Alveolar Hemorrhage Associated With Antineutrophil Cytoplasmic Antibodies in Rheumatoid Arthritis

Antonio Torralbo, M.D.; José A. Herrero, M.D.; Jose Portolés, M.D.; and Alberto Barrientos, M.D.

A 65-year-old woman with previously known rheumatoid arthritis and chronic renal failure of possible glomerular origin was admitted to the hospital because of hemoptysis and respiratory insufficiency. Antineutrophil cytoplasmic antibodies (ANCAs) with antimeyeloperoxidase activity were detected in her serum. The lung biopsy specimen evidenced alveolar hemorrhage. Under immunosuppressive therapy with steroids and cyclophosphamide, the patient’s condition improved both clinically and radiologically, and the ANCA became negative after 6 months’ therapy.

(Ches 1994; 105:1590-92)

The pulmonary manifestations of rheumatoid arthritis (RA) include pleural effusion, diffuse interstitial fibrosis and pneumonitis, necrobiotic nodules, Caplan’s syndrome, pulmonary hypertension out of proportion to interstitial lung disease (pulmonary vascular disease), upper lobe fibrobulous disease, bronchiolitis, and bronchogenic carcinoma. Renal disease and alveolar hemorrhage (AH) have been infrequently described in RA. In three previously reported cases, no autoantibodies other than rheumatoid factor were detected, though antineutrophil cytoplasmic antibodies (ANCAs) were not tested. We describe a patient with RA and AH associated with serum ANCA.

CASE REPORT

A 65-year-old woman had been diagnosed as having seropositive RA at another hospital in 1988. No data are available regarding her renal function over the 2 ensuing years.

In 1990, she was admitted to our hospital’s Nephrology Service because of asthenia, vomiting, and limb cramps. The clinical examination disclosed arterial hypertension (170/100 mm Hg), mucocutaneous pallor, ulnar deviation at the metacarpophalangeal joints in both hands with distal interphalangeal nodules, and absence of lower limb edema. The relevant laboratory results were as follows: hematocrit, 23.8 percent; creatinine, 1087.3 µmol/L (12.3 mg/dl); albumin, 27 g/L (2.7 g/dl); globulins, 35 g/L (3.5 g/dl); and proteinuria, 2.5 g/24 h. The rheumatoid factor was positive (153 UI/ml, nephelometry), antinuclear antibodies and cryoglobulins were negative, and the complement levels were within normal ranges. The plain chest radiograph showed moderate cardiomegaly and the radiographic study of the hands disclosed ulnar deviation, reduced metacarpophalangeal joint space, erosions in the metacarpal epiphyses, and increased soft-tissue shadows. The abdominal ultrasound revealed small kidneys bilaterally. A diagnosis of end-stage chronic renal failure was established, and the patient was entered in the periodic hemodialysis program.

In May 1992, the patient was again admitted to the hospital because of dyspnea and hemoptysis. The hematocrit at this time was 21 percent and gasometric values (breathing 28 percent oxygen) were PaO₂ of 55 mm Hg, PaCO₂ of 33 mm Hg, pH of 7.46 and CO₂H of 25 mmol/L. The plain chest radiograph evidenced a bilateral alveolar infiltrate pattern, most noticeable in the right field (Fig 1). At bronchoscopy, traces of blood were seen in the trachea and the right main bronchus, issuing from the right basolateral segment.

Under arteriographic control, embolization of the segmental arteries was performed and control of the hemoptysis was achieved. The patient received a transfusion of concentrated RBCs, but again developed anemia over the ensuing hours. The ANCAs were detected in serum 48 h after hospital admission, with a perinuclear indirect immunofluorescence pattern and antimeyeloperoxidase (anti-MPO) activity by enzyme-linked immunosorbent assay. The rheumatoid factor was positive (75 UI/ml); other autoantibodies, including antinuclear, anti-DNA, antihistone, and anti-basal membrane antibodies, were negative. Cryoglobulins and circulating immune complexes were negative, and the complement was normal.

