Aseptic hypertrophic pachymeningitis in a patient with Rheumatoid Arthritis - a case of involvement of the central nervous system by the disease?

Garcia S[1], Terroso G[1], Gomes A[2], Costa L[1]

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ABSTRACT

Hypertrophic pachymeningitis (HP) is a rare clinical entity which uncommonly occurs in rheumatoid arthritis (RA) patients. We describe the case of a rheumatoid factor and anti-citrullinated protein antibody positive RA male that was diagnosed with HP and multiple mononeuropathy. Although histological evaluation was not performed, after excluding infectious and neoplastic causes, it was possible to determine a probable inflammatory etiology. He was treated with glucocorticoids and rituximab with a good clinical evolution. This case represented a challenging differential diagnosis but the need for an accurate diagnosis should not delay the introduction of an effective therapy for a potentially lethal disease.

Keywords: Hypertrophic pachymeningitis; Rheumatoid Meningitis; IgG4-related disease;

BACKGROUND

Hypertrophic pachymeningitis (HP) is a rare clinical entity causing thickening of the dura. HP has multiple possible etiologies namely infections, autoimmune disorders, neoplasms or even idiopathic[1]. In rheumatoid arthritis (RA) patients, although this is a possible manifestation of the disease, specific serology and meningeal biopsy is needed to provide a definitive diagnosis[2].

CASE REPORT

We describe the case of a 66-year-old white male, treated for a rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positive RA, diagnosed in August 2013 and in clinical remission since 2016 with 20 mg of methotrexate and 5 mg of folic acid, weekly. He was admitted to the emergency department of a private hospital in July 2018 with a 6 months history of progressive bifrontal and bitemporal headaches associated with reduced verbal fluency and impairment of fine motor skills. Infection of the central nervous system was assumed. He was hospitalized and empirical antibiotic therapy was started with ceftriaxone, vancomycin, ampicillin and acyclovir, adjusted for ceftriaxone after an isolation of *Staphylococcus capitis in a blood culture*, which the patient complied with for 14 days. Despite this isolation, it is important to note that no other blood or cerebrospinal fluid (CSF) sample showed growth of any microorganism and, as such, it was considered as contamination.

He showed a further worsening of the condition, and was admitted to our hospital, a week later, after an episode of syncope with spontaneous resolution and without prodromes. He was apyretic and hemodynamically stable. Electrocardiogram showed no changes suggestive of myocardial ischemia and the highly sensitive troponin was negative.

Cerebral computed tomography (CT) scan was normal, but magnetic resonance imaging (MRI) demonstrated bilateral hyperintense frontoparietal cortico-pial (predominantly frontal), as well as paqui and leptomeningeal enhancement, compatible with HP (Figure 1A and 1D).

Blood tests revealed: erythrocyte sedimentation rate of 67 mm/1ªh, C-reactive protein (CRP) of 11 mg/L (normal value < 3.0 mg/L), normochromic normocytic anemia and absence of leukocytosis or changes in the ionogram or renal function. He presented a mild hypergammaglobulinemia in protein electrophoresis but without monoclonal peak, normal angiotensin-converting enzyme, negative anti-nuclear, anti-Ro/SSA and La/SSB autoantibodies and antineutrophil cytoplasmic

