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Cranial nerve impairment in granulomatosis with polyangeitis (GPA) C-ANCA negative

Acometimento de nervos cranianos na granulomatose com poliangeíte (GPA) C-ANCA negativo

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Abstract

This report aims to show an unusual case of granulomatosis with polyangeitis (GPA), previously known as Wegener's granulomatosis. It is a multisystemic disease characterized by necrotizing granulomatous inflammation and vasculitis involving mainly the upper and lower respiratory tract, although not infrequently, there is neurological impairment.

Keywords: Granulomatosis with polyangeitis; Neurological manifestations; Cranial nerves

Resumo

O presente relato tem o objetivo de mostrar um caso incomum de Granulomatose com Poliangeíte (GPA), que previamente era denominada Granulomatose de Wegener. Trata-se de é uma doença multissistêmica, caracterizada por inflamação granulomatosa necrotizante e vasculite que envolve principalmente o trato respiratório superior e inferior, embora não raramente, exista comprometimento neurológico.

Descritores: Granulomatose com poliangeíte; Manifestações neurológicas; Nervos cranianos

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Introduction

Although initially described in the literature by Kilinger[1] in 1931, only in 1936 with Friedrich Wegener[2] in a review of three patients with nasal granuloma the disease now known as granulomatosis with polyangeitis (previously known as Wegener's granulomatosis) was isolated and characterized as an entity distinct of the other systemic vasculitis previously described. In 1939, Fiemberg[3] together with Carrington and Liebow[4] described the limited GW, a disease with pathology restricted to one or more organs. In 1954, Godman and Churg[5] published the GPA systemic affection with the definition of the three classic criteria: necrotizing granulomatous lesions in the respiratory tract, systemic vasculitis, and glomerulonephritis.

GPA is a rare disease/condition with a probable autoimmune mechanism of unknown etiology and systemic involvement, with necrotizing vasculitis of small and medium vessels (e.g., Capillaries, venules, arterioles, arteries and veins), with formation of granuloma.[6] Necrotizing glomerulonephritis also is common, in addition to ocular vasculitis and pulmonary capillaritis. Granulomatous and non-granulomatous extravascular inflammation is associated, although limited or restricted forms to a single organ or system may occur. It also affects men and women, predominating in individuals from the fourth to the fifth decade of life. [7] The estimated prevalence is 3 to 5 cases per 100,000 inhabitants. (8,9)

The diagnosis of GPA is based on clinical, radiological, serological and anatomopathological criteria. The American Academy of Rheumatology defines the following as classification criteria,[10] published in 1990:

(1) Nasal or oral inflammation (e.g., Colored or non-colored oral ulcers; Bloody nasal discharge);

(2) Abnormal chest radiograph with nodules, fixed infiltrates or cavitations;

(3) Urinary sediment with microhematuria or hematic cylinders;

(4) Granulomatous inflammation in biopsy (e.g.: Artery wall, perivascular or extravascular region of arterioles or arteries).

The presence of two or more criteria defines the diagnosis of GW, with a sensitivity of 88.2% and a specificity of 92.0%.[10]

The presence of C-ANCA[11] (Autoantibody directed against the cytoplasm of neutrophils) in the serological exam of the patient can aid in the diagnosis, with sensitivity of 91% (It can reach 97% in case of typical Clinical-Radiological Syndrome) and specificity of 99%.[12] Currently, the confirmation of a positive C-ANCA, the performance of antibody-antiproteinase-3 is imperative. However, the sensitivity depends on the activity and extent of the disease.[12,13] Unfortunately the C-ANCA standard and its above-mentioned correlated antibody are not useful for monitoring disease activity and predicting recurrence.

Recognition of neurological complications became evident in 1936, when Drachman[14] analyzed the spectrum of neurological manifestations by separating them into central and peripheral nervous system abnormalities. In 1993, Nishino et. analyzed the neurological involvement in 324 patients diagnosed with GPA, and showed that 109 (33.6%) had evident neurological alterations, 53 (16.3%) had peripheral neuropathy, 21 (6.4%) had neurological disorders with cerebral involvement, mainly II, VI and VII(15), 16 (4.9%) with external ophthalmoplegia, 13 (4.01%) with cerebrovascular events, 10 (3.08%) with epilepsy, 5 (1.5%) with cerebitis, and 25 (7.7%) with diverse manifestations. Of the peripheral neuropathies, 42 (12.9%) of patients presented multiple mononeuropathy, 6 (1.8%) symmetrical distal mononeuropathy, and 5 (1.5%) had no possible classification.

The following case description aims to describe and disseminate an atypical GPA case, with initial manifestation of unilateral necrotizing scleritis associated with refractory secondary headache, which with clinical evolution and follow-up in the subsequent months progressed to a condition with multiple unusual neurological syndromes.

