Neuropatia Craniana como Manifestação de Vasculite Sistémica: Caso Clínico

Cranial Neuropathy as Sign of Systemic Vasculitis: Clinical Case

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Resumo:

As vasculites são um grupo heterogéneo de doenças caracterizadas por inflamação e necrose da parede dos vasos sanguíneos. As vasculites associadas a anticorpos anti-citoplasma de neutrófilos (ANCA) são vasculites de pequenos vasos e incluem a poliangeíte microscópica, a granulomatose com poliangeíte e a granulomatose eosinofílica com poliangeíte. As vasculites podem ameaçar a vida. A imunossupressão é a base do tratamento.

Apresentamos o caso de um homem de 55 anos, que em Setembro de 2020 recorreu ao serviço de urgência com febre, suores nocturnos, mialgias e astenia. Associadamente, referia aparecimento de púrpura palpável em ambas as pernas e artralgias de carácter inflamatório, simétrico e migratório. Internado no serviço de medicina interna, desenvolvendo ao longo da hospitalização cefaleia, paralisia facial periférica esquerda, hipoacúsia neurossensorial bilateral ligeira e nistagmo horizontal. O estudo analítico revelou positividade para ANCA proteinase 3 (PR3) e aumento dos parâmetros inflamatórios. O diagnóstico de vasculite sistémica ANCA PR3 positiva com neuropatia craniana envolvendo o VII e VIII pares cranianos foi estabelecido e o doente iniciou rituximab e corticoterapia em alta dose. Verificou-se regressão completa dos sintomas sistémicos e melhoria gradual da neuropatia craniana.

Apesar de incomum, a neuropatia craniana pode ser uma manifestação definidora de uma vasculite ANCA positiva, tal como mostramos neste caso clínico.

Palavras-chave: Doenças do Sistema Nervoso; Vasculites.

Abstract:

Vasculitides are a heterogeneous group of diseases, characterized by inflammation and necrosis of the blood vessel walls. Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a small vessels vasculitis and include microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis.

Vasculitides can be life threatening. Immunosuppression is the cornerstone of therapy.

We present the case of a 55-year-old man who in September of 2020 was evaluated in the emergency department for fever, night sweats, myalgia and asthenia. At the same time he had palpable purpura in both legs and inflammatory, symmetrical and migratory arthralgias. He was admitted to an internal medicine ward and during the hospitalization he developed headache, left peripheral facial paralysis, mild bilateral sensorineural hearing loss and horizontal nystagmus. Blood analysis revealed positive proteinase 3 (PR3) ANCA and raised serum inflammatory markers. The diagnosis of PR3-ANCA positive systemic vasculitis with cranial neuropathies involving the VII and VIII pairs was established and he started rituximab and high dose steroids with complete regression of the systemic symptoms and gradual improvement of the cranial neuropathies.

Although uncommon, cranial neuropathy can be the defining manifestation of ANCA-positive vasculitis, as shown in this clinical case.

Keywords: *Nervous System Diseases; Vasculitis.*

Introduction

Vasculitides are a heterogeneous group of diseases, characterized by inflammation and necrosis of the blood vessel walls, mainly arteries. We can divide them into primary and secondary vasculitides.[1-3]

According to the 2012 revision of the Chapel Hill Consensus Conference (CHCC), vasculitides are divided in seven groups: small, medium or large vessels vasculitis, vasculitis of varying vessel size, single organ vasculitis, associated with systemic disease and associated with probable etiology. However, this classification continues to evolve as knowledge of the pathogenesis advances and the ACR and EULAR are currently revising the classification and diagnosis criteria for the Diagnostic and Classification Criteria for Vasculitis study (DCVAS). Vasculitides associated with anti-neutrophil cytoplasmic antibody (ANCA) are small vessels vasculitis and this group includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[4,5]

Worldwide, giant cell arteritis is the most common vasculitis in adults with the annual incidence around 240 per million,

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while GPA, MPA and EGPA have been reported at an incidence anywhere from 1 to 10 per million.[1]

The etiology of primary vasculitis is unknown, involving genetic and environmental factors.[1,4]

Vasculitides usually present with nonspecific clinical manifestations including fever, myalgia, arthralgia, significant weight loss and general malaise. Normocytic and normochromic anemia, thrombocytosis and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are common findings, revealing an inflammatory state. Each type of vasculitis also has particular symptoms and findings.[4,6]

Most of these diseases are life-threatening conditions, but prognosis is variable, relating not only to the disease itself, but also to the patient, response to treatment and its side effects.[1,4]

Case Report

We describe the case of a 55-year-old man, former smoker of 5 pack-year, with a relevant personal history of untreated hypertriglyceridemia and a tubular adenoma with low-grade dysplasia of the ascending colon, removed in 2018. The patient presented to the emergency department complaining of a 2-week history of vespertine fever, night sweats, myalgias and asthenia. He also reported symmetrical, migratory polyarthralgias, first of the elbows, later migrating to the ankles bilaterally and then the right knee, and a non-pruritic-rash in the lower limbs and inguinal regions. The signs and symptoms started after a 4-day trip to a rural area, but the patient denied contact with animals or other risk contacts.

