Wegener's granulomatosis and alveolar hemorrhage – Case report

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ACTA REUMATOL PORT. 2013;38:295-298

ABSTRACT

The authors present a clinical case of 55 years old female patient with limited form of Wegener s granulomatosis (WG), which first manifestation was non-erosive polyarthritis with rheumatoid factor positive that antedated one decade the pulmonary manifestations. She had acute episodes with purulent expectoration, fever and hemoptysis, with resolution in a week. The chest x-rays demonstrated migratory bilateral pulmonary infiltrates. Transthoracic lung biopsy was performed and revealed capilaritis and signs of old and recent hemorrhage. At that time, autoimmunity study was repeated and showed positive for rheumatoid factor, negative anti-cyclic citrullinated peptide antibodies (anti--CCP) and high sustained PR3 anti-neutrophil cytoplasmic antibodies. The diagnosis of WG was established and cyclophosphamide started. This patient had a less common presentation and a less common histological pattern compared to the typical necrotizing granulomatous inflammation. She was treated with immunosuppression therapy which could have contributed to a mild clinical expression and a lower diagnostic yield. In suspicious cases, repeat the autoimmunity study, when facing new findings, could confirm the correct diagnosis.

Keywords: Vasculitis; Anti-neutrophil cytoplasmic antibodies; Hemoptysis; Arthritis.

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INTRODUCTION

Wegener granulomatosis (WG) is a rare disease, defined as multisystem granulomatous vasculitis, which preferentially affect the small-vessels. The lung is the most frequently and sometimes the only organ involved[1,2]. Its etiology is not clearly understood, however anti-neutrophil cytoplasmic antibodies (ANCA) seem to be implicated in the pathogenesis and development of tissue lesion[3-5]. Their characterization had led to improved understanding of vasculitis[4].

CLINICAL CASE

The authors present a clinical case of a 55 years old female patient, caucasian, housekeeper, non-smoker, who had a history of non-erosive polyarthritis since 1998, initially seronegative. She was followed in Rheumatology out-patient department and treated with corticosteroid and hydroxychloroquine since that date. In May 2008, she was sent to Pulmonology out-patient department by the Primary Care Physician, for two episodes of pneumonia in the past year, both associated with hemoptysis. The previous chest x-ray showed bilateral heterogeneous infiltrates, in the middle lung fields (Figure 1). In the first observation the patient was clinically stable. Physical examination was normal. The autoimmunity study revealed positive rheumatoid factor (RF). The chest x-ray did not show any change and chest CT identified occasionally micronodules and bronchiectasis in the middle lobe. The respiratory functional study performed was normal. The bronchoscopy was also normal, however showed increasing blood staining of bronchoalveolar lavage (BAL) fluid, and its cellularity analysis revealed neutrophilic and lymphocytic alveolitis, CD4/CD8 ratio slightly elevated and macrophages stain with Pearls Prussian Blue - Golden

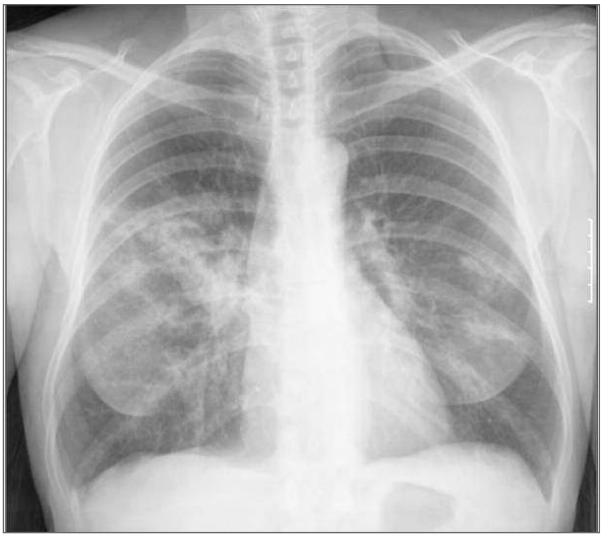

FIGURE 1. Chest x-ray showing heterogeneous infiltrates in the middle of both lung fields

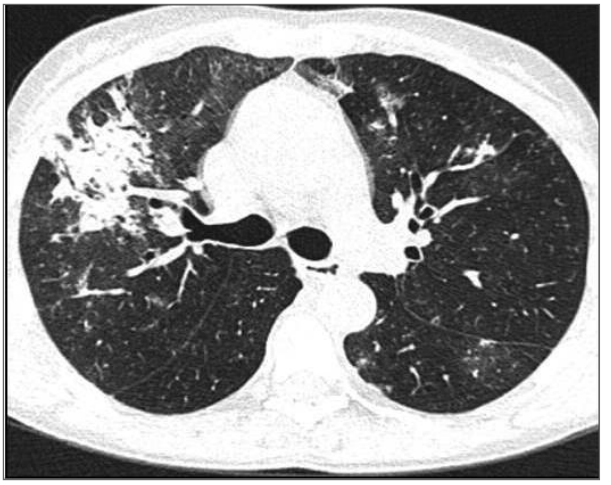

FIGURE 3. Chest CT demonstrating diffuse bilateral consolidations, with bronchovascular distribution, involving peripheral and inferior areas