Case Report

A 34-year-old female, white, married, evaluated at the Otorhinolaryngology Emergency Room with a 7-day history of right hemicranial throbbing headache of high intensity and without relieve with the use of dipyrone, associated with otalgia, paraesthesia in the right hemitongue, fever, epistaxis, dysphagia, odynophagia and dysuria.

Hysterectomy 3 months before admission due to endometritis. Sclera transplant performed 35 days before admission due to necrotising scleritis in the right eye.

The general physical examination revealed: regular general condition, stained and hydrated mucosae, acyanotic, anicteric, afebrile at the time, and bipalpebral edema. Pulmonary auscultation: vesicular murmurs present bilaterally, without adventitious noise, respiratory rate: 14ipm, euphonic in ambient air. Heart auscultation: Rhythmic and normophonestic bulbs at 2 time, without audible murmur, HR 132bpm, PA 110x85. Examination of the abdomen: semi-globose, normotensive, hydroaeurical noises present, without palpable visceralgia, painful palpation of the epigastric region. Limb examination: without evidenced edema, free calves, without evident alterations.

Neurological examination: guidance: vigilant, auto and alo oriented. Balance and coordination: Romberg negative, eudiacodocinetic and eumetric. Motility: Strength preserved globally, tremors in both hands of intent, and preserved tone. Sensitivity: paraesthesia in the right hemitongue, tactile and deep sensitivity preserved. Reflectivity: Hypoactive reflexes in lower limbs and hyperactive grade 3 in upper limbs. Cranial nerves: decreased visual acuity on the right, bilateral convergent strabismus, hypoesthesia of the right hemitongue, deletion of the nasolabial sulcus on the left, paresis of the right tongue, decreased right auditory acuity (Weber on the right, conduction pattern). Neurovegetative system: preserved. Trophicity: preserved. Words and language: preserved. Sphincters: involuntary urinary loss. Mental functions: nervousness, emotional lability.

Ophthalmic examination: bipalpebral ecchymosis, vascularized and topical sclera transplant, intact topical sutures, and transparent cornea. Visual acuity without correction 20/70 and 20/20. Eye fundus unchanged.

Entrance examinations: Hemogram: red series: Hb 4.5 Hc 13.4 Ht 49.0; White series: Lc 13,300 (Differential: 2-65-3-0-24-6); Platelet series: 421,000. PCR 335.2 and HSV 43.0. Urea 23.4, creatinine 0.62, sodium 141, potassium 4.02. Urine test: turbid, pH 6.0, density 1.030, Hc 250.000 Lc> 1,000,000, protein 3+, hemoglobin 3+, bilirubin 1+, absent nitrites. Uroculture sensitive to E. coli.

A syndromic diagnosis of Pain syndrome and/or Infectious syndrome (repetitive UTI), Motor deficiency Syndrome (Tetraparesis of right predominance), Cranial nerve syndrome and Inflammatory syndrome (increased HSV and CRP) was performed.

Investigation was started for systemic disease and for better elucidation of the case. Complementary tests were requested that evidenced:

Autoantibodies: Anti-ANCA (Anti-ANCA and Anti-ANCA), Anti-RNP, Anti-3M, Anti-CCP, HLA-B27, Anti-Mi 2, Anti-SSO, Anti-TPO, Anti-Thyroglobulin, Anti-TSH trab, Anti-LA/SSB, Anti-Jo1 and FAN being all negative. The Rheumatoid Factor was 17. Thyroglobulin of 8.79.

Liquor: Clear and colorless, 0 cells, glucose 51, protein 33, chloride 691, lactate 16, negative VDRL, negative china ink and negative GRAM.

Serologies: HBsAg, Anti HBS, HIV 1 and 2 and VDRL non-reactive. Toxoplasmosis IgG positive and IgM negative. Anti-HCV undetermined. CMV IgG and IgM positive (CO index = 1.15).

Supplementary imaging exams described in Figures 1, 2.

Electronuromyography (ENMG): The test revealed stable sensory-motor peripheral neuropathy of motor predominance (Table 1).

