Pulmonary Alveolar Hemorrhage in a Patient with Ulcerative Colitis and Primary Sclerosing Cholangitis

Yosefa Bar-Dayan MD MHA[1], Simon Ben-Zikrie MD[2], Gerald Fraser MD FRCP[1], Ziv Ben-Ari MD[3], Marius Braun MD[1], Mordechai R. Kremer MD[4] and Yaron Niv MD[1]

[1] Department of Gastroenterology, [2]Department of Medicine, Hepatology Unit[3], and [4]Institute of Pulmonology, Rabin Medical Center (Beilinson Campus) Petah Tiqva, Israel

Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: alveolar hemorrhage, pulmonary vasculitis, ulcerative colitis, primary sclerosing cholangitis

IMAJ 2002;4:464-465

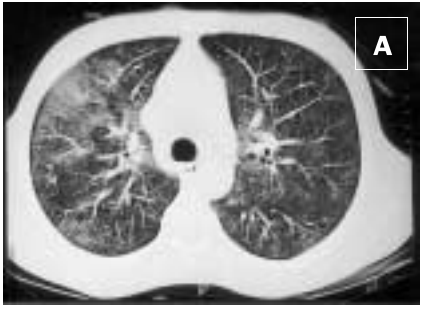
For Editorial see page 461

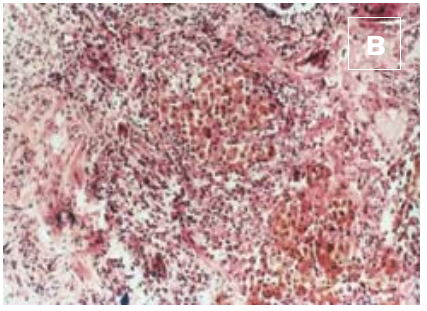
Extra-intestinal features of ulcerative colitis are common and well recognized. Pulmonary manifestations are unusual and can involve the airways, lung parenchyma or serosal surfaces. Pulmonary vasculitis has rarely been reported in association with ulcerative colitis [1–3].

We describe a patient with long-standing ulcerative colitis and primary sclerosing cholangitis who developed diffuse alveolar hemorrhage due to pulmonary vasculitis.

Patient Description

A 25 year old man with ulcerative colitis and primary sclerosing cholangitis was followed for the last 15 years in the gastroenterology department at our institution. Diagnosis was based on typical endoscopic features and was supported by histologic evidence. In July 2000, the patient experienced three episodes of upper gastrointestinal bleeding. Esophageal varices were diagnosed and treatment consisted of ligation and sclerotherapy. After an additional episode of bleeding, transjugular intrahepatic portosystemic shunting was performed, and the patient was listed for liver transplantation. He was treated with sulfasalazine, ursodeoxycholic acid, propanolol and spironolactone.





[A] CT scan of the lung demonstrates ground-glass appearance. **[B]** Alveolar spaces filled with hemosiderin-pigmented macrophages

* The first two authors contributed equally to this work.

Four months later, the patient was readmitted for increasing breathlessness and cough productive of blood-stained sputum. On examination he was dyspneic and febrile. Blood pressure and heart rate were normal. Auscultation revealed decreased air entrance over the right lung base, and bilateral crepitations were heard. Leukocyte count was 9,720/ml with hemoglobin 8.5 g/dl. Thrombocyte count was 122,000/ml. The blood coagulation profile was in the normal range. Creatinine level was 0.7 mg/dl (normal 0.7–1.4 mg/dl). Blood gases revealed pH 7.44, PCO_2 30.3 mmHg, bicarbonate level 20.2 mEq/L, PO_2 82.3 mmHg, and O_2 saturation 96.4%. Patchy bilateral alveolar infiltrates were demonstrated on chest X-ray film. Sputum culture grew normal respiratory flora but no mycobacteria or fungi. The purified protein derivative test was negative. Intravenous ceftriaxone therapy was started, and sulfasalazine was discontinued. Computerized tomography of the chest showed a unique ground-glass appearance of the lungs [Figure A]. Tests for antinuclear antibody, anti-double-stranded DNA and anti-glomerular basement membrane were all in the normal range. Tests for antineutrophilic cytoplasmic antibodies showed elevation of anti-lactoferrin antibody to 16 u/ml (normal <10 u/ml). C3 and C4 values were 106 /dl and 12.5 mg/dl respectively (normal range for C3 88–201 mg/dl and for C4 16–47 mg/dl). No pathogens grew in repeated blood, urine and sputum cultures. Pulmonary function tests showed moderate restrictive lung disease with reduced lung diffusion. Bronchoscopy revealed diffuse bilateral pulmonic hemorrhages. Bronchial washings were negative for *Mycobacteria*, *Pneumocystis carinii*, fungi, viruses and tumor cells. Transbronchial biopsy showed alveolar spaces filled with hemosiderin-pigmented macrophages with scattered erythrocytes and neutrophils [Figure B]. Diffuse alveolar hemorrhage was diagnosed. The patient was treated with intravenous methylprednisolone and cyclophosphamide, with a good response.