On admission, a palpable purpura involving the lower limbs was noticed, as well as petechiae in the soft palate and edema and tenderness of both ankles. Initial blood work is shown in Table 1. A thoracoabdominopelvic computed tomography (CT) revealed only mild hepatosplenomegaly.

Because of the possibility of a zoonosis, the patient was started on doxycycline 100 mg twice daily and admitted for etiological study. The arthralgias and skin rash rapidly resolved and therefore skin biopsy was not performed. However, fever was sustained, with two to three episodes per day.

An extensive study to exclude infectious causes was performed (Table 2). Transthoracic echocardiogram showed no signs of endocarditis. Peripheral blood immunophenotyping showed no evidence of lymphoproliferative disease.

On the ninth day of hospitalization, the patient developed frontal headache and left peripheral facial palsy (PFP) grade 5 on the House-Brackman scale. Brain and ear CT scans revealed no lesions. A lumbar puncture was performed and the obtained cerebrospinal fluid (CSF) was clear with 1 cell and very mild proteinorrachia (48.1 mg/dL, for a normal range of 15-45). PCR for *Herpes simplex* type 1 and 2 was negative. Oligoclonal bands in CSF were also negative. Treatment for PFP was started with prednisolone 60 mg per day and artificial tears, ocular occlusion at night and physiotherapy. From that moment, the fever completely resolved and all analytical parameters improved.

However, on the fourteenth day of hospitalization, hearing loss was noticed. Otoscopy showed no signs of otitis. The audiogram was compatible with bilateral mild sensorineural hearing loss. A right horizontal nystagmus was noticed on physical

Table 1: Initial blood work.

	Result	Normal Range
Hemoglobin (g/dL)	13.6	13-18
Leucocyte count (x103/µL)	3.82	4-11
Lymphocyte count (x103/µL)	0.2	0-0.7
Creatinine (mg/dL)	0.8	0.7-1.3
Lactate dehydrogenase (U/L)	359	125-220
Aspartate aminotransferase (U/L)	241	5-34
Alanine aminotransferase (U/L)	317	< 55
Total bilirubin (mg/dL)	1	0.2-1.2
Gamma glutamyl transferase (U/L)	199	12-64
Alkaline phosphatase (U/L)	161	40-150
C-reactive protein (mg/L)	185.40	< 5
Erythrocyte sedimentation rate (mm/1st hour)	22	0-22
Procalcitonin (ng/mL)	4.58	< 0.5
Ferritin (ng/mL)	794.85	21.81-274.66
Urinary sediment	Normal	

Table 2: Infection serologies.

	Result
Blood cultures	Negative
HIV serology	Negative
PCR for SARS-CoV-2	Negative
Coxiella burnetti serology	IgG and IgM negative
Borrelia burgdorferi serology	IgG and IgM negative
Rickettsia conorii serology	IgG and IgM negative
Epstein-Barr virus serology	IgG and IgM negative
Parvovirus B19 serology	IgG and IgM negative
Cytomegalovirus serology	IgG and IgM negative
Herpes simplex type 1 serology	IgG and IgM negative
Herpes simplex type 2 serology	IgG and IgM negative
Wright reaction	Negative
PCR for *Chlamydia trachomatis* in urine	Negative
PCR for *Neisseria gonorrhea* in urine	Negative
PCR for *Ureaplasma urealyticum* in urine	Negative
PCR for *Mycoplasma genitalium* in urine	Negative
PCR for *Borrelia burgdorferi*	Negative
PCR for *Leptospira* spp	Negative
Hepatitis B serology	Not immune
Hepatitis C antibody	Negative
IGRA test	Negative

examination, without other neurological deficits. Cerebral magnetic resonance angiography was normal. The results of the immunological study revealed a positive proteinase 3 (PR3) ANCA (5.7 U/mL, for a normal of <2 U/mL). Myeloperoxidase (MPO) ANCA, antinuclear antibodies, extractable nuclear antigen antibodies panel, rheumatoid factor, human leukocyte antigen B27 and complement (C3 and C4) were normal.

