Sulfasalazine Pulmonary Toxicity in Ulcerative Colitis Mimicking Clinical Features of Wegener’s Granulomatosis*

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The centrally accentuated antineutrophil cytoplasmic antibody test (c-ANCA) is widely regarded as a sensitive and specific marker for Wegener’s granulomatosis (WG). There are increasing reports, however, of false-positive c-ANCA, usually in the setting of other vasculitides. We report a case of a 27-year-old man with ulcerative colitis who developed pulmonary symptoms, peripheral nodular lung infiltrates, and an elevated c-ANCA suggesting WG. Chest CT and open lung biopsy specimens were consistent with WG. The symptoms and pulmonary infiltrates resolved after discontinuation of sulfasalazine therapy. The c-ANCA remained elevated due to the occurrence of false-positive values in ulcerative colitis. We conclude sulfasalazine toxicity can mimic clinical aspects of WG and that c-ANCA testing should be interpreted with caution in patients with ulcerative colitis.

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Key words: antinuclear cytoplasmic antibody; sulfasalazine; ulcerative colitis; Wegener’s granulomatosis

Abbreviations: ANCA=antinuclear cytoplasmic antibody; BOOP=bronchiolitis obliterans with organizing pneumonia; c-ANCA=centrally accentuated antineutrophil cytoplasmic antibody; CXR=chest radiograph; p-ANCA=perinuclear accentuated antineutrophil cytoplasmic antibody; UC=ulcerative colitis; WG=Wegener’s granulomatosis

Noninfectious causes of bilateral pulmonary infiltrates include Wegener’s granulomatosis (WG) and other vasculitides, embolic diseases, connective tissue disorders, drug reactions, and eosinophilic lung diseases. Because symptoms and radiographic findings in these disorders may be nonspecific, the diagnosis usually depends on laboratory and histologic data.

Because WG is a relatively uncommon illness, an antineutrophil cytoplasmic antibody (ANCA) test is often obtained to confirm clinical suspicion of the disorder. A centrally accentuated ANCA (c-ANCA) is believed to be highly specific for WG, with only occasional false-positives noted.1-4

Although a positive perinuclear accentuated ANCA (p-ANCA) is common in inflammatory bowel disease, a positive c-ANCA is not.5-8

We now describe a patient with ulcerative colitis (UC) who presented with noninfectious peripheral pulmonary infiltrates, a persistently elevated c-ANCA, and pulmonary symptoms mimicking WG who was later diagnosed as having sulfasalazine pulmonary toxicity.

CASE REPORT

A 27-year-old man had an 18-month history of ulcerative proctosigmoiditis. He had taken sulfasalazine, 1,000 mg po bid, since diagnosis with no disease activity until flares at 3 and 2 months before onset of pulmonary symptoms. Both ulcerative colitis exacerbations were responsive to hydrocortisone enemas and oral prednisone therapy. Two weeks before onset of pulmonary symptoms, treatment with his second prednisone burst was tapered off, and the sulfasalazine dose was increased to 1,000 mg po qid.

Two weeks later, the patient noted abdominal cramping, nausea, fatigue, myalgias, and nonproductive cough. The cough was believed to be from an upper respiratory tract infection. His sulfasalazine dose was decreased to 1,000 mg po bid to relieve the GI symptoms. Three weeks after onset of symptoms, the patient reported a fever of 38.4°C and a worsened cough. A chest radiograph (CXR) was obtained that demonstrated patchy bilateral lower lobe and left upper lobe nodular infiltrates (Fig 1, top). He was treated with erythromycin, 500 mg po qid, for the presumptive diagnosis of a community-acquired pneumonia. One week later, the patient was still febrile and presented to the emergency department with increasing dyspnea.

On examination, the patient was a thin white man in mild respiratory distress. He had a temperature of 38.3°C, a respiratory rate of 18, a BP of 118/65 mm Hg, and a pulse of 90. Chest examination revealed mild bivascular crackles on inspiration over his lower posterior lung fields. No rashes, joint effusions, or heart murmurs were noted. Results of neurologic and ears, nose, and throat examination were normal.

