

Multiple pulmonary nodules: a complex case of Wegener's granulomatosis

Mariya Apostolova, Mahmoud Shoib, Samer Nasser

Conemaugh Memorial Medical Center, Department of Internal Medicine, Johnstown, PA, USA

Abstract

Wegener's granulomatosis is a granulomatous vasculitis that can present with a wide spectrum of clinical manifestations. This disease entity predominantly affects the respiratory tract and the kidneys. Two forms of Wegener's granulomatosis have been recognized: systemic and limited. It has not been established if the two forms represent separate disease entities or different stages of the same condition. In the limited form of Wegener's granulomatosis there is no immediate threat to the function of vital organs and there is no evidence of glomerulonephritis. Environmental factors that could serve as triggers for the activation of Wegener's granulomatosis have not been clearly defined. We report a case of a 78-year old male who was found to have bilateral pulmonary nodules on pre-operative chest X-ray and was diagnosed with the limited form of Wegener's granulomatosis. The patient developed *Clostridium difficile* infection, and shortly after that active glomerulonephritis, a manifestation of systemic Wegener's granulomatosis.

Case Report

A 78-year old male with past medical history significant for chronic shortness of breath (for the last two years), chronic systolic heart failure secondary to non-ischemic dilated cardiomyopathy, pulmonary hypertension, essential hypertension, coal miner's pneumoconiosis, and chronic obstructive lung disease was found to have bilateral pulmonary nodules on pre-operative chest X-ray. The work-up for the pulmonary nodules was initially planned on an outpatient basis. However, two weeks later the patient was admitted to the hospital with progressive shortness of breath. Upon admission, vital signs included temperature 35.8°C, pulse 56 beats/min, respiratory rate 22 breaths/min, and blood pressure 110/54 mmHg. Oxygen saturation on room air was 96%. On review of systems he reported decreased appetite for the past three months and a 20 pound weight loss. He denied hema-

turia, rhinorrhea, rashes, sinus pain, muscle aches, ear ache, hearing loss or hemoptysis. Physical exam was significant for bilateral rhonchi on auscultation of the lungs. Fecal occult blood was negative. Electrolytes were within normal limits. Blood urea nitrogen was 18 mg/dL, creatinine 1.2 mg/dL, glomerular filtration rate 59 mL/min. The patient's urine microscopy was initially negative. Chest X-ray revealed bilateral hilar and right upper lobe areas of infiltrate increased from the prior imaging examination. Computed tomography (CT) scan revealed multiple cavitary lesions, the largest on the right, with a large air fluid level suspicious for infection. The day after admission the patient underwent CT guided fine needle aspiration of the right lung. A catheter was placed and a 10 cc of frankly purulent material was aspirated. Pathological examination showed acute inflammation. Tissue cultures showed no growth. No acid fast bacteria were seen on smear. Potassium hydroxide preparation was negative and no fungus was isolated. All blood cultures were the negative and so were cultures of the pleural fluid and the surgical specimen. One of the expectorant sputum samples grew *Rhodococcus equi*. The patient was then started empirically on ciprofloxacin and rifampin for *Rhodococcus equi*. However, the antibiotics were soon discontinued secondary to low suspicion for the presence of active infection. At that point the diagnosis of vasculitis was entertained and a vasculitis panel was significant for elevated sedimentation rate at 84 mm/h. Anti-glomerular basement membrane antibody level was negative, but proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) level was elevated at 3.8 units. Liver function tests were normal.

Lung biopsy revealed chronic and acute inflammation and granuloma formation. Two weeks after hospital admission the patient complained of diarrhea. Laboratory results indicated that he was in renal failure. Stool studies were positive for *Clostridium difficile* for which the patient was started on flagyl. Repeat urinalysis showed brown colored urine with pH 6, specific gravity 1.023, moderate occult blood, bile negative, small leukocyte esterase, nitrate negative, 9-10 red blood cells (RBC)/high power field (HPF), 9-10 white blood cells/HPF, rare squamous epithelial cells, rare hyaline casts, 30A protein. Urine microscopy was positive for RBC casts. At that time the patient also developed purpuric rash over his extremities. The patient was empirically started on oral cyclophosphamide and IV methylprednisolone. Kidney biopsy was inadequate for diagnosis. During the course of his treatment he also completed 5 cycles of plasmapheresis. The patient remained dialysis dependent at 2 months follow-up.

Correspondence: Samer Nasser, Conemaugh Memorial Medical Center, Department of Internal Medicine, 1086 Franklin Street, Johnstown, PA 15905, USA.
E-mail: nsamer54@gmail.com

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Discussion

Wegener's granulomatosis (WG) is ANCA associated vasculitis of small and medium sized vessels. WG should be considered in patients found to have multiple pulmonary nodules. The disease has variable presentation and diagnosis is made on the basis of clinical, laboratory, pathologic and imaging studies. Usually patients present with upper respiratory tract symptoms such as nasal ulcer, nasal discharge, rhinorrhea and sinus pain.¹ Approximately ninety percent of patients develop pulmonary features at some stage of their condition.^{1,3} Eighty to eighty three percent of cases develop renal involvement.^{1,3} Kidney involvement manifests as acute renal failure with red cells, red cell casts and proteinuria. Although WG is mainly characterized by respiratory disease and nephritis, it can also affect the nervous system, heart, eyes, skin, joints and spleen.