A diagnosis of ANCA positive vasculitis, probable GPA, presenting with cranial neuropathies involving the VII and VIII pairs was assumed and the patient started treatment with 4 weekly doses of rituximab 375 mg/m^2. Corticoid was gradually tapered. Two months later, facial peripheral paralysis was the only remaining *sequelae*, no other symptoms were reported, and inflammatory markers were normal.

Discussion

According to epiReuma.pt (the online Portuguese register of rheumatological diseases), the most frequent ANCA-associated vasculitis in Portugal is GPA.[7] This disease is characterized by necrotizing granulomatous inflammation associated with antibodies against PR3 and affects predominantly small to medium vessels.[8]

The presence of PR3-ANCA is not pathognomonic of this pathology. It can be positive in infectious diseases (like tuberculosis, endocarditis and *Pseudomonas aeruginosa, Staphylococcus aureus*, hepatitis B, hepatitis C and HIV infections), other autoimmune diseases (like systemic lupus erythematosus, ulcerative colitis and rheumatoid arthritis), cystic fibrosis and after usage of different drugs (like hydralazine, minocycline, methimazole, propylthiouracil, sofosbuvir, allopurinol, penicillamine, procainamide, clozapine, phenytoin, rifampicin, cefotaxime, isoniazid, indomethacin and cocaine). Also, ANCA are negative in 6%-18% of patients with either GPA or MPA, and 20% to 30% of patients with clinical GPA are MPO-ANCA (instead of PR3).[4,5,9-12]

The most common involved sites in GPA are the upper and lower respiratory tract, the ear, and the kidney. Symptoms and signs reported include nasal, oral, and pharyngeal ulcers, epistaxis, nasal polyps, chronic sinusitis, nasal cartilage destruction, otitis, cough, dyspnea, hemoptysis, diffuse alveolar

hemorrhage and cavitated pulmonary nodules. Glomerulonephritis is also frequently present.[13]

Neurological complications develop in 30%-50% of all cases. Mononeuritis multiplex is the most frequent neurological manifestation (70%-90%). Involvement of the central nervous system (CNS) is much less frequent and proposed mechanisms include contiguous spread of granulomatous tissue from adjacent sites such as the middle ear or sinuses, primary granuloma formation in the CNS and vasculitis. Cerebrovascular events such as bleeding venous thrombosis and infarctions can develop. Granulomatous involvement of the meninges (pachymeningitis) is a rare manifestation that can present as headache and seizures.[13,14]

The diagnosis of GPA limited to the CNS is challenging. Seventy percent of patients have lymphocytic pleocytosis and mild proteinorrachia. Brain magnetic resonance imaging (MRI) reveals enhancement of the leptomeninges, focal thickening of the dura and non-specific white matter lesions. Cranial neuropathies (involving almost any cranial nerve) are uncommon, affecting less than 10% of patients, but it can be the presenting sign in some cases, suggesting that cranial neuropathy could be a unique inaugural mode of manifestation of vasculitis.[13,14]

Immunosuppressive therapy is the basis of treatment, and the choice of immunosuppression will take into account the assessment of the Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI). According to the EULAR recommendations the presence of ANCA-associated vasculitis without life-threatening manifestations is treated with a combination of glucocorticoids with methotrexate or mycophenolate mofetil; if a life-threatening manifestation occurs, the recommended regimen is a combination of glucocorticoids with rituximab or cyclophosphamide to induce remission. In case of diffuse alveolar hemorrhage or renal failure, plasmapheresis should be performed. When remission is achieved, glucocorticoid tapering must ensue and azathioprine, methotrexate or rituximab should be initiated. After 2 years of remission, immunosuppressants can eventually be discontinued. In our clinical case, the patient presented a disfiguring and potential life-threatening involvement - cranial neuropathy - the reason why he started the combination of rituximab with glucocorticoid.[15]

The long-term follow-up of these patients involves determination of the ANCA activity because their increase or persistence can indicate a greater risk of recurrence. Elevated C-reactive protein and erythrocyte sedimentation rate are indirect and nonspecific markers. ANCA-associated vasculitides have a poor prognosis and they have a big impact on morbidity, mortality, quality of life and health costs.[15]

Conclusion

Through this clinical case, we were able to highlight a complex and potential life-threatening syndrome that is many times misdiagnosed. ■

Apresentações / Presentations

This clinical case was already presented on 27th National Congress of Internal Medicine, in 2021, like an e-poster.

Declaração de Contribuição

DN, RLF, PRR, IC - Elaboração do manuscrito e aprovação final.
Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

DN, RLF, PRR, IC - Preparation of the manuscript and final approval.
All authors approved the final draft

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