1. Reumatologia, Centro Hospitalar de São João
2. Neurologia, Centro Hospitalar de São João

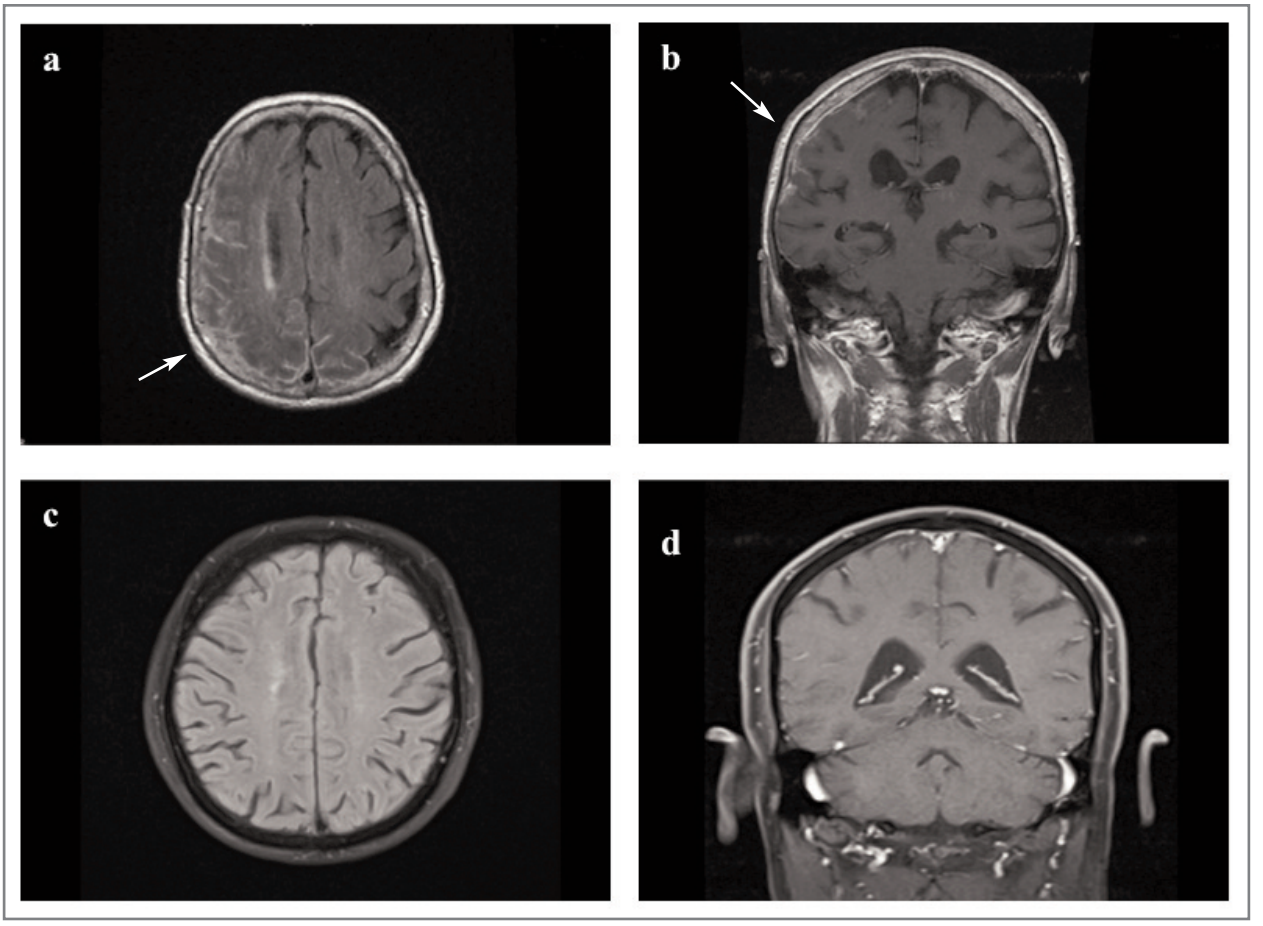

FIGURE 1. Brain magnetic resonance imaging (MRI) before and after rituximab (RTX) therapy. a) Axial T2 flair and b) Coronal T1 pos gadolineum, both images regarding brain MRI before RTX therapy showing increased leptomeningeal and dural thickening with worsening of leptomeningeal enhancement over the left posterior parietal lobe. c) Axial T2 flair and d) Coronal T1 pos gadolineum, both images regarding brain MRI one year after RTX therapy, showing no alterations.