Table 1
Study of the neuroconduction of sensory and motor nerves

Sensory nerve conduction study						
Nerves	**Stimulus Point**	**Registration point**	**UV amplitude**	**Latency ms**	**Latency ms**	**VCS m/s**
Right median	II finger	fist	36.7	2.68	12.5	46.6
Right ulnar	V finger	fist	12	2	10	50
Left median	II finger	fist	30	2.4	12.5	52.1
Left ulnar	V finger	fist	10	2	10	50
Right sural	calf	ankle	20	3.16	13.5	42.7
Left sural	calf	ankle	18	3.12	13.5	43.3
Sensory nerve conduction study						
Nerves	**Stimulus Point**	**Registration point**	**UV amplitude**	**Latency ms**	**Distance cm**	**VCS m/s**
Mediano direito	fist	APB	9.13	3.24		
	elbow	APB	8.13	7.84	25	54.3
Onda-F				26		
Ulnar direito	fist	ADM	7	1.92		
	elbow	ADM	6	6,9	25	50.2
Onda-F				26		
Mediano esquerdo	fist	APB	11	3.04		
	elbow	APB	10.7	7.24	25	59.5
Onda-F				26.2		
Ulnar esquerdo	fist	ADM	7	2		
	elbow	ADM	6.5	6.76	25	52.5
Onda-F				26		
Sensory nerve conduction study						
Nerves	**Stimulus Point**	**Registration point**	**UV amplitude**	**Latency ms**	**Distance cm**	**VCS m/s**
Right fibular	ankle	EDB	5.4	4.08		
	fibula head	EDB	4.73	11.8	32	41.7
F-wave				44		
Left fibula	ankle	EDB	3.6	4.44		
	fibula head	EDB	2.9	12.3	32	40.7
F-wave				44.5		
Right H-reflex				NO		
Left H-reflex				NO		
F-wave				26		

Clinical development

The patient underwent biopsy of the pulmonary nodule, which showed: Areas of parenchymal necrosis surrounded by malformed granulomas.

Points of lipoididial pneumonia (macrophage + fat), hyperplasia of type II pneumocytes and alveolar hemorrhage.

Infectious diseases excluded.

She evolved with improvement of the general condition with the treatment instituted, antibiotic therapy (ceftriaxone and tazocin), for the ongoing urinary infection, and after clinical correlation with the findings of chest CT, MRI of the skull and ENMG, the hypothesis of Granulomatosis with Poliangeitis ANCA-negative was raised.

The patient was treated with a pulse therapy regimen with cyclophosphamide and methylprednisolone. Maintenance corticosteroid therapy was kept, and the patient was discharged 27 days after admission for ambulatory follow-up, in good general condition, without pain complaints nor urinary incontinence and altered neurological examination.

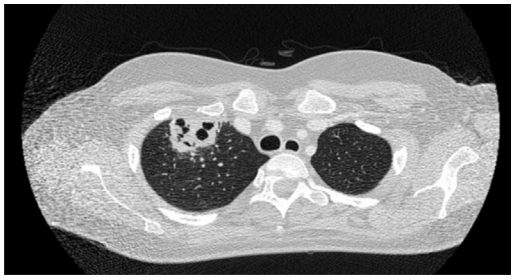

Figure 1: Chest computed tomography: Nodules and lung masses distributed peripherally in medium and mainly upper lung fields with central excavated areas bilaterally. Associated with clinical history, consider vasculitis in the differential diagnosis (Granulomatosis with Polyangeitis?).

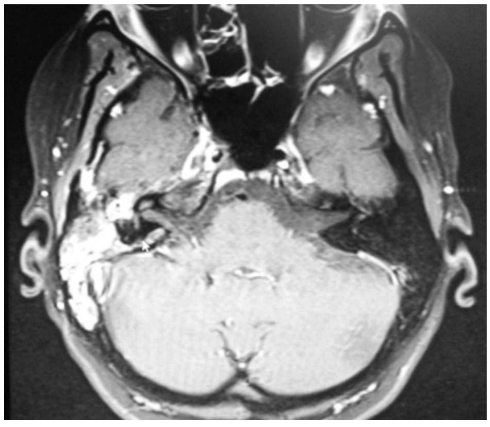

Figure 2: Magnetic nuclear resonance (MRI) of the skull: Apparent anomalous pachymenngeal enhancement around the cerebral hemispheres and mastoidopathy on the right.

Discussion

It is a rare disease whose involvement may involve any organ or system. Neurological involvement in granulomatosis with polyangeitis is a rare feature of it and tends to be primarily a neuropathy of cranial nerves associated or not with peripheral neuropathy. Peripheral neuropathy occurs in up to 67% of cases in the form of sensory-motor peripheral polyneuropathy or Multiple Mononeuropathy secondary to vasa vasoritis of vasa nervorum, and may represent the first manifestation of the disease. [16]

Neuro-ophthalmologic involvement is common during the course, and cranial nerve involvement may be isolated or multiple pairs. Typically involved are optic and olfactory nerves (27% of patients), involvement of those involved in extrinsic ocular motility, but all of them may be impaired, especially in the peripheral extracranial pathway due to a locally destructive and/or granulomatous inflammatory process. Of these, orbital granulomatous masses tend to be more frequent, determining compressive cranial neuropathies. [14]

Despite potent and aggressive immunosuppression, rates of morbidity, damage, and impairment of the nervous system tend to be high, emphasizing the need for its early recognition and treatment in order to minimize chronic sequelae. [16]

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