Fever, Pulmonary Infiltrates, and Pleural Effusion following Acyclovir Therapy for Herpes Zoster Ophthalmicus*

Dorothy W. Puaeteri, M.D.; and Robert B. Muder, M.D.

A 71-year-old man presented with herpes zoster ophthalmicus and ocular involvement. Following the institution of intravenous therapy with acyclovir, the patient developed fever, hemoptysis, and a pleural friction rub. A ventilation-perfusion lung scan showed no defects; roentgenograms showed bilateral infiltrates and a left-sided pleural effusion. The fever abated promptly following discontinuation of acyclovir, and radiographic abnormalities resolved over ten days. No other anti-infective therapy was given. To our knowledge, the syndrome of fever, pulmonary infiltrates, and pleural effusion following use of acyclovir has not been previously reported.

(Chest 1990; 98:754-56)

Herpes zoster is a frequent clinical problem primarily affecting patients who are elderly or immunocompromised. Acyclovir, an inhibitor of viral replication, has been shown to be effective in the therapy of herpes zoster in immunocompromised patients.1 In immunocompetent patients, acyclovir appears to be beneficial in shortening the duration of acute symptoms of herpes zoster2 and in preventing the ocular complications of herpes zoster ophthalmicus.3

We report a previously undocumented syndrome of fever, pulmonary infiltrate, and pleural effusion associated with the administration of acyclovir for the treatment of herpes zoster ophthalmicus and scleral ulceration.

CASE REPORT

A 71-year-old white man presented to the emergency department with a history of a painful rash over the right side of his face for four days. He also complained of moderate pain in the right eye but denied any subjective change in his visual acuity. He also denied fever, cough, or chest pain. His history was significant for coronary artery disease requiring bypass grafting in 1982 and a subsequent hospitalization for congestive heart failure in 1984. At the time of presentation, the patient had been free of cardiac symptoms for over six months. Medications on admission included digoxin, furosemide, dilatiazem, and dipyridamole. There was no history of use of other drugs, and the patient had no history of allergies to drugs.

Initial physical examination showed the patient to be afebrile. The characteristic vesicular rash of herpes zoster was present in the distribution of the right ophthalmic nerve. The conjunctiva of the right eye was inflamed, and the sclera was ulcerated. The chest was clear to auscultation; cardiac examination showed a fourth heart sound and a short apical systolic murmur. Jugular venous distension and edema were absent. On admission, a roentgenogram of the chest showed a heart of normal size and no infiltrates or effusions. The serum level of creatinine on admission was 1.4 mg/dl. Therapy with 200 mg of acyclovir intravenously (4.1 mg/kg, based on weight of 61 kg) every eight hours was begun. Administration of N-acetylsulfanilamide (Sulfacetamide) sodium solution and a combination of dexamethasone (0.1 percent), neomycin sulfate (0.3 percent), and polymyxin B (10,000 units/g) was initiated topically to the right eye. Meperidine was administered for pain.

On the third day of hospitalization, the patient developed a temperature of 38.3°C (101°F). On the fourth day, he again had fever to 38.9°C (102°F), as well as hemoptysis. A left-sided pleural friction rub was present. Jugular venous distension, rales, a third heart sound, and edema were absent. A ventilation-perfusion scan showed no defects suggesting pulmonary embolism. An accompanying chest roentgenogram showed bilateral perihilar infiltrates and blunting of the left costophrenic angle (Fig 1A); there was no increase in the heart size. On repeat examination 48 hours later, a moderate left-sided pleural effusion was evident (Fig 1B). Bacterial cultures of secretions and washings obtained at bronchoscopy were positive only for rare α-hemolytic streptococci. Viral, Legionella, mycobacterial, and fungal cultures were negative, as were multiple cultures of blood. On the sixth day of hospitalization, the therapy...
with acyclovir was discontinued. No additional anti-infective agents were given, and all other medications, including the ophthalmic preparations, were continued. The fever abated promptly upon discontinuation of acyclovir (Fig 2). The patient's pulmonary infiltrates and effusion cleared radiographically over ten days. No ocular sequelae were present at the time of discharge.