*From the Nephrology Service, Hospital Universitario San Carlos, Madrid, Spain. Reprint requests: Dr. Torralbo, c/Seville 1-3 14003 Cordoba, Spain.

\[AH=\text{alveolar hemorrhage}; \text{ANCAs} = \text{antineutrophil cytoplasmic antibody}; \text{MPO} = \text{myeloperoxidase}; \text{RA} = \text{rheumatoid arthritis}\]

Figure 1. Plain chest radiograph at the time of the second hospital admission, with predominantly right-sided bilateral alveolar infiltrate.

Figure 2. Photomicrograph showing an area of lung parenchyma with the alveolar spaces occupied by RBCs, fibrin, and hemosiderin pigment within the macrophages (hematoxylin-eosin, original magnification ×125).
### Table 1—Features of Four Patients With Rheumatoid Arthritis and Pulmonary-Renal Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/sex</strong></td>
<td>49/M</td>
<td>52/M</td>
<td>47/M</td>
<td>65/F</td>
</tr>
<tr>
<td><strong>Presenting features</strong></td>
<td>Hemoptysis</td>
<td>Hemoptysis</td>
<td>Hemoptysis</td>
<td>ESRD</td>
</tr>
<tr>
<td><strong>Features other than AH/RF</strong></td>
<td>ESRD</td>
<td>Purpura; peroneal mononeuropathy</td>
<td>Sjögren and carpal tunnel syndromes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Features of AH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity†</td>
<td>4+</td>
<td>4+</td>
<td>2+</td>
<td>5+</td>
</tr>
<tr>
<td>Relation to RF‡</td>
<td>Simultaneous</td>
<td>AH (4 wk)</td>
<td>AH (4 yr)</td>
<td>RF (2 yr)</td>
</tr>
<tr>
<td>Chest film§</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Patchy</td>
<td>Patchy</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Alveolar hemorrhage</td>
</tr>
<tr>
<td>Outcome¶</td>
<td>Resolved, no recurrence (3 yr)</td>
<td>Resolved, no recurrence (1 yr)</td>
<td>Recurrence (4 yr)</td>
<td>Resolved, no recurrence (6 mo)</td>
</tr>
<tr>
<td><strong>Features of RF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine∥</td>
<td>13.0/ESRD</td>
<td>1.0/8.9</td>
<td>1.0/ESRD</td>
<td>12.3/ESRD</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>34+</td>
<td>1+</td>
<td>0.5 g/24 h</td>
<td>2.5 g/24 h</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Segmental necrotizing GN, 100% crescents, necrotizing arteriitis; IF granular</td>
<td>Focal-segmental necrotizing GN, 25% crescents; IF negative</td>
<td>Diffuse-segmental necrotizing GN, 75% crescents, necrotizing arteritis; IF granular</td>
<td>Not done</td>
</tr>
<tr>
<td>Outcome</td>
<td>Long-term dialysis</td>
<td>Creatinine 2.0</td>
<td>Long-term dialysis</td>
<td>Long-term dialysis</td>
</tr>
<tr>
<td>Immunology**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Not reported</td>
<td>1/2560</td>
<td>1/1250</td>
<td>73 U/l * ml</td>
</tr>
<tr>
<td>ANCA</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Positive</td>
</tr>
<tr>
<td>Complement</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Other autoantibodies</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Therapy</td>
<td>M+P+C</td>
<td>M+P+C</td>
<td>P+M+P+C</td>
<td>M+P+C</td>
</tr>
</tbody>
</table>

*AH=alveolar hemorrhage; RF=renal failure; ESRD=end-stage renal disease; IF=immunofluorescence; M=methylprednisolone; P=prednisone; C=cyclophosphamide; Pl=plasmapheresis.

†++=blood-tinged sputum, + frank hemoptysis, 3+=hemoptysis with dyspnea, 4+=ventilatory support required.