antibodies (ANCA) and raised IgG4 immunoglobulins levels in serum and CSF (334 mg/dL, normal range < 140 mg/dL and 4.98 mg/dL,with an index of 0.96). Blood cultures were negative (including mycobacteriological examination) and interferon-gamma release assay and tuberculin skin test were negative. A lumbar puncture was performed and the CSF analysis showed: 85 cells with 79 leukocytes (with a predominance of polymorphonuclear cells, no carcinomatous cells) with an elevated protein concentration (1.97 g/l), normal glucose level (52 mg/dL) and negative microbiologic analysis (bacterial and fungus culture, PCR or serology for HIV, EBV, HSV-1 and HSV-2, varicella zoster virus, syphilis, *Listeria sp.* and *Mycobacterium tuberculosis*). A biopsy of minor salivary glands (SGB) was performed to rule out IgG4 related disease, which showed no infiltration by IgG4. Thoracoabdominopelvic CT was normal.

During hospitalization, the patient complained of paresthesias and hypoesthesia of both feet, especially of the plantar region, and in this context an electromyography was performed revealing asymmetric sensitive polyneuropathy, compatible with multiple mononeuropathy.

Given these results, and due to the clinical suspicion of inflammatory pachymeningitis probably in the context of RA, he was treated with 1 g of methylprednisolone/day (3 consecutive days), switching to oral corticosteroid therapy (1 mg/Kg/day) in a gradual reduction scheme. He showed a clinical improvement: both at neurological level, with improvement of the deficits, and also in imaging, with revaluation brain MRI sho-

wing regression of the changes and the uptake of meningeal contrast.

Three months after the initiation of corticosteroids, he did a positron emission tomography (PET) scan that was normal and a biopsy of the sural nerve that revealed scar changes compatible with severe neuropathy with slightly asymmetric involvement, which may correspond to a previous vasculitic process.

As a steroid sparing therapy, treatment with rituximab was started five months after the initiation of corticosteroids, at a dose of 1000 mg, given twice, two weeks apart, every 6 months.

One year later, improvement enabled decreasing the prednisone until 7.5 mg/day. The control MRI did not show a pachy-leptomeninges enhancement (Figure 1C and 1D). To date, the patient has minor plantar hypoesthesia and RA is in remission.

DISCUSSION

The inflammatory involvement of the central nervous system by RA should be considered in any patient with neurological symptoms, in which infectious and malignant processes are ruled out and especially in the presence of high RF and ACPA titers, as most of the reported cases in RA patients occurred in that subset of the disease[3].

Recently it has been suggested that IgG4-related sclerosing disease represents a subset of HP cases previously diagnosed as idiopathic HP, and despite the high sensitivity of current imaging, histology of the afected organ is still important since the diagnostic doubt often persists[4,5,6]. In this case, it is important to highlight the presence of increased levels of IgG4 immunoglobulins in serum and in CSF, despite no other signs of systemic IgG4-related disease (IgG4-RD) were present, namely tumor-like swelling of involved organs, lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and fibrosis of involved organs. A SGB was performed and, although it is insufficient for the diagnosis of IgG4-RD because of its low sensitivity, a smal size study showed a high specificity of SGB for the diagnosis of IgG4-RD[7]. Further research is needed to clarify the ability of a minor salivary gland biopsy to rule out IgG4-RD.

However, the need for an accurate diagnosis should not delay the introduction of an effective therapy for a potentially lethal disease. In fact, therapeutic options are often identical. Corticosteroids and rituximab have been used for the treatment of RA, ANCA and IgG4 associated vasculitis and idiopathic HP, with good results, although the evidence is limited to a few case reports[8,9].

The case presented here is a therapeutic success despite the maintenance of the diagnostic doubt and should remind us of the need of quick treatment initiation to prevent neurological complications in HP patients.

CORRESPONDENCE TO
Salomé Garcia
Serviço de Reumatologia, Centro Hospitalar de São João
Porto, Portugal
E-mail: salomefernandesgarcia@gmail.com

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