He was admitted to the hospital and treated with erythromycin, 500 mg po qid, and ceftriazone, 1 g IV qd. Blood, sputum, and stool cultures grew no pathogens. His CXR and symptoms did not change after 3 days of therapy. A room air arterial blood gas specimen revealed mild hyponatremia at 138/139/80/85.3%. Results of liver function tests, BUN and creatinine, a urinalysis, and serum electrolytes were normal. A CBC count showed WBC count of 15.6x10^9/L with 13% lymphocytes, 6% monocytes, and 79% neutrophils. The platelet count was normal, and the hematocrit was at the patient’s baseline of 35.6%. A purified protein derivative was negative with positive controls. Three induced sputum samples for acid-fast bacilli were negative. An absolute eosinophil count was normal at 158/mm^3.

Chest CT was performed to further characterize the pulmonary infiltrates, revealing multiple bilateral peripheral wedge-shaped infiltrates. One of the right lower lobe nodules had central cavitation (Fig 2, top). No significant mediastinal abnormalities were found. The CT was believed to be consistent with a differential diagnosis of WG, other vasculitides, idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP), eosinophilic pneumonia, drug-induced lung disease, nodular sarcoidosis, multifocal lobar pulmonary embolism, fungal pneumonia, and tuberculosis.

A BAL was obtained the next day and showed 8% neutrophils, 45% alveolar macrophages, 36% lymphocytes, and 11% bronchial epithelial cells. There were 165 RBCs per cubic millimeter and 173 WBCs per cubic millimeter. Stains for Pneumocystis carinii, cytomegalovirus, Legionella, acid-fast bacilli, and fungi were unremarkable. The BAL cultures grew no pathogens. A transbronchial biopsy specimen showed nonspecific pneumonitis, but a definitive

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556
tissue diagnosis could not be made. Because WG was in the differential diagnosis, the patient had serial urinalyses and nasopharyngoscopy which were both normal. A c-ANCA test performed by the indirect immunofluorescence technique (Corning MetPath Clinical Laboratories; Teterboro, NJ) was positive in a 1:35 titer and confirmed by a repeat sample using the same method at the National Institutes of Health, also positive in a 1:320 titer.

Due to uncertainty over the diagnosis, an open lung biopsy specimen was obtained. The biopsy specimen showed a lymphocytic small-vessel vasculitis with poorly formed granulomas and diffuse BOOP. There was also diffuse blood and hemosiderin-laden macrophages in the alveolar spaces. One area of definite necrosis at the edge of a medium-sized blood vessel was seen composed of debris-laden macrophages, epithelioid histiocytes, and rare giant cells. Photomicrographs of the open lung biopsy specimen are shown in Figure 3. The biopsy specimen was believed to be consistent with WG, hypersensitivity pneumonitis, benign lymphocytic angiitis and granulomatosis, and idiopathic BOOP. The specimen was reviewed by two outside pathologists who concurred with the differential diagnosis.

Given the uncertainty of the biopsy report and the possibility of sulfasalazine toxicity, a trial off this medication was performed. The patient’s symptoms markedly improved within 1 week and at 2 weeks a CXR showed clearing of the pulmonary infiltrates. Twelve weeks later, the radiographic and CT findings had largely vanished (Figs 1, bottom and 2, bottom), and the patient was asymptomatic. A repeated c-ANCA was obtained that was still positive in a 1:66 titer.

**Discussion**

The present report describes the mimicry of pulmonary aspects of WG by sulfasalazine lung toxicity. We also describe the first report (to our knowledge) of a false-positive c-ANCA in a patient with UC and pulmonary disease.

