WEGENER GRANULOMATOSIS PRESENTED WITH EPISTAXIS, HEMOPTYSIS AND POLYARTHRALGIA: A CASE REPORT

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ABSTRACT

Wegener granulomatosis (WG) is a rare, multisystem, autoimmune disease with necrotizing granulomatous inflammation, tissue necrosis, vasculitis in small and medium-sized blood-vessels. The classic clinical pattern is a triad involving upper airways, lungs and kidneys. A 33-year-old woman was admitted to hospital because of dry cough, shortness of breath, polyarthralgia, intermittent fever, epistaxis, hemoptysis. Chest X-ray presented multiple, small infiltrates bilaterally. Laboratory results: Hgb 90g/L, hematocrit 30%, erythrocytes 3,6×1012/L, leucocytes 13,8×109/L, platelet 4,45×109/L, CRP 110mg/L, sedimentation 70mm/h. Urine sediment: erythrocytes(16-18), proteins(+), epithelial cells(++), 24hour-proteinuria 0,5g/L. ECG: sinus tachycardia 120 beats/min. Gas analyses: partial respiratory failure, hypoxemia 7,5kPa, hypocapnia 3,6kPa, saturation 91%. Lung-CT revealed multiple bilateral infiltrates. Chest-ultrasound with bilateral, subpleural, hypoechogenic changes with central necrosis. Because of intermittent fever, polyarthralgia, chest X-ray changes, elevated sedimentation, rheumatologist was consulted and tests for autoimmune disease were performed (positive c-ANCA 95U/ml, RF 158IU/ml, ASO 88U/ml). Ophthalmologist revealed punctiform conjunctival bleeding. Bronchoscopy: intranasal coagulum without changes of nasal mucosa, transoral intubation presented diffuse erythema and edema of the vulnerable tracheobronchial mucosa without ulcerous lesions or infiltrative changes. Bronchial alveolar lavage detected small increase of neutrophils (total cell counts 320/αL, neutrophils 19,2%, macrophages 85,0%, lymphocytes 7,4%, eosinophils 0,0%), no growth of bacterial culture, negative Gene X-pert. Transbronchial biopsy was performed, histologic analysis detected necrotic granulomas with multinucleated giant cells accompanied by inflammatory cells. According to all investigations, the diagnosis was WG. The patient was successfully treated multidisciplinary with high-dose steroids and cyclophosphamide. Recognition of multisystem disease involving joints, kidney, eye and lung is critical for diagnosis.

Key words: Polyangiitis, Autoimmune disease, Necrotizing granulomatous vasculitis, Granulomatosis.

INTRODUCTION

Wegener granulomatosis (WG) is a rare, multisystem, autoimmune disease with necrotizing granulomatous inflammation, tissue necrosis, vasculitis in small and medium-sized blood-vessels, first described by German pathologist Friedrich Wegener in 1936 (1,2). The classical clinical triad consists of upper airway involvement (sinusitis, otitis, nasal mucosa ulcers, bone deformities, subglottic stenosis), lower respiratory tract involvement (cough, chest pain, hemoptysis, dyspnea, fever) and glomerulonephritis (in 80%). It is believed that the disease begins as a localized respiratory tract granulomatosis,

which then generalizes into a vasculitis that affects small and medium-sized vessels (1,3). WG most commonly occurs in whites and affects men and women equally. The mean age at diagnosis is 40 years, but the disease can develop at any age (2). Patient presentation varies and depends on the organ system affected. Some patients present with chronic nasal obstruction, which may be misdiagnosed as chronic sinusitis, others may present with acute renal or respiratory failure. Patients with pulmonary involvement, mononeuritis multiplex or unexplained multisystem disease (1,3). Elevation of serum c-antineutrophil antibodies against protease 3 in cytoplasmic granules (c-ANCA) titers frequently occurs in patients with WG and can be used to assess disease activity. The reference standard for diagnosis is biopsy. Renal biopsy, the most common approach, usually shows a nonspecific glomerulonephritis. Lung biopsy may show a granulomatous small-vessel necrotizing vasculitis (2,4). Some infectious diseases, such as bacterial endocarditis may sometimes show high titers of ANCA, mimicking vasculitis (5). Lung nodules are the most common manifestation of WG on chest X-ray and occur in approximately 40–70% of patients (6,7). Treatment includes immunosuppressant therapy, most commonly systemic steroids and cyclophosphamide. Remission rates are approximately 90%, but relapses may occur (6). Before the routine use of glucocorticoids and cyclophosphamide, the one year mortality was 82% (1).