Comment

Diffuse alveolar hemorrhage is a rare yet serious and frequently life-threatening complication of a variety of conditions. It is characterized clinically by dyspnea and hemoptysis, anemia and diffuse bilateral alveolar infiltrates on chest radiograph [4]. DAH may result from coagulation disorders, inhaled toxins, or infections. Most cases, however, are due to pulmonary capillaritis associated with a wide range of systemic autoimmune diseases, such as antineutrophil cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease and systemic lupus erythematosus [4]. In some cases, capillaritis may be the sole pulmonary vascular manifestation, without clinical or serologic evidence of any systemic disease. Isolated pulmonary capillaritis has been reported to respond to corticosteroid therapy with the addition of cyclophosphamide. Early recognition is crucial because the prompt initiation of supportive measures and immunosuppressive therapy is necessary for survival [4].

Patients with pulmonary capillaritis often present with DAH. In our case, there was no evidence of infection, coagulation disorders, inhaled toxins, or any systemic autoimmune disease. Hence, we assumed that the patient's condition could be explained solely by pulmonary vasculitis. Our assumption was reinforced by the patient's good response to directed therapy.

An interesting finding was the mild elevation of anti-lactoferrin antibody. ANCA are autoantibodies directed against cytoplasmic constituents of neutrophil granulocytes. Antibodies with specificity for proteinase 3 and myeloperoxidase are seromarkers for systemic vasculitides. ANCA with specificity for lactoferrin has been reported in patients with such idiopathic inflammatory diseases as inflammatory bowel diseases and rheumatoid arthritis. Studies of inflammatory bowel disease and primary sclerosing cholangitis have shown that in inflammatory bowel disease, the presence of anti-lactoferrin antibody was not related to disease activity, duration of disease, disease extent, or therapy. In primary sclerosing cholangitis, the presence of autoantibodies to lactoferrin did not correlate with duration of disease or the presence of cirrhosis. However, patients with primary sclerosing cholangitis and coexistent ulcerative colitis had significantly more antibodies to lactoferrin than did primary sclerosing cholangitis patients without inflammatory bowel disease [5].

Although systemic vasculitis, such as Takayasu's disease, Wegener's granulomatosis and periarteritis nodosa, have been reported in patients with ulcerative colitis, we are aware of only four reported cases of isolated pulmonary vasculitis associated with ulcerative colitis in adults [1–3]. In 1968, Isenberg et al. [1] described a patient with ulcerative colitis in association with nodular pulmonary infiltrates and pulmonary vasculitis. The pulmonary lesions regressed after colectomy. Two other cases of pulmonary vasculitis and ulcerative colitis were diagnosed without lung biopsy [3]. Sargent et al. [3] reported a patient with biopsy-proven pulmonary vasculitis that was associated with flares in ulcerative colitis, which were ameliorated following treatment with sulfasalazine and prednisone.

In summary, our case supports the existence of pulmonary vasculitis as a rare but important complication of ulcerative colitis. Corticosteroid therapy with cyclophosphamide appears to be a rational step in the management of this condition.

DAH = diffuse alveolar hemorrhage
ANCA = antineutrophil cytoplasmic antibodies

References

1. Isenberg JI, Goldstein H, Korn AR, Ozeran RS, Rosen V. Pulmonary vasculitis – an uncommon complication of ulcerative colitis. Report of a case. *N Engl J Med* 1968; 279:1376–7.
2. Vesel HT, Eithz C. Pulmonary vasculitis as an extraintestinal manifestation in ulcerative colitis. *Ugeskr Laeger* 1998;160:2116–17.
3. Sargent D, Sessions JT, Fairman RP. Pulmonary vasculitis complicating ulcerative colitis. *South Med J* 1985; 8:624–5.
4. Ulrich S. Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol* 2001;13: 12–17.
5. Roozendaal C, Horst G, Pogany K, et al. Prevalence and clinical significance of antilactoferrin autoantibodies in inflammatory bowel diseases and primary sclerosing cholangitis. *Adv Exp Med Biol* 1998;443:313–19.

Correspondence: Dr. Y. Niv, Dept. of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49100, Israel.
Phone: (972-3) 937-7237,
Fax: (972-3) 921-0313
email: yniv @clalit.org.il