Pulmonary infillrates with Eosinophilia due to Naproxen*


Various drugs have been implicated in the development of the syndrome of pulmonary infillrates with eosinophilia (PIE). In this study of a man who was being treated with naproxen, the findings are presented of the first such case of pulmonary hypersensitivity to naproxen as noted in our review of the literature.

An increasing number of drugs has been implicated in the etiology of transient eosinophilic pneumonia characterized by a benign clinical course, the development of pulmonary infiltrates, and blood eosinophilia. Naproxen is a widely used nonsteroidal anti-inflammatory drug which may be added to the list of pharmacologic agents which induce lung disease. A case of acute pulmonary hypersensitivity with eosinophilia, believed to have been caused by naproxen, is described.

CASE REPORT

A 72-year-old man was referred to the pulmonary service for evaluation with a three-day history of fever (38.9°C), nonproductive cough, wheezing, and abnormal findings on chest roentgenogram. Additional history revealed that the patient had been taking ibuprofen during the previous six months for osteoarthrits. Two weeks prior to the onset of respiratory symptoms, ibuprofen had been discontinued, and naproxen was prescribed because of progressive osteoarthritic pain.

Physical examination revealed the following: temperature,

*From the Pulmonary Division, Department of Internal Medicine; and the Clinical Investigation Center, Naval Regional Medical Center, San Diego.

The opinions or assertions expressed in this paper are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or the naval service at large.

Reprint requests: Dr. Schillaci, Clinical Investigation, Naval Hospital, San Diego 92134

REFERENCES

1. Blalock A, Taussig HB. The surgical treatment of malformation of the heart in which there is pulmonary stenosis or pulmonary atresla. JAMA 1945; 129:189-202.
peripheral

FIGURE 38.6°C; blood pressure, 130/74 mm Hg; pulse, 90 beats per minute; and respiratory rate, 20 breaths per minute. Auscultation of the chest revealed bilateral mid- and upper-lung-zone fine crackling end-inspiratory rales. The cardiac examination did not reveal the presence of a murmur or a gallop rhythm. There was no lymphadenopathy or edema. A chest roentgenogram revealed bilateral apical and peripheral infiltrates with "central sparing" (Fig 1). A 5 mCi gallium-67 citrate whole body scan revealed 4+ activity in both lung apices (Fig 2).

Abnormal laboratory studies included arterial blood gas levels while breathing room air: Po2 73 mm Hg, PCO2 34 mm Hg, and pH, 7.46. The white blood cell count was 14,300/cu mm with a differential of 67 percent segmented neutrophils, 8 percent lymphocytes, 3 percent monocytes, and 22 percent eosinophiles. The hemoglobin level was 12.9/100 ml with a hematocrit value of 38.1 percent. The platelet count was 364,000/cu mm, and the erythrocyte sedimentation rate was 115 mm per hour.

The following laboratory values were normal or negative: calcium, uric acid, creatinine, blood urea nitrogen, total bilirubin, total protein, albumin, serum electrolytes, urine analysis, mycobacterial and fungal cultures or sputum, histoplasmosis and coccidioidomycosis titers, and stools for ova and parasites. The ECG revealed a normal sinus rhythm.

A transbronchial lung biopsy was performed. The microscopic evaluation of the lung biopsy specimen revealed evidence of interstitial fibrosis, fibrous thickening of alveolar septa, and proliferation of alveolar macrophages. There was an inflammatory interstitial infiltration of lymphocytes, histiocytes, and predominantly eosinophiles, consistent with eosinophilic interstitial pneumonitis.

The naproxen therapy was discontinued. Within three weeks, the patient's fever and cough resolved. The chest roentgenogram demonstrated complete resolution of all infiltrates and a repeat gallium scan revealed no abnormal activity. The white blood cell count diminished to 8,400/cu mm with 3 percent eosinophiles.

Two months following the initial evaluation, informed consent was obtained and the patient was challenged with naproxen, 250 mg tablets administered every six hours. After three doses and within 24 hours, the patient developed symptoms of fever, cough, and wheezing. A chest roentgenogram demonstrated recurrence of the apical and peripheral infiltrates; and the white blood cell count was 12,700 cu mm with 5 percent eosinophiles. Gallium-67 scanning again revealed biapical concentration of the radioisotope.

The naproxen was permanently discontinued, and within 24 hours, the patient's symptoms subsided, the chest roentgenogram cleared, and the white blood cell count returned to normal.

