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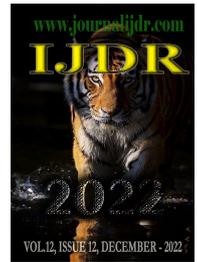
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CASE REPORT

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NEUROLOGICAL INVOLVEMENT BY IGG4-RELATED DISEASE: A CASE REPORT

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ABSTRACT

IgG4-related disease is a chronic fibroinflammatory condition characterized by swelling lesions, dense lymphoplasmacytic infiltrates, and abundant plasma cells containing IgG4 in affected tissues. The disease, although it can affect the central nervous system, does not have it as the main site of involvement. Thus, it is important to describe these cases to the scientific community. This article presents a case report of a 23-year-old female patient with IgG4-related disease, presenting with neurological involvement, with headache and eyelid ptosis, and several characteristic findings of the disease on imaging, histopathological and immunohistochemical analysis. The patient, still under follow-up, achieved partial improvement with the use of prednisone, requiring rescue therapy with corticosteroid-sparing agents.

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INTRODUCTION

IgG4-related disease is a chronic fibroinflammatory condition characterized by swelling lesions, dense lymphoplasmacytic infiltrates, and abundant plasma cells containing IgG4 in affected tissues (Cassione; Stone, 2017), in addition to increased serum levels of total IgG and IgG4 (in about two-thirds of patients), fibrosis of the lesions and a good response to corticosteroids (Ishikawa; Terao, 2020). The disease was first described in 2003, when conditions considered as unrelated entities for decades – such as type I autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, hypertrophic pachymeningitis, among others – occurred simultaneously in a proportion of patients, with histological findings in common. Around the world, diagnostic and therapeutic tools for the management of patients with the disease remain restricted to tertiary care centers, and the disease is still misdiagnosed as neoplastic, inflammatory and infectious conditions (Lanzillotta; Mancuso; Della-Torre, 2020). About epidemiology, although almost 75% of reported patients are Japanese, the disease has been described

in almost all ethnic groups. Japanese authors estimate a prevalence of about 1 in 600,000 inhabitants. The incidence of the disease peaks between the fifth and seventh decades of life, with a clear male predominance (61-80%), although the proportion between the sexes may be different depending on the organ affected (Maritati; Peyronel; Vaglio, 2020). Immunoglobulins of class G (IgG) exert several important biological functions by interacting with various cell types (Marzocchi-Machado; Lucisano-Valim, 2005). There are four subclasses of IgG, numbered from 1 to 4 in order of discovery and serum concentration, with IgG1 being the oldest and most prevalent, and IgG4 the most recent and the least amount (Reis et al, 2020). In the pathophysiology of the disease, the presentation of an autoantigen by B lymphocytes to CD4 cytotoxic T lymphocytes occurs. Cytotoxic T lymphocytes along with antigen-presenting cells express a molecule called SLAMF7 (signalling lymphocytic activation molecule F7), which is involved in cytotoxicity, humoral immunity, autoimmunity, cell survival, cell adhesion, and lymphocyte development. CD4 cytotoxic T lymphocytes express proteins and enzymes that contribute to cell death and tissue fibrosis formation such as interferon-gamma (IFN- γ), interleukin 1-beta (IL-1 β), perforin and

granzymes. T helper lymphocytes drive the production of IgG4 by B lymphocytes and plasma cells through the secretion of interleukin 4 (IL-4) and interleukin 10 (IL-10) (Zhang; Stone, 2019). IgG4 has a low ability to activate complement and form immune complexes; in this sense, it should be considered more as a disease marker and not as a pathogenic factor itself (Garrido *et al.*, 2021). The main presentation of the disease is a pseudotumoral swelling in an organ (or adjacent organs), discovered clinically or radiologically. Onset is usually subacute, with no constitutional symptoms. Allergic manifestations such as atopic dermatitis, atopic asthma or chronic sinusitis are found in 40% of patients. Other manifestations depend on the place of involvement. Pancreatitis is the most common manifestation, affecting the bile ducts in most cases. Other sites of involvement include mediastinal or abdominal lymph nodes (80% of cases), lacrimal or salivary glands (40%), kidneys (30%), lungs (13%) and retroperitoneum (10%) (Palazzo E; Palazzo C; Palazzo M, 2014). This article presents the case report of a patient diagnosed with IgG4-related disease, who had neurological involvement as the main clinical manifestation.