‡AH or RF refers to which of the two first occurred, with the interval until the other became evident in parentheses.

§Diffuse refers to opacification of virtually all lung fields; patchy denotes less extensive alveolar infiltrates in two or more lobes.

¶Course of AH following initiation of therapy, with interval since last episode of AH in parentheses.

∥First recorded creatinine level after onset of AH or RF/highest recorded creatinine level.

**Determinations performed at the time of AH; in patient 3, determinations performed at the time of second episode.

An open lung biopsy specimen disclosed alveolar hemorrhage; some arteries evidenced intimal fibrosis with reduction of the lumens, but no vasculitis (Fig 2).

Intravenous immunosuppressor therapy was instituted with methylprednisolone (1 g/d for 3 days) and cyclophosphamide (0.5 g/d for 3 days) and then continued orally with prednisone (1 mg/kg/d) and cyclophosphamide (1.5 mg/kg/d). The patient evidenced rapid clinical, gasometric, and radiologic improvement. The ANCA titer was lower at the time of the first control 3 months later, and became negative after 6 months’ therapy.

**DISCUSSION**

The characteristic exploratory and radiologic findings and the positive test for rheumatoid factor are consistent with the diagnosis of seropositive RA. When the patient was first admitted to our Service, she evidenced clinical, analytical, and radiologic findings consistent with end-stage chronic renal failure, so that a kidney biopsy was not considered indicated and she was entered in a periodic hemodialysis program. The presence of arterial hypertension, proteinuria above 2.0 g/24 h, and hypoalbuminemia is not conclusive for her having a chronic glomerular disease, but this diagnosis is possible. Two years after entering the hemodialysis program, the patient evidenced AH associated with positive serum ANCA (MPO antibodies), which led us to think of the possibility of vasculitis and to institute aggressive immunosuppressor therapy.

Three cases have been reported of patients with RA and pulmonary-renal syndrome (Table 1). In none of these patients could autoantibodies other than the rheumatoid factor be detected, although ANCA were not tested for. In the case reported herein, we consider that cross-reactivity between ANCA and rheumatoid factor can be ruled out, as the enzyme-linked immunosorbent assay performed for ANCA determination detects only IgG antibodies, while the test for rheumatoid factor detects mainly IgM rheumatoid factor. Furthermore, the ANCA titer present at the time of hospital admission (with hemoptysis and respiratory insufficiency) became negative after 6 months’ immunosuppressive therapy, in concordance with the clinical and radiologic improvement.

The presence of antibodies producing a perinuclear staining of ethanol-fixed neutrophils (p-ANCA) with MPO specificity is highly suggestive for one of the necrotizing systemic vasculitides, including idiopathic necrotizing and crescentic glomerulonephritis. A close correlation between MPO antibodies and disease activity has been found.4 The presence of MPO antibodies in RA is a rare finding; p-ANCA of undefined antigenic specificity have been detected in 90 to 100 percent of patients with RA complicated by Felty's syndrome, 50 to 70 percent of patients with RA complicated by vasculitis, and in 20 to 40 percent of patients with uncomplicated RA.4
We consider the case reported herein a good example of the justification of aggressive immunosuppressive therapy in patients with positive ANCA in a clinical context suggestive of vasculitis, even when the histologic findings are not conclusive. The ANCA's (MPO antibodies) might be either markers or mediators in patients with RA and pulmonary-renal syndrome.

REFERENCES

Nebulized Lidocaine in the Treatment of Refractory Cough*

Scott Trochtenberg, M.D.

A 52-year-old man with intractable cough refractory to standard therapy was treated successfully with chronic nebulized lidocaine. He has experienced no adverse effects from the lidocaine except for occasional mild dysphonia. Measured serum levels of lidocaine after treatment have never exceeded 4.0 mg/dl. This case shows prolonged therapy with nebulized lidocaine is a safe and effective treatment for refractory cough.

