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CHALLENGES IN THE DIAGNOSIS OF A CASE OF GRANULOMATOSIS WITH POLYANGEITIS

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Abstract
Granulomatosis with polyangiitis is a multisystem disease characterized by a necrotizing granulomatous vasculitis, typically associated with the presence of anti-neutrophil cytoplasmic antibodies. The lung is the most common organ involved in comparison to other vasculitis, but in the case presented by us the onset is otorhinolaryngology field, with a multitude of symptoms and immunological tests are initially negative. Over time, immunological tests become positive, but all this leading to a delay in diagnosis by 4 years and of course to a delay in treatment. In this paper we emphasize the usefulness of biopsy for diagnosis and use of anti-neutrophil cytoplasmic antibodies to classify the disease.
Keywords: *Vasculitis, granulomatosis with polyangiitis, anti-neutrophil cytoplasmic antibody*

Rezumat
Granulomatoza cu poliangeită este o boală multisistemică caracterizată prin vasculită granulomatoasă necrotizantă, în mod normal asociată cu prezența anticorpilor anti-citoplasma neutrofilelor. Plămânul este organul cel mai frecvent implicat în comparație cu alte vasculite, dar în cazul prezentat de noi debutul este în sfera otorinolaringologiei, cu o multitudine de simptome și cu testele imunologice inițiale negative. În timp, testele imunologice devin pozitive, dar toate acestea duc la o întârziere în diagnostic cu 4 ani și, bineînțeles, o întârziere în tratament. În această lucrare noi subliniem utilitatea biopsiei pentru diagnostic și folosirea anticorpilor anti-citoplasma neutrofilelor pentru a clasifica boala.
Cuvinte cheie: *vascilite, granulomatoză cu poliangeită, anticorpi anti-citoplasma neutrofilelor.*



Internal Medicine

Clinical Cases

Introduction

Granulomatosis with polyangiitis (GPA) is a necrotizing systemic vasculitis of the small caliber blood vessels typically associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA), 80-90% of patients have anti-proteinase 3 antibodies (c-ANCA), and the rest of anti-myeloperoxidase antibodies (p-ANCA); very rarely both types of antibodies may be present[1,2,3]. GPA is a rare disease with an annual incidence about 5-10 cases/100 000 inhabitants, with greater incidence in Northern Europe[3,4].

In 1931 Klinger described the disease as variant of polyarteritis nodosa, and in 1936 Friedrich Wegener described for the first time as a separated syndrome. The name ”Wegener's granulomatosis” was gave by Godman and Churg in 1954. The first criteria to diagnose the disease consists in: granuloma in the upper airways; glomerulonephritis; and necrotizing vasculitis. In 1985, Wan der Woude et al. reported that c-ANCA are highly specific for GPA, especially in the active phase[3].

Typical clinical manifestations are constitutional (fever, drowsiness, fatigue, decreased bodyweight, etc.), from otorhinolaryngology fields, pulmonary (pulmonary infiltrates, alveolar hemorrhage), ocular (keratitis, corneal ulcers, scleritis, etc.), renal (rapidly progressive glomerulonephritis). The classic picture of the disease is characterized by necrotising granulomatous lesions of the respiratory tract and in the sphere of the system otolaryngologist; vasculitis and glomerulonephritis[2,5,3]. Laboratory diagnosis of GPA reveals leukocytosis, thrombocytosis, markers of inflammation increased, normocytic normochromic anemia[4]. GPA recurs in a quarter of patients 2 years after onset and in half of the patients at 5 years. In the first year of life after diagnosis, the main causes of patient mortality are infections (32%) and renal failure (18%)[1,6].

Diagnosis of GPA is based on a combination of clinical manifestations with positive serology and histological evidence of necrotising vasculitis, granulomatous inflammation or necrotising glomerulonephritis. But the positive ANCA serology is not essential for the diagnosis of GPA if clinical and histological are relevant[3].

GPA is a fatal condition untreated, with 82% of patients die within 1 year. The therapy increased the 10-year survival rate to 40-70%. Therefore, it is important to recognize the disease early and to start treatment quickly[3,7].

In this article, we present the case of a patient with granulomatosis polyangiitis, with c-ANCA negative initially, positive later, with systemic damage (otorhinolaryngology, pulmonary, ocular, articular) diagnosed 4 years after the onset of the first symptoms.

Clinical case presentation

A 44- year -old patient is admitted to our clinic in December 2020, accusing physical asthenia, mainly morning cough, hemoptysis, migratory polyarthralgia, rhinorrhea, bilateral conjunctivitis, and heartburn.

From its medical history, the onset of the current disease occurred in 2016, on the 2nd day after insect bite on the left lower limb by of rash in the form of purple (Figure 1), accompanied by swelling of the joints of the bilateral leg, arthralgia of the radiocarpal joints, bilateral elbow, migratory, labial ulcer, and bloody sputum (Figure 2).