Traditionally, open lung biopsy has served as the gold standard to diagnose WG. However, in recent years, some authors have suggested that a positive ANCA test result could replace open lung biopsy in patients with no infectious etiology and characteristic manifestations of WG. In our case, a clinical dilemma resulted when a positive c-ANCA test, symptoms consistent with limited WG, and compatible radiographic features were present with an equivocal open lung biopsy specimen. Although WG classically presents with vasculitis, necrosis, and granulomatous inflammation, atypical histologic appearances are possible. There may be geographic necrosis, microabscesses, and granulomatous

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**Figure 1.** Top: posteroanterior (PA) CXR showing patchy bilateral lower lobe and left upper lobe peripheral air space consolidation at time of hospital admission for dyspnea, fever, and cough. Bottom: PA CXR 2 weeks after discontinuation of sulfasalazine therapy showing resolution of most of the above changes.

**Figure 2.** Top: CT of the chest showing peripheral right lower lobe nodular infiltrate with central cavitation. Bottom: CT of the chest 2 weeks after discontinuation of sulfasalazine therapy with residual minimal subpleural ground-glass appearance showing resolution of most of the above changes.
inflammation without classic vasculitis. WG may also present with isolated capillaritis, intra-alveolar hemorrhage, and BOOP. This case showed only a single focus of necrosis, but demonstrated extensive organizing pneumonia, in addition to the granulomatous inflammation and vasculitis. Therefore, our lung biopsy specimen was consistent with but not pathognomonic of WG. This led to stronger consideration that the patient may have a different underlying source for his pulmonary disease and a false-positive c-ANCA.

Indirect immunofluorescence shows two major patterns of ANCA reactivity: centrally accentuated and perinuclear associated. A centrally accentuated cytoplasmic (c-ANCA) fluorescence pattern is regarded to be a sensitive (30 to 90%) and highly specific (>97%) marker for WG. Nevertheless, false-positives have been reported. In these cases, most false-positive c-ANCA were found in association with other vasculitis syndromes such as microscopic polyarteritis, Takayasu's vasculitis, lymphoid granulomatosis, polyarteritis nodosa, and rapidly progressive glomerulonephritis. The only description of an unequivocally false-positive c-ANCA in UC can be found in a single study of the Chinese population in which two UC subjects without lung disease tested positive. Another report describes a nonperinuclear, homogeneous ANCA staining pattern occurring in patients with inflammatory bowel disease but clearly states this was not a classic c-ANCA pattern. To our knowledge, the present case is the first in which the false-positive c-ANCA had a misleading influence on the evaluation of pulmonary symptoms in a patient with UC.

The other type of ANCA fluorescence pattern is the perinuclear associated (p-ANCA) type. A positive p-ANCA lacks specificity and may be found in a large proportion of patients with systemic vasculitides, autoimmune liver disease, and rheumatoid arthritis. Up to 75% of patients with UC have a p-ANCA fluorescence pattern. Pulmonary manifestations may accompany p-ANCA-related illnesses, but these are often nonspecific.

Coexistence of WG and UC has been described with biopsy confirmation, but without c-ANCA testing in two patients. The first patient presented with pleuritic chest pain, but without other symptoms. She was not taking sulfasalazine but had taken steroids until 8 weeks prior to presentation. A CXR showed a pleural-based nodule in the right lower lobe that was sampled at open lung biopsy. The biopsy specimen was consistent with WG, and the symptoms and lesion resolved without treatment. The second patient presented with pleuritic chest pain and fever. She had a pleural-based density in the left upper lobe that was consistent with WG at open lung biopsy. The patient was treated with steroids and had no recurrence. This patient also had no sulfasalazine exposure.

There are reports of pulmonary involvement in patients with inflammatory bowel disease not taking medications, with 23 cases to date. BOOP, inflammatory tracheal stenosis, panbronchiolitis, serositis with or without myocarditis, and vasculitis have all been described. These pulmonary manifestations were not conclusively related to periods of GI disease activity but often seemed to improve with steroids in uncontrolled studies. ANCA testing was not described in most of these cases.

