Granulomatosis with polyangeitis in the posterior fosa. Report of a case.

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Granulomatosis with polyangiitis, or Wegner's granulomatosis, has an incidence of 5-10 cases per million of inhabitants, and only 2-11% of cases present manifestations in the central nervous system. There are no standardized diagnostic criteria; however, clinical suspicion, positive serology for ANCA'S, histological evidence of necrotizing vasculitis, necrotizing glomerulonephritis, or granulomatous inflammation of organs such as skin, lung or kidney, may suggest this pathology. Neurosurgery is a diagnostic and therapeutic option and could be a possibility in those cases in which the lesions are in accessible areas and have low risk of generating comorbidities. We present the case of a 39-year-old female patient with granulomatosis and polyangiitis with involvement in the posterior fossa. After surgical management, it presents meningeal infection. Additionally, we conducted a review of the pathology.

Keywords: *Granulomatosis with Polyangiitis, Wegener Granulomatosis, Antibodies, Antineutrophil Cytoplasmic, Neurologic Manifestations, Neurosurgery.*

Introduction

Granulomatosis with Polyangiitis (GP) is part of the vasculitic diseases associated with Neutrophil Anticytoplasmic Antibodies[(1)]. It presents an annual incidence of 5-10 cases per million inhabitants[(3)]. The compromise of thenervous system is predominantly peripheral in 45% of cases[(9,12)] and central involvement in 0-4% of cases[(1,7)]. We present the case of a 39-year-old female patient with a history of GP and involvement in the posterior fossa, in addition to a review of the literature on said pathology.

Case

A 39-year-old female patient was seen at the emergency department due to a frontoccipital headache associated with nausea, right tinnitus, vertigo, and phonophobia. The headache had lasted for a month and did not improve with the consumption of conventional analgesics. She had a GP history, diagnosed 3 years prior,