CASE PRESENTATION

A 33-year-old woman was admitted to our hospital with a history of progressively worsening dry cough, shortness of breath, polyarthralgia, fever, epistaxis, general fatigue and hemoptysis. Three months before admission, she had episodes of nasal bleeding, dry cough, intermittent fever not more than 38.2γC. Her primary physician did not detect any abnormal findings in the chest radiogram performed at that time. After three months, she consulted the doctor again due to symptom worsening. The second chest X-ray was with multiple small infiltrates in both lungs (Figure 1). Because of the chest radiogram and laboratory result with high sedimentation rate, the patient was immediately admitted to hospital. She had a smoking history of 10 pack-year, mother of one 10year-old child, without any problems during pregnancy and delivery, no allergies reported, no regular therapy used, one operation of left-sided inguinal hernia twenty years ago. She reported family illness, diabetes mellitus type 2 (by her mother's side).

Physical examination on admission, blood pressure was 120/80mmHg, the pulse 120 beats per minute, temperature 38γC, oxygen saturation 91%, weight 61kg. Her skin was pale, without any rashes, normal lung auscultation, heart rate rhythmic, tachycardic, without murmurs. Abdomen without pain or tenderness on palpation. Mild, bilateral, ankle edema, but other joints were without swelling or any other changes on inspection or palpation. Eyes with emphasized conjunctival, vascular pattern. Small clots in the nose.

Laboratory results revealed anemia with Hgb 90g/L, hematocrit 30%, erythrocytes 3,6×1012/L, leucocytes 13,8×109/L (85,9% neutrophils, 10,8% lymphocytes), platelet count 4,45×109/L, C-reactive protein (CRP) 110mg/L (normal values less than 3,03 mg/L), sedimentation rate (SR) 70mm/h per first hour (normal values 0-20 mm per hour). Renal, liver function tests, hemostasis were within normal limits. D-dimer 4000ng/ml. Urine sediment – erythrocytes 16-18, proteins +, epithelial cells ++. 24hour proteinuria 0,5g/L (upper limit 0,2g/L). ECG with sinus tachycardia of 120 beats/min. Gas analyses in partial respiratory failure with hypoxemia 7,5kPa and hypocapnia 3,6kPa, oxygen saturation 91%. Chest radiography and lung computed tomography (CT) showed multiple bilateral infiltrates (Figure 2). Chest ultrasound with bilateral, subpleural, hypoechogenic changes with zones of central necrosis, maximal diameter 26x18,9mm (Figure 3). Because of persistent fever, chest X ray and lung CT scan, significantly elevated SR, rheumatologist was consulted and tests for autoimmune disease were performed. Rheumatoid antibodies: positive c-ANCA 95U/ml (normal up to 30U/ml), RF 158IU/ml, ASO 88U/ml. Because of the significant 24hour proteinuria and hematuria, an examination by nephrologist was asked. Renal ultrasound revealed no pathological changes, and nephrologist's opinion was that there was no need of renal biopsy in that stage, because of preserved renal function. Ophthalmologist examination detected punctiform conjunctival bleeding. Bronchoscopy finding of intranasal coagulum without changes of nasal mucosa. Transoral intubation revealed diffuse erythema and edema of the vulnerable tracheobronchial mucosa without any ulcerous lesions or infiltrative changes (Figure 4 a, b). Bronchial alveolar lavage (BAL) was performed. Cytology report showed small increase of neutrophils (total cell counts 320/γL, neutrophils 19,2%, macrophages 85,0%, lymphocytes 7,4%, eosinophils: 0,0%). BAL gram stain

and culture showed no growth. BAL sample for Gene X-pert PCR was negative. Transbronchial biopsy was performed and histologic analysis revealed necrotic granulomas with multinucleated giant cells accompanied by inflammatory cells in the bronchial and parenchymal lesions using hematoxylin and eosin stains. According to the pathology result the diagnosis was granulomatosis with polyangiitis, Wegener's granulomatosis.