Our case is similar in some respects to previously published reports on sulfasalazine pulmonary toxicity. This disorder is rare, with only 40 cases described in the literature. Notably, most cases of sulfasalazine-induced lung disease occurred in patients with UC with the exception of two patients with Crohn's disease and six patients being treated for rheumatologic symptoms. Clinical symptoms of fever, nonproductive cough, and dyspnea are common and are usually mild to moderate in severity. Occasionally, patients may be asymptomatic.

Upper lobe peripheral opacities are the most common radiographic finding in sulfasalazine pulmonary toxicity, although lower lobe or diffuse infiltrates have occurred in a minority of cases. CT findings in sulfasalazine lung disease have not been well characterized in most prior case reports. To our knowledge, our case represents the first report of an area of central cavitation in a pulmonary lesion caused by sulfasalazine noted on CT.

Time to onset of symptoms after initiation of sulfasalazine therapy varies widely from weeks to years. We believe the increase in sulfasalazine several weeks before presentation may have precipitated our patient's reaction. Another possibility is the decrease in prednisone therapy may have unmasked or initiated the drug reaction.
The most common presentation of sulfasalazine pulmonary toxicity is simple eosinophilic pneumonia diagnosed by peripheral pulmonary infiltrates and blood eosinophilia, with 19 cases described in this manner. Several patterns of sulfasalazine-related lung damage have been described on tissue biopsy specimens, including interstitial pneumonitis, eosinophilic pneumonia, and BOOP, suggesting a variety of different mechanisms for lung damage.

Although our patient recovered rapidly after sulfasalazine therapy discontinuation, other patients have a less favorable outcome. Three fatalities have been reported, one after long-term sulfasalazine therapy and two several weeks after starting treatment with the medication.11

We conclude that sulfasalazine pulmonary toxicity can mimic limited WG clinically and radiologically. We also believe that although c-ANCA has been reported as highly sensitive and specific marker for WG, false-positives can occur in UC.

REFERENCES

Hyperacute Rejection Following Lung Transplantation*

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Although hyperacute rejection has been clinically and pathologically fully described in recipients of other solid organ transplants, to our knowledge, there have been no previous fully documented cases in recipients of lung transplants. This case of clinical hyperacute rejection is corroborated by a positive, donor-antigen-specific IgG-mediated lymphocytotoxic crossmatch (LXM), and demonstrated histopathologic, immunofluorescent, and electron microscopic features consistent with hyperacute rejection as described in other organs. Features of diffuse alveolar damage, neutrophil infiltrates, and endothelial and epithelial damage with IgG-fluorescent staining within alveolar spaces and septae were demonstrated. The management of hyperacute rejection and its outcome are reviewed. Historically a pretransplant crossmatch is not considered a routine part of lung transplantation. The outcome of this patient suggests that LXM should be performed routinely prior to lung transplant in all patients with high panel-reactive antibodies, and should be performed whenever circumstances permit.

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Key words: hyperacute rejection; lung transplant; lymphocytotoxic crossmatch

Abbreviations: LXM=lymphocytotoxic crossmatch; PRA=panel-reactive antibody

Hyperacute rejection is a well-recognized cause of immediate graft failure in recipients of transplanted hearts and kidneys. Although histologic descriptions of hyperacute rejection have been described in animal lung xenografts, hyperacute rejection has not, to our knowledge, been documented and fully described histologically in recipients of lung transplants. The limitations of current preservation techniques preclude prolonged ischemic times, making pretransplant crossmatches a luxury relative to some other frequently transplanted organs, and thus the possibility of hyperacute rejection is theoretically greater. We report the first fully documented case of hyperacute rejection following lung transplantation.

CASE REPORT

A 48-year-old white woman, blood type O, had smoking-associated emphysema. Radiologic features of her emphysema were suggestive of α1-antitrypsin deficiency, but α1-antitrypsin levels were normal, and her Pi type was MS. The patient was gravid 2 para 2. Her last pregnancy was 24 years prior to transplantation. There was no history of blood transfusion. Routine pretransplant

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