Figure 1. *Rash on the left lower limb*

After 2 weeks, some ulcers appeared on the palate, pharynx, uvula and at that time the patient had a weight loss of 10 kilograms. The symptoms worsened, the patient is hospitalized in the infectious diseases department and investigated for an infectious cause (anti-*Borrelia burgdorferi antibody*; liver virus B or C; Human Immunodeficiency Virus - HIV, *Shigella spp.*, *Salmonella spp.* – all negative) without being found what triggered these symptoms. The suspicion of Behcet's disease rises. A week later, he was hospitalized in our clinic, laboratory tests showing moderate microcytic normochromic anemia, mild lymphopenia, granulocytosis, and thrombocytosis. Immunological tests are presented in Table 1.



Figure 2. *Labial ulcer*

Surprising at our clinic, *Enterococcus spp.* is positive in urine culture. Upper digestive endoscopy discloses: two ulcers in the lower third of the esophagus and transhiatal gastric hernia, on duodenal mucosal biopsy with the appearance of nonspecific inflammation, *Helicobacter pylori* test is positive. While lower digestive endoscopy shows normal appearance (is excluded Crohn's disease).

The diagnosis of reactive arthritis is established given that several criteria (HLA B27 positive, migratory oligoarthritis, uveitis and a urogenital infection) were in favor of this pathology and insufficient criteria for vasculitis. Although the suspicion remains because the diagnosis does not explain the whole picture of the disease.

The treatment followed by the patient according to the diagnosis was Colchicine 1

mg/day and Medrol 8 mg/day and *Helicobacter pylori* eradication cure. In 3 months, the symptoms resolved. Exacerbations of the disease occurred every 6 months without the addition of other types of antibodies to the biological picture.

In 2018, the patient has a severe recurrent episode with acute arthritis, purpura in the lower limbs (Figure 3), epistaxis, accompanied by moderate microcytic hypochromic anemia. Subsequently, the evolution was favorable for the patient continuing at home treatment with Colchicine, without relapses until August 2020; when fatigue, polyarthralgia, hemoptysis and epistaxis reappear. The patient continued treatment with Colchicine and added Medrol 32 mg daily with a progressive decrease of 5 mg every 7 days. After one month the patient developed an episode of infectious otitis and he received antibiotic treatment for 10 days, followed by a period of favorable evolution.

In December he was admitted to our clinic for the recurrence of symptoms. Laboratory tests showed significant inflammatory syndrome (C-reactive protein - CRP 107.16 mg / dl, erythrocyte sedimentation rate - ESR 70 mm / h), lymphopenia, granulocytosis. From immunological analyzes, c-ANCA was positive > 100U / ml, (Normal <5 U / ml), and p-ANCA and anti-glomerular basement membrane antibodies were negative, hypercomplementation. Proteinuria and hematuria were not detected, and urinary sediment was within normal limits.

Medium intensity nodular opacities disseminated in the left lung field were detected on lung radiography (Figure 4), and on computed tomography with contrast, multiple bilateral pulmonary nodular images of various sizes between millimeter values and up to 2 cm were highlighted, interstitial and interlobular densifications in bilateral posterior-basal matte glass, more significantly on the left (Figure 5).



Figure 3. *Purpura in the lower limbs*

Bronchoscopy was performed, the explored areas being of normal endoscopic

Rheumatoid factor	Negative
Antinuclear antibody	Negative
Double-stranded deoxyribonucleic	Negative
c-ANCA	Negative
p-ANCA	Negative
Anti-citrullinated protein antibody	Negative
Antibody ribonucleoprotein	Negative
Human leukocyte antigen (HLA)-B27	Positive
HLA B51	Negative

Table 1. Immunological test

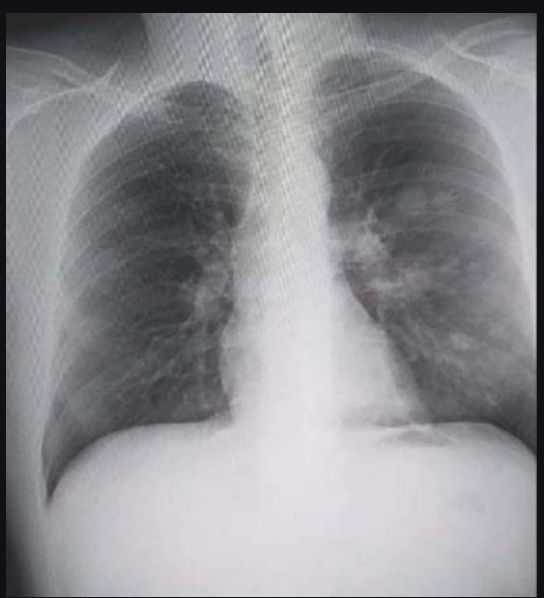


Figure 4. *Lung radiography - medium intensity nodular opacities disseminated in the left lung field*