During the hospital stay until diagnosis, the patient was treated with broad spectrum antibiotics, antifever drugs, fluids, systemic corticosteroids, low-molecular weight heparin, gastro-protective therapy, oxygen, supportive therapy. The treatment continued multidisciplinary after confirmed diagnosis WG, with high-dose of systemic steroids (prednisolone, with gradual decreasing of the dose) and cyclophosphamide. The symptoms, chest X-ray results and c-ANCA level, were significantly reduced after two months follow-up.

DISCUSSION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), belongs to the group of ANCA-associated necrotizing vasculitides (8, 9). The clinical manifestations are diverse, and this is reflected in the manner of their presentation (4). It is a rare disease, during the past 15 years, the epidemiology of Wegener's granulomatosis (WG) has become better understood. Descriptive epidemiological studies carried out primarily in European countries estimate a prevalence of WG ranging from 24 to 157 per million and annual incidence rates from 3 to 14 per million, depending on geographic location (10). Chest radiographic findings are often the first to suggest the diagnosis, but CT has superior sensitivity and specificity for evaluation. Common pulmonary radiologic findings include waxing and waning nodules, masses, ground-glass opacities, and consolidation. Airway involvement is usually characterized by circumferential tracheobronchial thickening, which can be smooth or nodular. Pleural effusions are the most common manifestation of pleural disease and can result from primary involvement or be secondary to renal failure (11).

This is a case report of granulomatosis with polyangiitis (Wegener's granulomatosis) in a younger patient than the average onset of WG, 33 years old, where the diagnosis was identified by transbronchial biopsy which identified granuloma with giant cells. These findings led to a diagnosis of WG. Clinical course, positive c-ANCA, negative RF, chest imaging results, urine analysis were considered diagnostic for WG. Flexible bronchoscopy and transbronchial biopsy were very helpful procedures in this case. Usually, renal involvement is severe and the leading cause of mortality, but our patient's renal function was preserved. The significant proteinuria was also suggestive of WG-associated glomerulonephritis (4). Differential diagnosis included systemic lupus erythematosus, Churg-Strauss Syndrome, rheumatoid arthritis.

According to the medical intervention in WG, the immune system has been the major target of therapy with immunosuppressive drugs such as prednisolone, cyclophosphamide, azathioprine, and more recently, methotrexate and mofetil mycophenolate. Also, it is proposed treatment with the antibiotic trimethoprim-sulfamethoxazole (co-trimoxazole) for reducing the incidence of disease relapses in WG (12). Open-label clinical studies suggest a beneficial effect of infliximab or rituximab in addition to standard therapy in refractory Wegener's granulomatosis (13). Plasma exchange is the best complement to immunosuppressants in advanced renal disease at present (14).

Conclusion

Despite recent progress, the prevention of relapses and treatment of refractory cases remain the greatest challenge in the treatment of Wegener's granulomatosis (12, 15). Long-term treatment and disease-related morbidity are major threats, there is a need for safer and more effective medications. Early diagnosis and multi-specialty collaboration among physicians is necessary to adequately manage the disease and the potential complications that may result from drugs used in the treatment of the disease (15).

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ADDITIONS

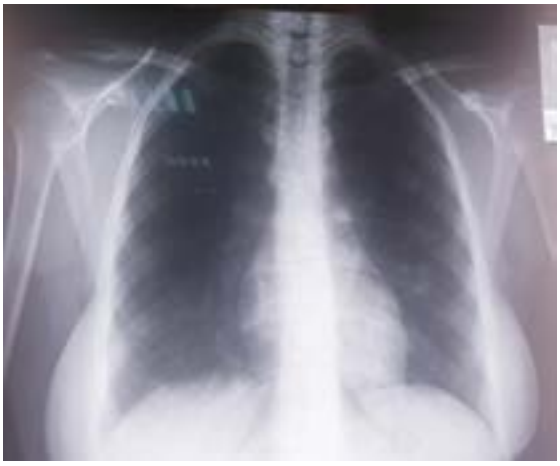


Figure 1. Chest radiography showing small, multiple, bilateral lung infiltrates.

