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Granulomatosis with polyangiitis: An atypical initial presentation

Catarina Vilaça Pereira *, Filipa Silva, Fernando Nogueira, José Cunha Marques, Edite Pereira, Carlos Dias, Jorge Almeida

Centro Hospitalar e Universitário São João, Portugal

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis of small and medium vessels with involvement of the upper and lower respiratory tract and necrotizing pauci-immune glomerulonephritis [1]. This vasculitis has a higher incidence in men in the sixth decade of life and more than 80% of patients have positive anti-neutrophil cytoplasm (ANCA) antibodies [1,2].

We present the case of a 23-year-old man with two weeks of evolution with polyarthralgia, asthenia, and cough with hemoptoic sputum. He did a chest radiography that showed diffuse bilateral alveolar infiltrates, on the second stage. The patient presented a rapid clinical worsening, with moderate hemoptysis and severe respiratory failure requiring invasive mechanical ventilation.

The autoimmune study revealed positivity for ANCA PR3 in titer >200, having started pulses of methylprednisolone, plasmapheresis and later cyclophosphamide, with clinical improvement. His high-resolution chest computed tomography (CT) showed areas of diffuse ground glass densification suggesting capillaritis/alveolar hemorrhage and two subpleural nodular areas suggestive of granulomatous vasculitis. CT of the nasal sinuses showing findings compatible with acute inflammatory changes, with histology of the nasal mucosa inconclusive. Thus, this case shows an exuberant and potentially fatal form of diffuse alveolar hemorrhage that culminated in the initial diagnosis of granulomatous vasculitis in a young adult.

1. Introduction

Granulomatosis with polyangiitis (GPA) is characterized by necrotizing vasculitis that preferably affects small and medium vessels, with granulomatous inflammation in histology [1]. The etiology of this disease remains unknown, and there are several hypotheses that try to support it [2,3]. It is characterized for being potentially systemic with greater involvement of the upper and lower respiratory tract and necrotizing pauci-immune glomerulonephritis [1]. Epidemiologically, it has a higher incidence in men and a peak incidence between 65 and 75 years old. Analytically, more than 80% of patients have ANCA positive antibodies, the most with a PR3 pattern [1,4]. The diagnosis is mainly clinic, complemented by the analytical study and imaging studies. When possible biopsy of the affected organ should be performed [2]. Excluding other conditions such as infections, drugs or malignancy is mandatory. In relation to organ damage, most patients (51–80%) have renal involvement and more than 90–95% of patients have an upper respiratory tract involvement [1,2], with alveolar hemorrhage being described in only 5–15% of cases, depending on the series. GPA presents a course with some unpredictability, with clinical conditions with different degrees of severity, ranging from mild symptoms to potentially fatal symptoms [2,5,6].

The therapeutic approach includes, naturally, as other autoimmune diseases, immunosuppression (different regimens, depending on the severity of the disease), and remission without therapy is possible, but recurrence is frequent, particularly in GPA [2,7].

2. Case presentation

We present the case of a 23-year-old Caucasian male, with no significant medical history who presents polyarthralgia, myalgia, coughing and asthenia with about two weeks of evolution. The arthralgias were in the medium-sized joints (wrists, elbows, knees and ankles), symmetrical, constant and exacerbated by activity. He also had a non-productive cough. He denied other complaints, namely skin, visual or gastrointestinal changes. He had no complaints of low back pain or axial arthralgia, night sweats, fever, weight loss, anorexia or other constitutional symptoms. Initially, he was evaluated in primary health care, diagnosed with

* Corresponding author.
E-mail address: catarinavilacapereira@gmail.com (C.V. Pereira).

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respiratory infection and treated empirically with cetirizine, acetylcysteine, paracetamol and amoxicillin/clavulanic acid. Due to the persistence of symptoms and the worsening of their intensity and the appearance of a cough with hemoptoic expectoration, he went to the emergency department of the hospital in his area of residence.

In admission to the emergency department, he was alert and oriented, with a normal blood pressure and heart rate, apyretic, eupneic, with no signs of respiratory distress and with 98% peripheral saturation (FiO2 21%). Examination of the oropharynx and otoscopy showed no changes. Cardiac and pulmonary auscultation, as well as remaining objective examination without relevant changes, namely without inflammatory signs at the joints. Chest X-ray (Fig. 1) showed normal cardiothoracic index and with no evidence of infiltrates or consolidations and the arterial blood gas analysis did not show any significant changes, namely hypoxia. The blood tests on admission revealed leukocytosis (13 790/μL) with eosinophilia (1840/μL), seric sodium of 133 mmol/L and elevation of C-reactive protein 1.72 mg/dL (reference value 0.02–0.75), with speed normal sedimentation (3 mm 1st hour). Urinary sediment presented with proteinuria of 10 mg/dL (normal value < 10), erythrocyturia 14 cells/field (normal value 0-

2). He remained under observation in the emergency department and, approximately 24 hours later, he developed dyspnea, hemoptoic expectoration and hypoxemic respiratory failure. On physical examination, he was pale and polypneic (respiratory rate 26 cycles per minute), with peripheral oxygen saturation of 89% (FiO2 21%), without new relevant finding on examination. Repeated arterial blood gas analysis that showed now hypoxemic respiratory failure (FiO2 21%, pH 7.52; pO2 57 mmHg; pCO2 33 mmHg; HCO3- 26.9; Ratio PO2/FiO2 271).