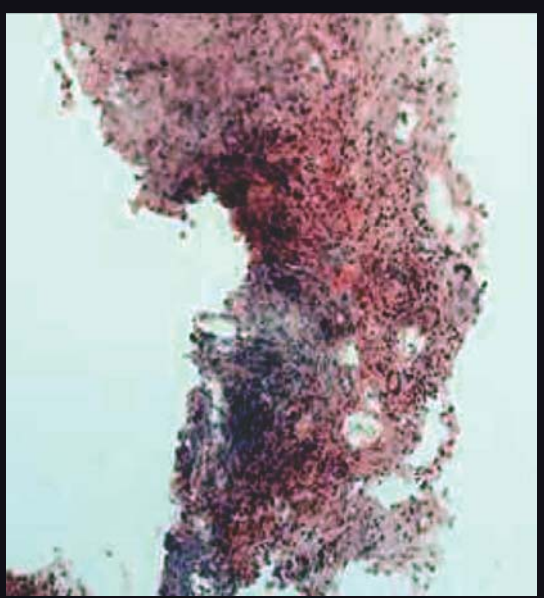


Figure 6. *Hematoxylin eosine coloring granulomatous inflammation with multinuclear giant cells and granuloma drawings*



Figure 5. *Computed tomography with contrast - multiple bilateral pulmonary nodular images, interstitial and interlobular densifications in bilateral posterior-basal matte glass*

appearance, without signs of active bleeding. Lung biopsy revealed granulomatous inflammation, with giant multinucleated cells and granuloma sketches (Figure 6), areas of necrosis, along with alveolar parenchyma with granulomatous inflammation. The diagnosis established for this patient was granulomatosis with polyangiitis, the systemic form with impairment otorhinolaryngology - ENT, pulmonary, ocular, and articular. We initiated treatment with cyclophosphamide in pulse therapy associated with glucocorticoid, trimethoprim-sulfamethoxazole and mesna, the patient's condition being favorable.

Discussions

ANCA have a high specificity for GPA, and at first there was great optimism about their potential for diagnosis, but this serological marker has many limitations. ANCA are useful in two cases: as a diagnostic test and as a marker of disease activity. The serological maker sensitivity depends on the stage and the degree of activity of the disease. In some studies, it is shown that the sensitivity of ANCA in the active phase of the disease is 91% and in the remission period of 63%. The enzyme-linked immunosorbent assay (ELISA) test has a very high sensitivity, but their specificity may vary. Therefore it is recommended to use qualitative assays of ANCA immunofluorescence and quantitative ELISA test for increased sensitivity and specificity[3,8,9,10].

However, approximately 10-20% of patients with GPA are ANCA negative, which tells us that a negative ANCA test dose not exclude the diagnosis[11, 12]. Few cases of GPA are reported, in which ANCA was negative and it has been positive over time. In the case presented, the ELISA method was used and probably the titre of the antibody being down at the beginning of the disease, the method being not sensitive enough[13].

Patients diagnosed with non-ANCA GPA have localized forms, most often being affected by the otorhinolaryngological system (20-25% of patients). Mastoiditis may be the first and the only manifestations of GPA and oral lesions are considered a distinctive diagnostic criterion for disease. But the most common sites of involvement in the otorhinolaryngological system are the nasal cavity and the paranasal sinuses (85-100%)[3,14].

In GPA, common signs and symptoms at onset include pulmonary infiltrates, sinusitis, arthralgias, fever, otitis, hemoptysis, and ocular inflammation[15,16,17].

The most common nasal manifestations of GPA are the crusts, nasal obstruction, blood-stained rhinorrhoea and septal perforation[3]. The patients with cutaneous manifestations have frequently sever systemic manifestations of

vasculitis.[14] Reactive arthritis commonly affects young adults, most frequently carrying the HLA-B27 allele, associated with migratory oligoarthritis and extra-articular symptoms[18]. The prevalence of HLA-B27 in reactive arthritis is 30-50%. However reactive arthritis is a clinical diagnosis[19]. We considered this stage diagnosis in the absence of other diagnostic elements for vasculitis. An ENT biopsy would probably have been useful for a faster diagnosis.

The difficulty of establishing the diagnosis of GPA has result a delay in the administration of an aimed treatment, the disease progressed affecting other systems. In the case of our patient, the lungs damage occurred 4 years after the onset of the first symptoms, but this allowed us to reconsider the initial diagnosis of reactive arthritis. Four years after the onset of the first symptoms, our patient presented many typical symptoms for GPA: lungs damage (cough, hemoptysis, pulmonary infiltrates) in association with arthralgias, ocular inflammation, nasal congestion, and biologically c-ANCA have very high values.

GPA is characteristically a relapsing disease with 50% of relapses at 5 years. Now the main therapeutic challenge is maintenance treatment. Cyclophosphamide is strongly associated with the risk of hemorrhagic cystitis and bladder cancer[20,1,16].

The complications of disease are permanent damage to lungs and respiratory tract, kidneys and, total or partial loss of hearing.20 ANCA-associated vasculitis has a predilection for kidney with more that 75% of patients having renal involvement.[7]

Conclusions

This case highlights the difficulty of diagnosing GPA at an early stage due to the multitude of nonspecific symptoms that may be present in several rheumatic pathologies. Clinical suspicion of GPA in the absence of positive ANCAs should be considered and alternative criteria should be sought, such as tissue biopsy, the most common biopsied tissue being the lung. We must keep in mind that the ANCA title depends on the diagnostic method used and the disease activity.

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