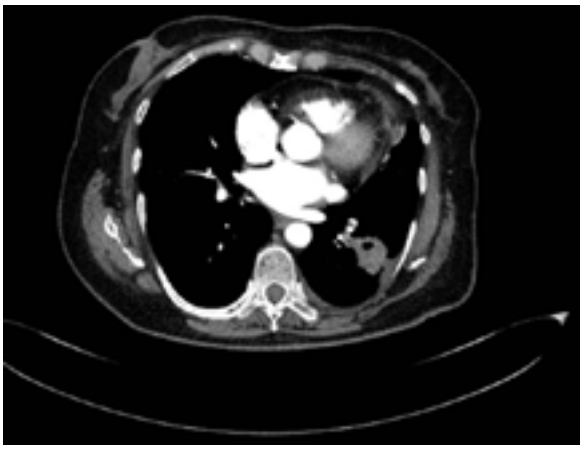


Figure 2. High resolution CT image showing nodule in lung parenchyma with spiculate margins and central necrosis.

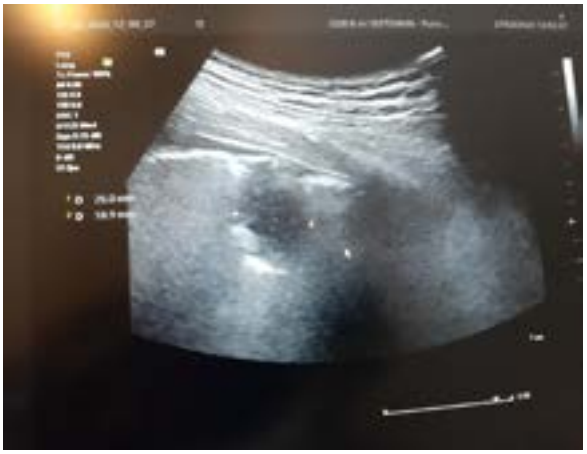
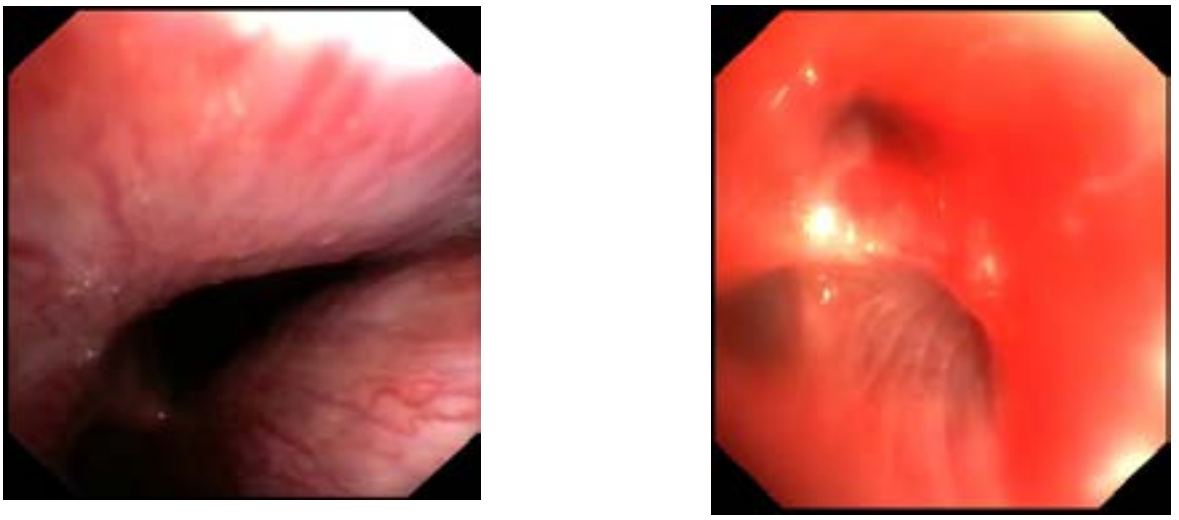


Figure 3. Chest ultrasound presenting subpleural, hypoechogenic change with central necrosis.



(a) (b)

Figure 4. Bronchoscopy findings of edematous mucosa and prominent capillary vessels, beginning from distal trachea (a), diffuse erythema and edema of the vulnerable tracheobronchial mucosa in right upper bronchus, with contact bleeding (b).