The chest X-ray now showed bilateral infiltrates (Fig. 1). The electrocardiogram presented with sinus rhythm, hadn't any relevant changes.

Ziehl-Neelsen staining on sputum and urine antigen tests for Legionella and Streptococcus pneumoniae were negative, as serological tests for HIV and hepatitis B and C were negative. Analytically, it maintains the leukocytosis previously described and showed a decrease of about 2 g of hemoglobin (11.1 g/dL) and C-reactive protein of 7.93 mg/dL, with a normal coagulation study. In view of this evolution, he started empirically oseltamivir, azithromycin, aminocaproic acid, codeine and supplemental oxygen therapy titrated up to a high concentration mask without satisfactory response.

In this context of severe respiratory failure, he was transferred to an Intermediate Care Unit.

In view of the chest radiography nonspecific findings, he performed a computed tomography scan of the chest that revealed areas of densification of the pulmonary parenchyma, both in he upper and lower lobes, most evident on the right, some in ground glass, of probable infectious nature (Fig. 2).

On the same day, he underwent bronchofibroscopy, which revealed

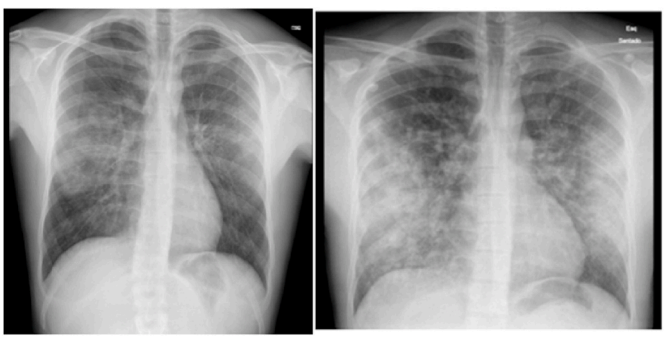

Fig. 1. Chest radiography at admission and 24h after admission.

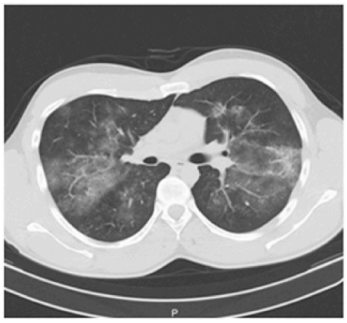

Fig. 2. Axial computerized tomography 24h after hospital admission.

marked hypertrophy of the nasal mucosa and presence signs of recent bleeding and hematic secretions throughout the bronchial tree. Bronchial and bronchoalveolar lavage was carried out and alcohol-acid resistant bacilli with *Ziehl-Neelsen* staining and PCR of *Mycobacterium tuberculosis* were negative, as well as a mycobacterial culture. In addition, a summary autoimmune study was undertaken. On 9/01, the patient condition worsens, with severe type 1 respiratory failure (ratio PO2/FiO2 110) in the context of diffuse alveolar hemorrhage, requiring sedation, orotracheal intubation and invasive mechanical ventilation, and he was transferred to our hospital for admission to the intensive care unit (UCI). At this point, the result of the autoimmune study previously performed is known, which revealed positivity for ANCA titers 1/160 (reference value < 1/20), with a c-ANCA PR3 177 U (reference: very strong positive> 30). Thus, treatment with corticosteroids was implemented (pulses with 1g EV methylprednisolone for 3 consecutive days) and five plasmapheresis sessions with total plasma replacement and subsequent switch to oral prednisolone (1 mg/kg/day).

At the ICU, a 4-day course with empirical antibiotics and antivirals (ceftriaxone + azithromycin + oseltamivir) was used. Bronchofibroscopy was repeated four days later and revealed intense neutrophilic alveolitis with mild eosinophilia and positive Pearls' staining, compatible with moderate hemorrhage. Bacteriological, mycobacteriological and virological exams were negative.

