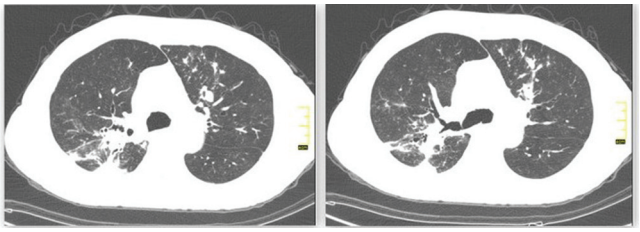

Fig. 1 – Tomography showing centrilobular pulmonary nodules, bronchiectasis, ground-glass opacities and pleural thickening.

ulonephritis with extracapillary proliferation.[5] For the other hand, in CLL there are studies showing renal involvement in up to 63%, but rarely as the cause of acute renal failure. The most common types of glomerulonephritis associated with CLL are: membranoproliferative, cryoglobulinemic, membranous, with minimal lesions, focal and segmental glomerulosclerosis and amyloidosis.[6]

Subsequently, the patient developed neutropenia, which could be explained by several mechanisms. Among them, the use of azathioprine (but the patient did use this drug for 10 months and had never had such a complication, autoimmune origin, or bone marrow failure. Individuals with CLL have a risk of 5-10% to develop autoimmune disease, mainly cytopenia. The most common is hemolytic anemia and, less frequently, thrombocytopenia and pure red cell aplasia.[7] Rare cases manifest autoimmune granulocytopenia, and it is believed that this complication is related to the presence of ANCA.[8]

After an asymptomatic period, the patient developed lung manifestations. The CT appearance was nonspecific, but consistent with manifestations of WG, and a lung biopsy discarded the possibility of CLL. In individuals with WG, there is lung involvement in about 80%, at some stage of the disease. These patients present with a wide spectrum of tomographic patterns, not necessarily improve with clinical remission of disease and its confirmation is obtained by lung biopsy. The most common CT findings are nodules, with or without cavitation, and less frequency masses, bronchial wall thickening, consolidation, ground-glass opacities and pleural effusion.[9]

The lymphoproliferative diseases represent a spectrum of lymphoid abnormalities that may involve the lung, from benign lesions to those with potential for neoplastic transformation. In CLL, a possible lung manifestation is lymphomatoid granulomatosis, characterized by an angiocentric lymphoid infiltrate and that has great similarity with the lung manifestations of WG. The patient may exhibit multisystem involvement, including ocular and neurologic manifestations.[10]

Concomitant with the pulmonary picture, the patient showed ocular involvement, diagnosed as uveitis. The ophthalmologic manifestations occur in up to 58% of patients with WG, and can affect any part of the eye. Uveitis, in particular, is not a common manifestation of WG, but has been previously reported. In some series, uveitis is the least common form of ocular involvement in cases of WG. The most common manifestation seems to be the orbital disease, followed by abnormalities of the sclera, episclera, cornea and nasolacrimal region.[11]

In CLL, the secondary involvement of ocular tissues is also common and can occur in 80-90% of individuals at some time during the illness. There is infiltration of neoplastic cells (lymphocytes) in ocular tissues and the diagnosis is made by immunohistochemical analysis.[12]

In the development of this case, imaging, pathologic, immunohistochemical and immunophenotyping studies were instrumental in the etiological determination of the manifestations presented. We conclude that these manifestations were secondary to vasculitis; therefore, an appropriate treatment was instituted and a satisfactory response was achieved, which favors the hypothesis of activity of vasculitis in association with quiescent CLL.

Conflicts of interest

The authors declare no conflicts of interest.

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