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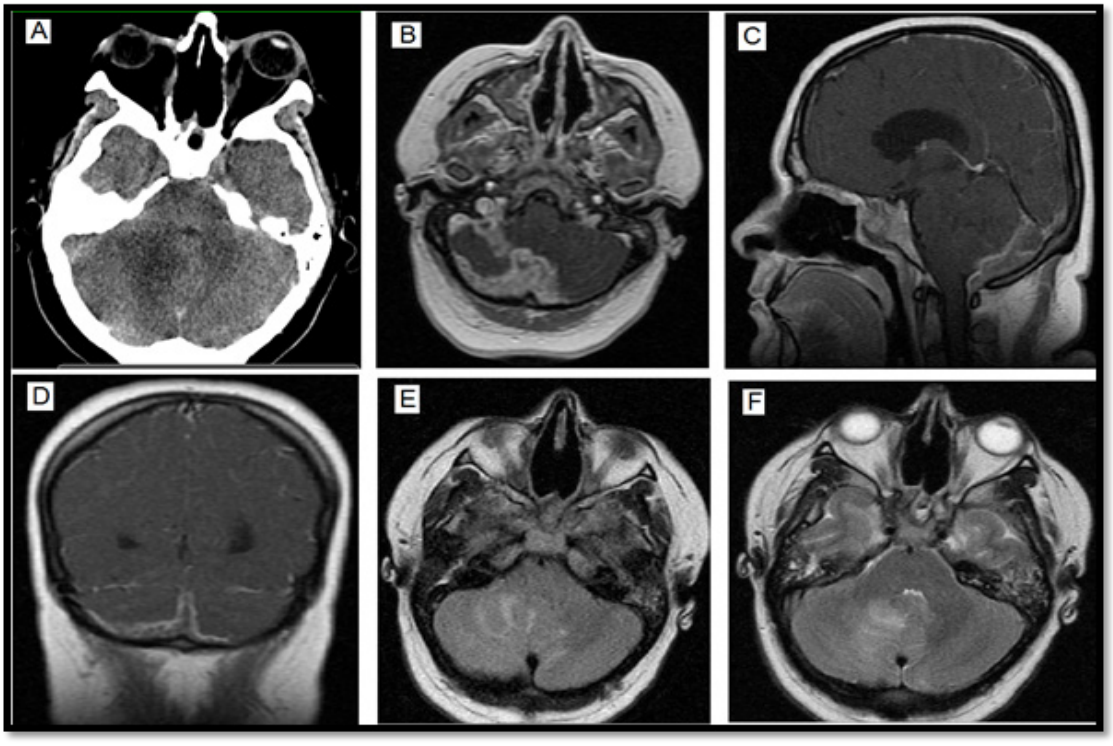
that was under management with Azathioprine and Methotrexate. She also had arterial hypertension, hypothyroidism, chronic sinusitis, subglottic stenosis, and a thyroidectomy due to papillary adenocarcinoma. During her physical examination, she presented stable vital signs and increased lift polygon. A computerized axial tomography of her skull was taken. It showed hypodense lesions in the right cerebellum, perilesional edema, obliteration of the IV ventricle, and obstructive hydrocephalus. Subsequently, both a simple and contrasted nuclear magnetic resonance imaging of the brain were performed. They showed an intra- and extra-axial, infratentorial lesion, predominantly in the right cerebellar hemisphere, which, with contrast enhancement, was suggestive of plaque meningioma (See image 1). Given these circumstances, it was decided that the patient should be taken to surgery, where a right occipitocervical approach was performed. Findings of interest were: a lesion that extended and infiltrated the dura with abundant vascularization, without an adequate plane of differentiation with the cerebellum, in addition to an extension beyond the midline, the jugular foramen, the sigmoid sinus, and the foramen magnum. The lesion's pathology study showed necrotizing granulomatous chronic inflammation in neural and meningeal tissue, with multinucleated giant cells, without malignancy, with negative Ziel Nielsen, PAS-D, and methenamine silver, which are suggestive of GP. In the following two months, the patient had two episodes of meningitis and infection of the surgical site favored by a cerebrospinal fluid fistula. The colonization of Klebsiella Pneumoniae was evidenced, so she was treated with treatment with Vancomycin and Cefepime for twenty-one days. Additionally, fistula correction and debridement were performed. After controlling the infectious process, a ventriculoperitoneal shunt was performed without further complication. The patient attended multidisciplinary follow-ups, with sustained clinical improvement and the absence of cerebrospinal fluid fistula.

Image 1. Pre-operative images: A: Simple skull tomography showing cerebellar hypodensity with displacement and reduction in the size of the fourth ventricle. B, C, D: Nuclear Magnetic Resonance of the skull contrasted in T1 sequence with a lesion of poorly defined intra-axial characteristics in the right cerebellum predominantly, with contrast medium uptake. E: FLAIR sequence. F: T2 sequence.



Discussion

GP, along with microscopic polyangiitis and polyangiitis with eosinophilic granulomatosis, is part of the vasculitic diseases associated with Anti-Neutrophil Cytoplasmic Autoantibody (ANCA).[1]. It was described for the first time in 1931 by Klinger as a variant of polyarteritis nodosa; however, Wegener described it as a separate syndrome in 1939. In 1954, Godman and Churg introduced the term Wegener's granulomatosis and proposed their diagnostic criteria,[2], which would later be changed to Granulomatosis with Polyangiitis[3,4].

The annual incidence of GP is 5-10 cases per million inhabitants, with a prevalence of 24-157 cases per million[3]. It increases in northern Europe, where 5 cases per 100,000 inhabitants are reported. The appearance of GP predominates in Caucasians; there is no difference by gender, and has a higher occurrence between the ages of 35-55[2,4]. Neurological involvement was identified in 22-54% of patients[5,6], with central nervous system manifestations in 2-11% of cases[4,7]; even 8-18% is reported when cranial nerve palsy is taken into account[5].