**DISCUSSION**

In the five years since its release for clinical use, acyclovir has been used extensively; major adverse reactions are infrequent. Gastrointestinal distress and vesicular eruption at the site of injection have been reported. Elevation of the serum concentration of creatinine has been noted after rapid intravenous administration of acyclovir. This effect is largely avoidable by maintenance of adequate hydration and control of the rate of administration. Neurotoxicity attributed to acyclovir has been reported. Acyclovir-associated fever has been the subject of previous reports, both with and without neurologic symptoms. To our knowledge, this is the first report of pleuropulmonary involvement and fever associated with administration of acyclovir.

We believe that the clinical syndrome seen in our patient was the result of a previously unreported adverse effect of intravenous acyclovir for several reasons. Clinical improvement and defervescence occurred promptly following cessation of the acyclovir. It is unlikely that the patient's fever and infiltrates were secondary to disseminated varicella-zoster infection, as there was no spread of the cutaneous lesions beyond the initially affected dermatome. No other potentially causative agent was isolated from cultures of respiratory secretions or blood, and the patient recovered without additional anti-infective therapy.

The findings on the ventilation-perfusion lung scan make the diagnosis of pulmonary embolism highly unlikely. We do not believe that the pulmonary infiltrates and effusions were secondary to heart failure for several reasons. First, the physical findings of left-sided or right-sided failure were not detected at any time during the patient's course. Secondly, serial chest roentgenograms showed no increase in the heart's size. Thirdly, the radiographic abnormalities were clearly associated with fever, pleuritic pain, and a pleural rub, features not commonly associated with cardiogenic pulmonary edema. Finally, the entire clinical and radiographic picture resolved without any alteration in the patient's regimen of cardiac medications.

A number of other drugs that the patient was receiving could have caused fever and pulmonary infiltrates; for example, sulfonamide derivatives have been associated with pulmonary hypersensitivity reactions. Topically administered N-acetyl sulfanilamide may cause systemic immunologic reactions, although we are not aware of any reports of pulmonary toxicity attributed to this agent; however, our patient's clinical syndrome resolved despite the continuation of all other drugs except acyclovir.

Other nucleoside analogues have been associated with adverse pulmonary reactions. Administration of cytarabine (cytosine arabinoside) for treatment of leukemia may result in noncardiac pulmonary edema with no evidence of inflammatory response on histologic examination. The presumed mechanism is by a direct toxic effect leading to decreased membrane integrity. Another nucleoside analogue used experimentally in the treatment of leukemia, fludarabine monophosphate, has been associated with interstitial pneumonitis responsive to corticosteroid administration, suggesting an immunologically mediated mechanism. The findings in our case do not permit any conclusion regarding the possible mechanism of the acyclovir-associated pulmonary syndrome.

As acyclovir is frequently used for the treatment of herpes virus infections in immunocompromised patients, the occurrence of fever and pulmonary infiltrates as a consequence of its use may pose difficult diagnostic and therapeutic problems. Fever and pulmonary infiltrates in this group of patients may be due to a wide variety of infectious and noninfectious causes, including a number of therapeutic agents. Based on our experience, acyclovir should be considered as a potential cause of this syndrome.

**REFERENCES**

11. Payne FE, Giesecke TF. Multiple system reaction to trimetho-
Obligate Mouth Breathing during Exercise*

Nasal and Laryngeal Sarcoidosis

Capt. Gregory L. Becker, M.D.;
Col. Michael F. Tenholder, M.D., F.C.C.P.; and
Col. Keith K. Hunt, M.D., F.C.C.P.

A young black man presented with simultaneous nasal and laryngeal sarcoidosis, each uncommon entities. Despite severe upper airway obstruction and emergent tracheostomy, there was an uncharacteristic rapid response to oral steroids alone. The patient's predominant initial complaint of early mouth breathing during routine army physical training demonstrates a symptom complex and an alternate mechanism of dyspnea to consider in sarcoidosis.