score 302. No microorganism was isolated in sputum microbiological examination. BAL microbiological and cytology examinations were both negatives. Because the BAL results could be explained in backward disease context and patient was clinical, functional and radiological stable, it was decided to keep just follow-up. In the beginning of 2009, she had another acute episode of purulent expectoration, fever and hemoptysis. White blood cell count was normal, with relative increase in neutrophils and no eosinophilia, and acute phase reactants were elevated. The chest x-ray

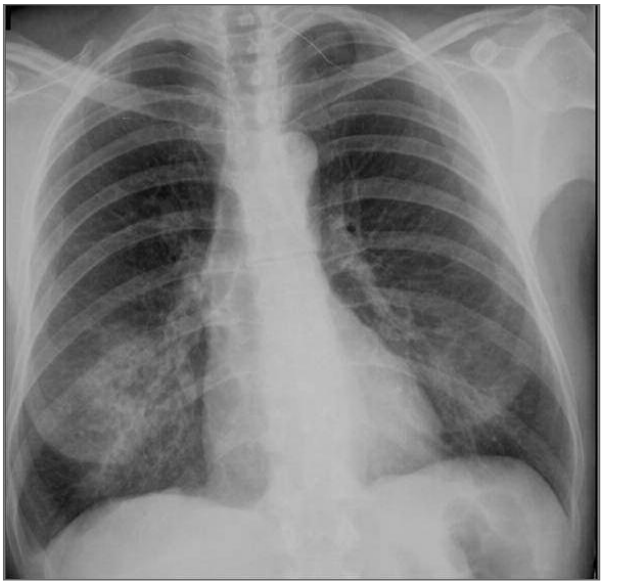

FIGURE 2. Chest x-ray showing basal bilateral pulmonary infiltrates

demonstrated basal and bilateral pulmonary infiltrates (Figure 2). She started antibiotic treatment and a high dose of corticosteroids. Transthoracic core needle biopsy was scheduled, but cancelled due to radiological resolution. She was oriented to maintain the follow-up however she kept asymptomatic with radiologic stability for a year. In February 2010, she had a similar episode, associated with myalgias, anorexia and weight loss. The chest CT showed bilateral diffuse consolidations, with bronchovascular distribution, involving peripheral and inferior areas (Figure 3). The patient was hospitalized and CT-guided transthoracic core needle biopsy was preformed. The lung histological exam revealed capilaritis and signs of old and recent hemorrhage. No necrotizing vasculitis or necrotizing granulomas were indentified. There were no bronchiolitis obliterans organizing pneumonia like lesions (Figures 4 e 5). We repeated autoimmunity study that was positive for RF, negative for anti-CCP antibodies and MPO-ANCA, and PR3- ANCA were steadily increased (PR3-ANCA was 138 U/ml when normal value is < 20 U/ml). WG diagnosis was established and cyclophosphamide was started, maintaining the previous treatment. The patient was oriented to the Rheumatology out-patient department and continued to be treated with monthly pulses of cyclophosphamide. She completed 5 pulses of cyclophosphamide, until the cumulative dose of 5 grams, with prednisolone 10mg/day, but then treatment with cyclophosphamide has stop-

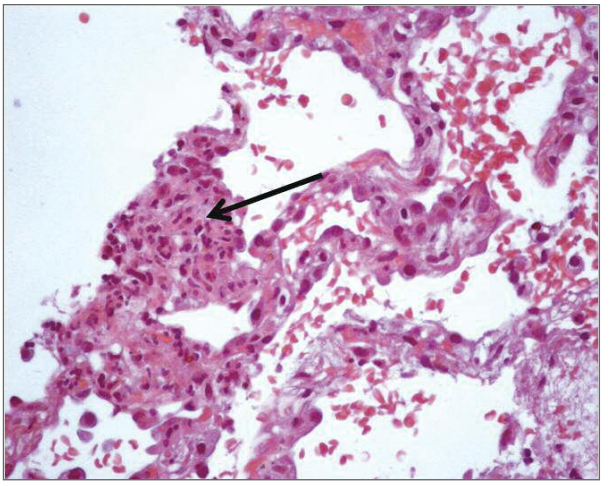

FIGURE 4. HE 200X – Capilaritis focal characterized by small areas of inflammation (arrow) and intraalveolar hemorrhage