Different pathogenesis have been proposed for GP, including those of infectious origin in the respiratory tract (sthapylococcus aureus, fungal, and viral), of environmental origin (contamination), and by toxins (cigarette, mercury, lead). Additionally, pharmacological (cefotaxime, minocycline, antithyroid medication, anti-tumor necrosis factor, antipsychotics, anticonvulsants), genetic predisposition in relation to HLA-DP1 * 040, HLA-DRB1 * 15 and HLADRB * 1501, and polymorphisms such as SERPINA1, PRTN3 and in the CTLA-4 gene, are also among the most important[3].

Although there are no diagnostic criteria for the disease, its diagnosis is based on the presence of clinical manifestations, positive serology for ANCA, and histological evidence of necrotizing vasculitis, necrotizing glomerulonephritis, or granulomatous inflammation of organs such as skin, lung, or kidney. [2]. Cytoplasmic ANCAs are positive in 83-96% of cases(4,5) and perinuclear cells in 20%[4], so they are used for the diagnosis and monitoring of the disease[2].

Some authors recognize two types of disease patterns in terms of their involvement in the central nervous system (CNS): granulomatous, with a cytokine pattern dependent on Th1 lymphocytes, and vasculitic, with a Th2 pattern[8,9]. In the central nervous system, it tends to affect mainly the pituitary gland, the meninges (Chronic Hypertrophic Pachymeningitis), as in the case of the present case's patient, and the cerebral vessels due to three main factors, which are their ability to invade neighboring structures (from the paranasal sinuses to the system central nervous system), remote intracerebral granulomatous involvement, and cerebral or spinal vasculitic involvement[1,4–6,8]. However, in 30% of cases, there is a combination of both mechanisms[5].

When CNS alterations appear, 60% of patients usually show pachymeningeal involvement. It should be noted that ANCAs are positive in 30% of isolated cases of pachymeningitis[7]. The tests for cerebrospinal fluid show nonspecific findings in 70% of cases, so it is used to rule out differential diagnoses(1,5). Within the differential diagnoses, lesions such as atypical meningiomas, lymphomas, tuberculomas, or fungal infections, sarcoidosis, pyogenic abscesses, among others, should be taken into account.[5,10].

Neurological involvement appears primarily as peripheral neuropathy, mostly mononeuritis multiplex, in 45% of the cases[9,12] or symmetric polyneuropathy in 55%[12]. In the CNS, it mainly affects the meninges and the pituitary gland and produces cerebral granulomatous vasculitis[1,7]. Meningeal involvement occurs in 0-4% of patients with the disease but represents more than 50% of cases with CNS involvement[1,7]. It is usually pachymening (81%) rather than leptomeningeal (27%)[12], and predominantly intracranial, producing symptoms such as headache and cranial nerve involvement, mainly in nerves II, V, VI, VII, VIII, and X[4,5,8,13].

Seizures, encephalopathy, meningism, and limb paralysis are reported in less than 25%[5]. Other manifestations include cerebellar ataxia and myelopathy[12]. When faced with meningeal involvement, two profiles can be identified: that of patients with positive Anti-Proteinase-3 or patients with positive Anti-MPO, the latter having more limited involvement to the CNS and with less frequent relapses[1].

Pituitary alterations occur between 1.1-1.3%

of cases, with an average diagnosis age of 48 and 50 years in men and women, respectively. It manifests with nonspecific endocrinological symptoms(1) and visual problems due to compromise of the visual pathway in 17% of cases[1,5].

Cerebral vasculitis is reported in 4% of cases[5] and can cause ischemic damage with focal or generalized deficits, motor impairment, ischemic myelopathy, encephalopathy, cognitive impairment, dementia, behavioral disorders, seizures, or cortical blindness, among others[1]. Other manifestations may appear as psychiatric syndromes[10].

Radiological findings at the meningeal level can show linear or focal dural thickening, with enhancement after administering gadolinium, which was evident in the images taken of the present case's patient, especially of the tentorium[7,8,10]. Patients with pituitary disease may have an enlarged gland or a sellar mass with peripheral enhancement and central cysts due to necrosis or compression of the pituitary stalk or infundibular thickening and enhancement[1,7]. Although MRI is sensitive in detecting ischemic lesions, it is not very specific and can show large cerebral infarcts and extensive white matter lesions, consistent with ischemic small vessel disease with increased signal in heavy T2 and FLAIR[1,7,14,15]. CT, MRI, and conventional angiography rarely show stenotic or aneurysmal lesions since the size of the affected vessels is frequently below the level of resolution of them[1].

