A 35-Year-Old Man With Persistent Cough, Fever, and Sore Throat*

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A 35-year-old white Belgian man with an uneventful medical history was referred from Port Said, Egypt, for fever of unknown origin. As a civil engineer, he was working on a tunnel project with 50% of his day spent underground in caissons. About 6 months before referral, he developed a sore throat, hoarseness, nasal congestion, cough, and slightly enlarged submandibular glands, with a temperature up to 39.5°C. Within a few days, slight-to-moderate sternal and anterior chest pains were noted. An initial clinical evaluation included a chest radiograph and CT scan that were interpreted as normal. His erythrocyte sedimentation rate was >100 mm/h. A hemogram was normal except for thrombocytosis and a mild normochromic normocytic anemia. A serologic test for Epstein-Barr virus and blood polymerase chain reaction assay for Mycobacterium tuberculosis were positive. HIV serology was negative. Empiric treatment with cefuroxime acetyl and roxithromycin was unsuccessful. After 6 months of persistent symptoms and a 10-kg weight loss, he was referred for evaluation.

Physical Examination

Physical examination revealed a man with a good general appearance. Temperature was 38°C; other vital signs were normal.

There was no skin rash, arthritis, hepatosplenomegaly, or enlarged lymph nodes. Results of ear, nose, and throat, ophthalmologic, and oral examinations were normal. Breath sounds were normal at quiet breathing, but at forced inspiration, there was a discrete stridulous sound. Heart sounds were normal.

Laboratory Examinations

Hemoglobin level was 10.9 g/dL, WBC count was 15,600/mm³ with a normal differential cell count, platelet count was 550,000/mm³, and sedimentation rate was >130 mm/h. Electrolytes and renal indexes were normal. There was a polyclonal hypergammaglobulinemia.

Serologic tests for common viruses (except for the presence of Epstein-Barr virus IgG), bacteria, and parasites were negative. Antineutrophil cytoplasmic antibody, RA antibodies, and antinuclear and precipitating antibodies were not detectable. Intradermal tests for tuberculin and common allergens were negative; direct examination and cultures obtained from sputum, urine, feces, and blood were negative. Chest radiograph was normal. CT scan of the chest (Fig 1) showed a thickened tracheal wall from glottis to main bronchi. Gallium scintigraphy (whole body, and single photon emission CT of the thoracic cage) showed increased uptake at all sternochondral cartilages and at the nose (Fig 2). Fiberbronchoscopy showed subglottic stenosis and edematous tracheal mucosa. Spirometry showed a flattened inspiratory loop of the flow-volume curve.

What is the most likely diagnosis in this patient?
Figure 2. Whole body gallium scintigraphy.
Diagnosis: Relapsing polychondritis

Relapsing polychondritis is a rare multisystem inflammatory disorder, characterized by potentially destructive inflammatory lesions of cartilaginous structures throughout the body. Although the exact pathogenetic mechanism remains unknown, there is strong evidence suggesting autoimmunologically mediated mechanisms: autoantibodies against native collagens (e.g., collagen II) and cell-mediated immune responses directed toward cartilage components have been reported.

Histologically, a loss of basophilic staining indicating depletion of proteoglycans from the cartilage matrix and infiltration by plasma cells, lymphocytes, and polymorphonuclear leukocytes usually is present. Relapsing polychondritis most often occurs between the ages of 40 and 60 years, and there is no sex predilection. Susceptibility to the disease is associated significantly with HLA-DR4.

Clinically, auricular chondritis (55%), ocular symptoms (e.g., conjunctivitis, episcleritis, and uveitis [32%]), nasal chondritis (30%), and arthritis (20%) are the most frequent findings at presentation. Laryngotracheal involvement (hoarseness, aphony, tracheal tenderness, and stenosis with cough, dyspnea, or stridor) occurs less frequently, although it may represent a critical and potentially lethal organic system involvement. Flow-volume analysis in patients with laryngotracheal involvement typically allows objectivation of central airway stenosis and may be helpful in follow-up evaluations: typically, a flattened inspiratory loop is observed in case of extrathoracic airway stenosis, a flattened expiratory loop is observed in case of intrathoracic stenosis. In case of fixed severe stenosis, both inspiratory and expiratory loops may be flattened.

If untreated, relapsing polychondritis is associated with a high mortality rate, usually because of respiratory (airway obstruction, pneumonia) or cardiovascular (aortic valve disease, aortic aneurysm) complications. Anti-inflammatory and/or immunosuppressive agents (corticosteroids, azathioprine, cyclophosphamide, dapsone, cyclosporine) are indicated in suppressing the acute manifestations of the disease, and usually reduce the frequency and severity of recurrences. Tracheotomy or Nd-YAG laser therapy with stenting may be necessary to treat central airway involvement in some patients.

The present patient was initially treated with antituberculous agents because of the bronchoscopic findings that suggested endobronchial tuberculosis. The results of the chest CT scan, which demonstrated tracheal wall thickening, and the gallium scan, which demonstrated gallium uptake in the cartilages of the nose and sternocostal junctions, suggested the diagnosis of relapsing polychondritis. Anticollagen II autoantibodies were detected at a titer of 1:400. Deep biopsy specimens of the trachea through a rigid bronchoscope and surgical biopsy specimens of anterior sternocostal rib cartilages were obtained. Tracheal biopsy specimens showed submucosal inflammatory changes, with perivascular involvement. Sternocostal rib cartilage biopsy specimens showed loss of basophilic staining of the cartilage, cartilage destruction with loss of chondrocytes and infiltration by lymphocytes, plasma cells, and polymorphonuclear leukocytes (Fig 3). Methylprednisolone (64 mg daily for 3 weeks, followed by 32 mg daily for 6 weeks, followed by a 3-month taper) was given. Within 2 weeks, all symptoms had disappeared, a weight gain of 4 kg had occurred, and serum inflammatory parameters (sedimentation rate, C-reactive protein) normalized. A follow-up flow-volume loop was normal.

**Clinical Pearls**

1. Relapsing polychondritis may not present with “typical” clinical symptoms of auricular cartilage inflammation, ocular involvement, and arthritis.

2. Although laryngeal and tracheobronchial involvement do not occur frequently in relapsing polychondritis, they may be the only affected sites at initial presentation.

3. Inflammation of central airway may produce critical degrees of stenosis and represents a major source of morbidity and mortality in this condition.

**Suggested Readings**

Lang B, Rothenfusser A, Lauchbury JS. Susceptibility to relapsing polychondritis is associated with HLA-DR4. Arthritis...