On January 15, a first dose of cyclophosphamide (15mg/kg) was administered, according to the Cyclops protocol [8,9]. During the ICU stay he had some complications such as urinary tract infection by multisensitive *Pseudomonas aeruginosa* (for which he completed seven days of piperacillin/tazobactam), hyperactive delirium which required titration of psychiatric drugs (dexmedetomidine, alprazolam, clonidine and quetiapine) and critical illness myopathy for which he started an active rehabilitation program. Due to a favorable clinical evolution, he was transferred to the ward of the Internal Medicine service on 24/01, where on admission he was asymptomatic, without respiratory failure. He was consulted by Ophthalmology, which excluded ocular vasculitis involvement. In the Internal Medicine ward, a high-resolution computed tomography is repeated, which revealed diffuse areas of ground glass, more diffuse in the lower lobes, probably reflecting the manifestation of capillaritis/alveolar hemorrhage and which described two areas of nodular densification in the subpleural aspect of the pulmonary bases 3 cm to the right and 2 cm to the left, the latter with small cavitation, aspects that in the context may be a manifestation of granulomatous vasculitis (Fig. 3).

Peripheral sinus CT scan and orbit was performed, which revealed bilateral maxillary sinus mucosal thickening (Fig. 4), with biopsy of this tissue revealing acute inflammatory lesions with focal ulceration, that is, non-specific inflammatory changes.

During the internment in an Internal Medicine Service, he maintained immunosuppressive treatment with prednisolone 60 mg/day and prophylaxis against *Pneumocystis jirovecii* infections with cotrimoxazole, and a second dose of cyclophosphamide (15mg/kg) was performed on the 14th day, according to the protocol previously mentioned. He was

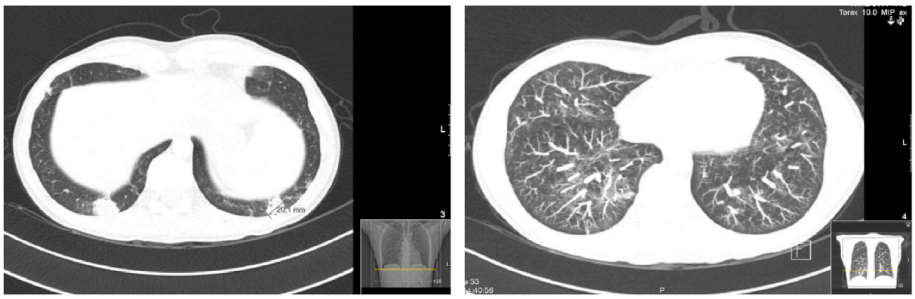

Fig. 3. Control thoracic axial computerized tomography.

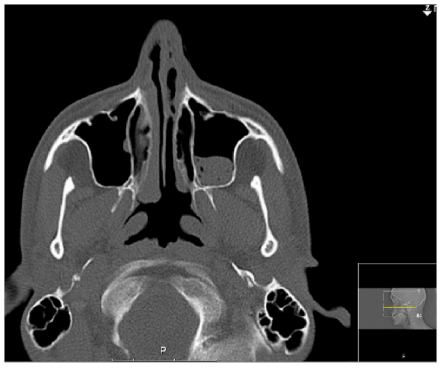

Fig. 4. Perinasal sinuses axial computerized tomography.

subject to a sperm cryopreservation program and maintained motor rehabilitation in the gym, with progressive and significant improvement in functional capacity.

Thus, the diagnosis of granulomatosis with polyangiitis ANCA PR3 with pulmonary involvement was made, which presented itself in a severe and potentially fatal form (alveolar hemorrhage and pulmonary granulomas, with severe respiratory failure, with need for orotracheal intubation and invasive mechanical ventilation) and presumably from the upper respiratory tract (despite the inconclusive biopsy), despite the Five Factor Score of 0.

Due to favorable clinical evolution, he was discharged with corticosteroids in a slow weaning scheme and 15mg/kg/pulse cyclophosphamide protocol, oriented to the Internal Medicine Internal Consultation - Autoimmune Diseases of our hospital. About 1 month after discharge he was asymptomatic and without any evidence of active disease (Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) score 0), having completed 7 pulses of cyclophosphamide (making a total of 7g) and subsequently starting maintenance therapy with azathioprine 150 mg/day.

3. Discussion

Granulomatosis with polyangiitis presents a systemic and potentially multiorgan affectation, with frequent involvement of the upper and lower respiratory and renal tracts.

This case exemplifies a severe and uncommon presentation of this autoimmune disease, which manifested itself through alveolar hemorrhage with severe respiratory failure and the need for mechanical ventilation, a rare presentation. The clinical case presented corresponds to a 23-year-old individual, in contrast to what is most often described in the literature regarding the prevalent age of diagnosis.

It should also be noted that, although there is often renal impairment (about 80% of cases), in the present clinical case there was never an impairment of renal function or findings suggestive of significant impairment of that organ. With regard to the role of histology and this remains controversial in the light of current knowledge [1,2], it was decided to perform a biopsy only on the nasal mucosa (which proved to be inconclusive), delaying and opting not to perform a lung biopsy because of the favorable clinical evolution and the suitable response to the immunosuppression initially instituted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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