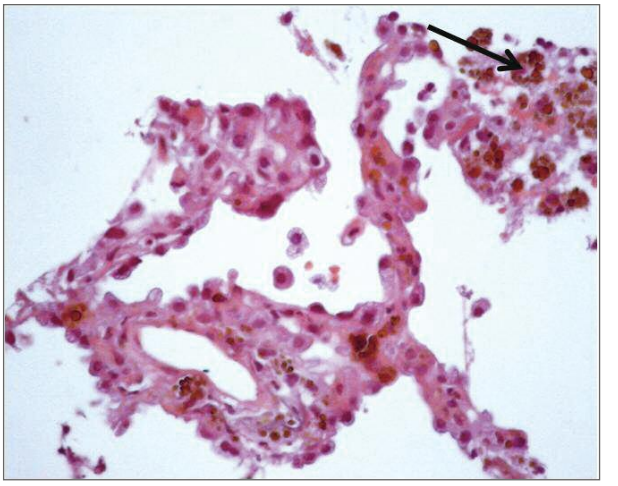

FIGURE 5. HE 200X – Hemosiderin in intraalveolar macrophage (arrow)

ped because she developed leukopenia, that improved after treatment suspension. The case was discussed with Hematology and decided not to start azathioprine due to the risk of hematologic toxicity. Patient maintained treatment with prednisolone 30mg/day (in dose reduction scheme), hydroxychloroquine, trimethoprim/sulfamethoxizole 3 times/week, calcium, vitamin D and folic acid. During the 3-years follow-up patient is stable without pulmonary relapse. No upper airway or renal involvement was documented. Paranasal sinuses CT did not show any abnormal signs and nasal mucosal biopsy was normal. She had normal renal function, normal creatinine clearance, and microscopic examination of urine sediment didn t show hematuria or proteinuria.

DISCUSSION

The first description of three cases of WG was published by Friedrich Wegener[6] in 1936. Later, Fiemberg[7] as well Carrington & Liebow[8] described limited forms of the disease that not necessarily involved simultaneous respiratory tract and kidneys. In WG, fever and weight loss are common and may be inaugural. Furthermore migratory arthralgia or arthritis can be present in 50-80% of patients, and is in some cases the first manifestation[9,10]. As we saw in this case, arthritis that antedates other manifestations may lead to a mistaken diagnosis of non-erosive rheumatoid arthritis, specially because rheumatoid factor may be positive[10]. Noritake et al. reported that an elevated RF was observed in about half of WG cases with rheumatic manifestation[11]. Pulmonary involvement is present initially in 45% of patients and in 66-85% during the course of illness[9-14]. The most common respiratory symptoms are cough, hemoptysis or pleuritic pain, but 34% of patients have asymptomatic abnormal chest x-ray[2,12]. Our patient had alveolar hemorrhage, which is a prominent and life-threatening pulmonary manifestation of WG, estimated to occur in 5% of patients. Diffuse alveolar hemorrhage has been associated with high early mortality and long term consequences as pulmonary fibrosis[15-18]. The most common radiology findings are pulmonary infiltrates and nodules, usually involved both sides of chest, and can be present in more than 85% of patients[9-14]. CT scan changes can be seen in 43%-63% of patient with a normal chest x-ray[19-20]. Most often, radiographs are helpful in confirming the diagnosis and in assessing the extent of pulmonary involvement.

WG has a strongly and specific association with c-ANCA, which are directed against proteinase-3 (PR3), a constituent of neutrophil azurophilic granules. The c-ANCA is positive on more than 90% of patients with active classic disease, of whom 10% have p-ANCA, which is usually against myeloperoxidase (MPO). In limited forms of WG only 60% of patients have detectable titers of ANCA[2-5]. The presence of ANCA is not required to make a diagnosis by either the American College of Rheumatology (ACR) or the Chapel Hill Consensus Conference (CHCC) definitions[21].

The same authors believe that elevation of ANCA titers could be associated with disease relapse[22]. We demonstrated that in suspicious cases, when we face new findings, the autimmunity study should be repeated because it could be the key to make the correct diagnosis.

The three major pathologic manifestations of classical WG are: parenchymal necrosis, vasculitis, and granulomatous inflammation. Capilaritis is present in 31% of specimens[23-25]. Our patient showed a less common histological pattern given that capilaritis and alveolar hemorrhage are less frequent compared with typical necrotizing granulomatous inflammation. The differential diagnosis with other ANCA associated vasculitis was considered, namely microscopic polyangiitis (MPA). However, rapidly progressive glomerulonephritis is essentially universal in MPA, whereas pulmonary involvement occurs in a minority of patients (10 to 30%), and ANCA is positive in 50-70% with most of these being MPO-ANCA[13]. Because patient disease tend to be focal, that could explain why the specimens collected might miss granulomatous inflammation. Also we consider the fact that she was under immunosuppressive therapy could have contributed to a mild clinical expression and a lower diagnostic yield. Whether or not is important to obtain pulmonary tissue for the diagnosis of vasculitis is controversial. However, in our case, the histological examination associated to PR3-ANCA was crucial to establish definitive diagnosis and start an adequate therapy regimen, which is essential to achieve disease control.

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