DISCUSSION

Eosinophilic pneumonia is a condition assumed to represent the clinical manifestation of an altered immunologic response or allergic reaction. Various drugs have been implicated in the development of transient eosinophilic pneumonia4,5 and nonsteroidal, anti-inflammatory agents have been specifically implicated as etiologic agents for acute interstitial pneumonitis.6

We believe this case represents a pulmonary hypersensitivity reaction to naproxen manifested by fever, cough, wheezing, peripheral lung infiltrates, and eosinophilia. This patient had rapid clinical improvement of his illness upon cessation of naproxen therapy without the use of steroid therapy. Rechallenge with naproxen produced a similar illness as verified by the clinical symptoms, chest roentgenogram, gallium scan, and eosinophilia.

The chest roentgenogram with dense, ill-defined infiltrates, peripherally opposed to the pleura in a photographic negative pattern of pulmonary edema, has been described as virtually diagnostic of eosinophilic pneumonia.7 The localization of gallium in the peripheral and apical lung zones serves as a complimentary study to the chest roentgenogram indicating the extent, localization, and degree of activity of the inflammatory process.8 The gallium scan also was valuable in following the course of the disease during the rechallenge process, permitting evaluation of the activity of the inflammatory process with greater accuracy than the chest roentgenogram.

No previous case report of pulmonary hypersensitivity to naproxen was discovered in our review of the literature and inquiry of the manufacturer. Clinicians should be alerted to the possibility of such a complication occurring in patients being treated with this drug.

FIGURE 1. PA roentgenogram demonstrating bilateral apical and peripheral infiltrates with central sparing.

FIGURE 2. A 5 mCi gallium-67 citrate lung scan demonstrating concentration of radioisotope corresponding to areas of infiltrate on plain film.
Pacemaker-Induced Pseudotricuspid Regurgitation*

Richard H. Kay, M.D.; John A. Ambrose, M.D.; Laurence Schek, M.D.; Jeffrey Blake, M.D.; David Rubin, M.D.; and Michael V. Herman, M.D.

A patient with aortic stenosis and a ventricular pacemaker had clinical findings suggesting tricuspid regurgitation. Her presentation was actually caused by regular and constant cannon waves resulting from ventriculocardiac conduction of paced beats. The correct diagnosis was confirmed by abolition of hepatic pulsations during atrial pacing at the time of cardiac catheterization. Therapy consisted of restoring antegrade atrioventricular conduction.

Tricuspid regurgitation is most commonly due to dilatation of the right ventricle and tricuspid valve ring. 1 It is less commonly caused by primary valvular lesions. Catheters that cross the valve can interfere with leaflet closure and cause tricuspid regurgitation. 4 Pacemaker wires can cause tricuspid regurgitation by a similar mechanism or by altering the normal synchrony of atrioventricular contraction. 3 Thromboses of catheters or pacemakers can also cause tricuspid regurgitation by interfering with normal valve function. 4

Recently, a patient was seen with a ventricular pacemaker and significant aortic stenosis in whom signs and symptoms suggesting tricuspid regurgitation were present in the absence of severe pulmonary hypertension and right ventricular dilatation. In this patient, the presentation resembling tricuspid regurgitation was related to cannon A waves caused by ventriculocardiac conduction during pacemaker rhythm. This case illustrates an important mimicry of severe symptomatic tricuspid regurgitation that was easily rectified after the diagnosis was established.

CASE REPORT

An 83-year-old woman was referred for cardiac catheterization. She had a history of a heart murmur for several years and six months of progressive dyspnea and angina. Three months prior to admission, she noted near syncopal episodes. Ambulatory monitoring revealed sinus pauses and a programmable transvenous ventricular pacemaker was inserted with resolution of the episodes. Two months prior to admission, the patient noted the onset of edema, which responded to increased diuretics. One month prior to admission, she noted the onset of increasing right upper quadrant discomfort, and a markedly pulsatile liver was palpated. She was referred for catheterization with the diagnoses of aortic stenosis and tricuspid insufficiency.

Admission physical examination was consistent with severe aortic stenosis. There were signs of mild pulmonary hypertension. The jugular venous pressure was estimated at 8 cm H2O without prominent pulsations. The liver was markedly pulsatile.

The ECG revealed a ventricular paced rhythm at a rate of 72 beats per minute, with retrograde P waves discernible in lead V1 (Fig 1). Echocardiography was consistent with aortic stenosis and concentric left ventricular hypertrophy.

Cardiac catheterization was performed by standard techniques using fluid filled catheters, Statham transducers, and a recorder (Electronics for Medicine VR12). Surface hepatic pulsations were

![Figure 1. Electrocardiogram shows ventricular paced rhythm at a rate of 72 beats per minute with retrograde P waves discernible in lead V1.](http://journal.publications.chestnet.org/pd/access.ashx?url=/data/journals/chest/21335/ on 06/27/2017)