Treatment begins with high-dose corticosteroids plus intravenous or oral cyclophosphamide[10], rituximab or, in rare cases, plasmapheresis. Maintenance therapy uses azathioprine or other immunosuppressants[1] that can be continued for up to 36 months and are associated with a 66% reduction in the risk of relapse[9]. The most frequent treatment in case of pituitary compromise is usually the combination of corticosteroids and cyclophosphamide, or alternatively rituximab, azathioprine, mycophenolate mofetil, methotrexate, and infliximab[1]. In the case of meningitis, it is usually the conventional or in refractory cases regimens with rituximab[1].

The use of rituximab has been effective in preventing relapses and is superior to azathioprine in maintaining remission; however, it is not yet clear whether it is effective for treating the disease with CNS involvement[9,10]. It is even suggested that it may have a greater effect in the treatment of vasculitis than of granulomas[1]. The doses used in these therapeutic regimens are Rituximab 375mg/m2 weekly for four weeks, Methotrexate 15-25mg per week with folic acid, and Methylprednisolone 500-1000mg intravenously per day for three days, followed by Prednisolone 0.5-1mg/kg/day for four weeks. The maintenance doses are Twelve to eighteen months with azathioprine 2mg/kg/day, methotrexate, leflunomide 20-30mg/day, rituximab 1g every six months for two years, and adjuvant with cotrimoxazole 800/160mg three times a week[3].

Surgery allows a wide resection of the granuloma, which allows taking adequate samples for diagnosis and aids the medical treatment. This reduces the disease, the amount of additional medication that is potentially harmful,[12] and morbidity[7]. Some authors recommend surgery when lesions are located in accessible spaces and without the involvement of critical areas since imaging studies are not useful to make an adequate differential diagnosis[12]. Low invasive approaches are recommended. If this were not possible, it is recommended that single-time surgical resections be planned[7]. In rare cases of primary meningeal involvement, a dura mater biopsy may be necessary to confirm the diagnosis; even transinusal or transsphenoidal approaches could be made[7].

The prognosis and remission are reported in more than 90% of cases with treatment, especially if they have not developed kidney damage[2]. Without treatment, 82% of patients die within a year[2]. The 10-year survival rate if the kidneys are compromised is 40% versus 60-70% if they are not [2]. CNS involvement is associated with a refractory course of the disease or failure with typical treatments[10]. The evolution in treated patients is favorable, with pituitary involvement having a clinical remission of 69%, and with lower relapses in patients initially treated with cyclophosphamide.[1]. The prevalence of sequelae in patients with cerebral pachymeningitis (31%) or pituitary involvement (0%) is low; however, patients with spinal cord pachymeningitis (100%) or ischemic or hemorrhagic

forms (73%) have a poor prognosis[7,9] and is associated with the need for a new induction regimen for refractory disease or relapse[9].

Among the complications reported in these patients is a local immunodeficiency with a low capacity to develop immunity against Staphylococcus aureus, which, added to the consumption of steroids and immunosuppressants, puts patients at high risk of infection [7]. This occurred in the present case, where the patient had a Klebsiella Pneumoniae infection.

Conclusions

We can conclude that GP with CNS involvement is a rare disease that poses a diagnostic challenge due to its nonspecific clinical manifestations and non-pathognomonic imaging findings. It requires a multidisciplinary approach, which includes neurosurgery, since invasive procedures can allow, in addition to a local resection, the taking of samples for histopathological studies that facilitate reaching an accurate diagnosis--as in the present case. Additionally, it is necessary to evaluate the postoperative risks due to immunosuppression, such as infection, derived from the disease and the consumption of medications, which leads to weighing the risk and benefit of these behaviors and making the best decision for the patient.

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