(CHEST 1994; 105:1592-93)

Intractable cough is an uncommon, but potentially disabling illness. Antihistamines, benzodiazepines, narcotics, and phenothiazines have been reported to palliate coughing. Nebulized lidocaine is used routinely as an antitussive before bronchoscopy. The following case presents a patient with intractable cough that has been treated successfully with nebulized lidocaine.

CASE REPORT

A 52-year-old white man was referred for evaluation of intractable nonproductive cough, which became unremitting after therapy with glyburide and lisinopril was initiated for diabetes mellitus and hypertension. His medical history was otherwise unremarkable. He denied chills, fever, hemoptysis, night sweats, sputum production, or weight change. He has never used tobacco. No environmental exposures were identified. His symptoms failed to improve after cessation of oral hypoglycemics and angiotensin converting enzyme inhibitors. He fell off a roof during a paroxysm of coughing, fracturing his wrist and shoulder.

On presentation, he was unable to speak in complete sentences due to coughing. Vital signs, ears, nose, oropharynx, and lymph node survey were normal. His lungs were clear to auscultation and percussion; inspiratory to expiratory ratio was normal. The rest of his examination was unremarkable. Laboratory evaluation revealed moderate hyperglycemia. Chest roentgenograms and computed tomograms of the chest and sinuses were normal. Methacholine challenge, pulmonary function testing, and tuberculosis skin testing were normal. Rhinolaryngoscopy and bronchoalveolar lavage (with cultures) gave negative results on two occasions. Barium swallow showed mild antritis; no reflux was revealed despite coughing during the examination.

Neither β-agonists, chlorpheniramine, cromolyn, diazepam, ipratropium, metoclopramide, ranitidine, systemic corticosteroids, nor theophylline improved his cough. Partial relief was obtained with acetaminophen with codeine No. 3 four times daily and phenothiazines (chlorpromazine 10 mg four times daily, later changed to promethazine 25 to 50 mg four times daily).

Eighteen months later esophagogastroduodenoscopy was performed to evaluate fecal occult blood; however, he was unable to tolerate the procedure due to coughing. Nebulized lidocaine completely suppressed his cough. The study revealed severe erosive esophagitis.

Over the past year, his symptoms have been well controlled by nebulized lidocaine (3 ml of 1 percent lidocaine) twice a day and acetaminophen with codeine No. 3 as needed. His only adverse reaction is mild hoarseness lasting several hours after each treatment. Serum lidocaine levels measured after several treatments have never been greater than 4.0 mg/dl. He remains on therapy with metoclopramide and ranitidine as prophylaxis for reflux esophagitis.

DISCUSSION

The cause of our patient's cough is unclear. The cough persisted despite cessation of ACE inhibitors. Reflux esophagitis may be contributing to his cough; however, no reflux was identified on initial barium swallow and his symptoms have failed to improve on maximal antireflux medications. Other studies failed to show toxic serum levels after nebulization of 4 or 10 percent lidocaine. Nebulized lidocaine offers several advantages over the traditional treatment of cough. Antihistamines are often sedating and may dry secretions, paradoxically worsening the cough. Phenothiazines may produce dystonic reactions, sedation, and tardive oral dyskinesia. This case suggests nebulized lidocaine is tolerated well and effective therapy for intractable cough.

ADDENDUM

Since acceptance of this manuscript for publication, two additional patients with refractory cough have been treated successfully with nebulized lidocaine. The first received lidocaine for 2 months to treat a lisinopril-induced cough that persisted after cessation of the drug. The second was treated with lidocaine for 6 weeks to treat paroxysms of coughing, which appeared to be a complication of paretic vocal cords. Neither patient suffered any adverse effects from the lidocaine.

REFERENCES

*From the Miller Medical Group, Nashville, Tenn.

1502

Nebulized Lidocaine for Refractory Cough (Scott Trochtenberg)