The diagnostic criteria published by the American College of Rheumatology include nasal or oral inflammation with ulcers or purulent bloody discharge; chest radiograph showing nodules, cavities or infiltrates; urinary sediment with red cell casts or microscopic hematuria; granulomatous inflammation on lung biopsy.^{1,4,5} Two of the four criteria need to be met for the diagnosis.^{1,4} The sensitivity of the criteria is 88% and the specificity is 92%.⁵

WG has a male predominance.¹ The mean age of patients affected is the 5th decade.¹ The pathogenesis of WG is not clearly understood. However, environmental factors associated with the condition include respiratory infections, allergy, and farming.^{6,7} Infection could

serve as a trigger for disease expression and is an established factor for disease relapse.¹ Under the effect of unknown antigen, neutrophils express cytoplasmic PR3, which leads to the production of anti-PR3 antibodies.⁸ This leads to vessel thrombosis and granuloma formation.⁸ ANCA is 85-90% sensitive in diagnosing active WG.¹

The differential diagnosis includes infection, neoplasm, microscopic polyarteritis, Goodpasture's syndrome. The most common radiologic abnormalities include masses and pulmonary nodules. CT scan imaging of ten shows bilateral nodules concentrated over the subpleural regions.² Laboratory studies include leukocytosis, elevated erythrocyte sedimentation rate, normocytic anemia, positive ANCA and rheumatoid factor. Histopathologic diagnosis could be established through lung or skin biopsy. Potential biopsy sites include affected areas such as nasal sinus, muscle, temporal artery, kidney, lung. Lung biopsies are done in patients presenting with alveolar hemorrhages. Kidney biopsies are done in patients with urinary sediment abnormalities, proteinuria or change in renal function.⁸ On histologic examination WG is characterized by vasculitis, inflammatory infiltration of medium and small vessels, and necrotizing granuloma formation.^{1,4,8}

There are two forms of WG: systemic and limited. The limited form of Wegener's usually does not affect the function of vital organs.⁹ The systemic form of WG is more common and only 25% of patients will have limited WG.³ Some authors state that the limited form may evolve into systemic disease, implying that the two forms are different stages of progression of the same disease. They further state that the lack of progression in some of the cases is due to improved treatment modalities.⁹ Others postulate that the two forms represent different disease entities.^{9,10} C-ANCA is present in 50% of patients with the limited form and 80% of patients with the systemic form of the disease.⁸

Initially our patient was found to have bilateral pulmonary nodules on preoperative chest X-ray. Differential diagnosis at that time included more common conditions such as lung metastasis, tuberculosis, sarcoidosis, rheumatoid nodules, lung infection (bacterial or fungal). The presence of vasculitic process was investigated after the above mentioned

conditions were ruled out. The patient did not present with upper respiratory findings or findings indicative of kidney involvement. Due to the absence of such findings he was suspected of having the limited form of WG. He later developed diarrhea and was diagnosed with *Clostridium difficile* infection. At that time the patient developed systemic manifestations of WG including renal failure, vasculitic rash and hemoptysis. The degree of kidney involvement could not be assessed secondary to failure to obtain satisfactory biopsy specimen. The infection could have triggered the involvement of his limited WG into systemic disease, supporting the theory that those two forms are different stages of the same disease entity. The patient's condition rapidly transformed from a limited form to a systemic form of WG in the course of two weeks. This highlights the importance of timely treatment in patients with limited WG in order to prevent disease progression.

When left untreated, WG is usually fatal.¹ Indicators of a poor prognosis include renal involvement and advanced age. The usual treatment regimens of WG include a combination of steroids and immunosuppressant agents. WG that does not involve the kidneys or other vital organs can be treated with less toxic regimens such as methotrexate or azathioprine.^{11,3} Limited WG may progress to involve kidneys and other organs and hence should be treated and closely monitored.

Conclusions

Wegener's granulomatosis is a small and medium vessel ANCA associated vasculitis. The classical triad includes upper respiratory tract, lower respiratory tract and renal involvement. However, patients do not always present with the triad and a high index of clinical suspicion is needed in order to make a prompt diagnosis. When patients present with limited disease, without renal involvement, diagnosis is delayed and immunosuppressive treatment is not recommended. There are no clear guidelines on how limited WG should be approached, followed up, or treated. Our case demonstrates that limited WG can evolve into systemic dis-

ease secondary to environmental triggers such as infection. This supports the notion that the two forms represent different stages of the same disease.

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