(Chest 1990; 98:756-57)

\[ D = \text{diffusing capacity of carbon monoxide} \]

Upper airway involvement in sarcoidosis has been recognized since Boek described signs and symptoms of nasal pathology in four of his original nine cases in 1905. We present a case of simultaneous nasal and laryngeal sarcoidosis which illustrates two important points. First, tests of airway function can be sensitive in the identification and documentation of treatment's success or failure in upper respiratory tract involvement. Secondly, in addition to pulmonary parenchymal disease, dyspnea in sarcoidosis can be caused by alterations of upper airway structure and may force the patient to choose mouth breathing as an uncomfortable alternative to nasal breathing early in exercise.

CASE REPORT

A 28-year-old black man presented with the chief complaint of an uncomfortable sensation of early mouth breathing and associated dyspnea during army physical training. In addition to a 12-month history of mild hoarseness, loss of voice volume, and nasal congestion, he complained that his time for the 2-mile run had lengthened from 12 to 21 minutes. The findings from his physical examination on admission were remarkable for complete obstruction of the nares by a vascular redundant mucosa, inspiratory stridor, and bilateral adenopathy of the neck. An initial chest x-ray film revealed minimal paratracheal adenopathy but no parenchymal infiltrates. Spirometry showed a FVC of 3.16 L (72 percent of predicted), an FEV, of 1.85 L (50 percent of predicted), with a ratio of FVC/FEV, of 58 percent. The Dco was 26 ml/min/mm Hg (60 percent of predicted), airway resistance was 6.20 cm H2O/L/s (normal, 0.5 to 2.0 cm H2O/L/s), and the flow-volume loop was consistent with a fixed upper airway obstruction (Fig 1A). We performed oral bronchoscopy, since the nares were impassable. A markedly inflamed, nodular, and distorted laryngeal mucosa with a 3-mm glottic aperture was seen (Fig 2A). After urgent tracheostomy, nasal mucosal and lymph node biopsies demonstrated numerous noncaseating granulomata with negative fungal and acid-fast stains.

The patient was treated with 60 mg of prednisone daily and noted a return of unobstructed nasal airflow during exercise. The tracheostomy was reversed within two months, when pulmonary function tests revealed a FVC of 3.35 L (75 percent of predicted), a FEV, of 2.81 L (78 percent of predicted), a ratio of FVC/FEV, of 84 percent, a Dco of 92 percent of predicted, and a normal airway resistance of 1.60 cm H2O/L/s. The repeat flow-volume loop was markedly improved (Fig 1B). A bronchoscope (5.9-mm tip diameter) now easily passed through the nares and demonstrated markedly diminished inflammatory nodularity of the laryngeal mucosa and a nearly normal glottic area (Fig 2B).

DISCUSSION

Sarcoidosis can cause a severe granulomatous inflammation of the upper respiratory tract; however, other diseases can exhibit a similar clinical and pathologic picture and include noninfectious disease such as Wegener's granulomatosis (and the closely related lethal midline granuloma) and infectious causes such as tuberculosis, histoplasmosis, blastomycosis, syphilis, and leprosy. Given this patient's

*From the Pulmonary Disease and Critical Care Service, Department of Medicine, Walter Reed Army Medical Center, Washington, DC, and the Uniformed Services University of Health Sciences, Bethesda, Md. The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of Defense or the Department of the Army. Reprint Requests: Dr. Becker, Walter Reed Army Medical Center, Washington, DC 20307-5000

![Flow-volume loop at presentation, showing fixed upper airway obstruction. B (right). After two months of prednisone, flow-volume loop is improved and shows extrathoracic variable obstruction.](http://journal.publications.chestnet.org/pdfaxaccess.ashx?url=/data/journals/chest/21618/ on 06/25/2017)