CASE REPORT

Patient, female, 23 years old, housewife, previously healthy, with a clinical presentation of holocranial and pulsating headache, strong intensity, without association with photophobia or phonophobia, which had started 2 years ago. After 2 months of daily symptoms, she developed right eyelid ptosis and diplopia. Cranial magnetic resonance imaging showed bone thickening with a sclerosis aspect involving the sphenoid with extension to the sellar floor and parasellar region on the right, with diffuse enhancement after the use of contrast medium, in addition to thickening of the cavernous sinus on the right with tissue formation, encompassing the carotid arteries and the cavernous portion. Adjacent meningeal thickening was also evidenced in the right temporal fossa on the inner most anterior surface near the temporal pole. The patient underwent biopsy of the sphenoid thickening visualized on MRI. The anatomopathological study showed fusocellular proliferation in storiform arrangements, without atypia, associated with a dense inflammatory infiltrate rich in plasma cells and lymphocytes. The immunohistochemical study showed that it was a sclerosing fibroblastic lesion with associated inflammatory infiltrate, with an IgG4/IgG ratio of about 30%. Hormonal dosage of the hypothalamic-pituitary axis, as well as serum IgG4, dosed only after starting corticosteroid therapy, were within normal limits. The patient also underwent computed tomography of the chest and abdomen, without significant alterations. The patient started treatment with prednisone at a dose of 1mg/kg/day, later associated with azathioprine as a steroid-sparing agent. She even showed improvement in symptoms, but with recurrence after weaning from corticosteroid. After that, methotrexate was added. Due to cutaneous allergic manifestation after starting methotrexate, it was decided to start pulse therapy with 1 gram of intravenous methylprednisolone for 3 days and monthly with cyclophosphamide, with suspension of methotrexate and azathioprine. The patient is still undergoing monthly cyclophosphamide, evolving with improvement of ptosis and headache, in addition to reduction of the intracranial lesion evidenced in a new magnetic resonance imaging performed six months after starting treatment.

DISCUSSION

The IgG4-related disease (IgG4-RD), a clinical entity considered rare, does not have the nervous system as the main site of involvement, although it can also be affected by the disease. The neurological manifestations of the disease were documented in only 2% of the cases described in the literature (Maamriet *et al.*, 2022). The most frequent are hypophysitis and hypertrophic pachymeningitis (inflammation and hypertrophy of the dura mater, a condition presented by the patient, in contiguity with a lesion in the sellar region) (Baptista *et al.*, 2017). About the case described, it presents an epidemiological profile different from the one most found in relation

to sex and age. The literature shows, however, that female patients tend to manifest the disease earlier, in addition to being predisposed to head and neck involvement, with a tendency to have disease exclusively in these sites rather than systemic disease (Saitakis; Chwalisz, 2021). The disease is diagnosed with a combination of typical radiological findings, histopathological findings of abundant infiltrate of IgG4-positive plasma cells and lymphocytes, storiform fibrosis and obliterative phlebitis, consistent with that presented by the patient, association with other IgG4-related diseases and response to steroids (Kamisawa; Okazaki, 2017). Serum IgG4 levels are not essential for diagnosis, as they may be normal depending on the level of disease activity, apart from reducing after the start of treatment (Hamano *et al.*, 2001). In 2019, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed the diagnostic criteria for the disease. The classification is based on a few steps: first, clinical, radiological and/or histopathological findings compatible with 1 of 11 possible organs; then, each potential case cannot fulfill any of the exclusion criteria, such as fever, lack of response to glucocorticoids or the presence of leukopenia/thrombocytopenia, among other criteria, this assessment being individualized depending on the patient's clinical scenario; finally, criteria composed of eight domains are applied, whose total score, if greater than or equal to 20, causes the case to be classified as an IgG4-related disease (Wallace *et al.*, 2020). During the creation of these criteria, however, more typical and common manifestations were chosen due to the desire to enroll homogeneous populations in clinical trials, excluding sites less affected by the disease, including the central nervous system. Thus, the clinical, laboratory, histological and immunohistochemical correlation remains as the most relevant for the diagnosis of the disease.

First-line therapy to induce remission in patients with active disease is glucocorticoids. Conventional steroid-sparing agents (azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, for example) are also used to maintain disease remission (Khosroshahet *et al.*, 2015). The patient in this case report showed partial improvement with corticosteroid therapy, evolving with further worsening during weaning from the medication, although using steroid sparing drugs. A poor response to steroids appears to be more likely in patients with more fibrotic changes, chronic stage of disease, and low serum IgG4 level (Yu *et al.*, 2015). Although rituximab, an anti-CD20 monoclonal antibody, is the most frequently used immunobiological agent in patients with IgG4-related disease, indicated as a second-line treatment in patients with recurrent or refractory disease (Bledsoe *et al.*, 2018), its unavailability due to costs, led to the use of cyclophosphamide in the pulse therapy modality. The early identification of IgG4-related disease is related to important implications for the prognosis related to organ dysfunction due to tissue fibrosis and related to treatment response (Olmos *et al.*, 2021).

CONCLUSION

This case report on the neurological involvement by the IgG4-related disease comes to the fore to highlight the need to be careful in placing it as a differential diagnosis among fibro-inflammatory diseases nowadays, since more and more lesions, previously described as of idiopathic etiology, are being configured as IgG4-related disease, and the early diagnosis can promote a better prognosis for the patient.

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