Metastatic Tumor and Pseudomonas
Problems of Diagnosis and Management

Clinical Evaluations by Piero Serra, M.D., and
William L. Hoppes, M.D.

**Case Summary**

M. N. Shinwarie, M.D.*, and F. Manfredi, M.D.**

This 46-year-old white man was admitted on May 9, 1974, with a chief complaint of headache and diplopia of several weeks' duration.

**Past Medical History**

The patient is a nonsmoker with a history of chronic alcoholism for 20 years. The patient has had several previous admissions to the Veterans Administration Hospital (1972 and 1974) for treatment of alcoholism. On these occasions, the results of chest examination, including radiologic findings, were within normal limits.

**Physical Examination**

On admission (May 9, 1974), the patient had normal vital signs. Papilledema and bilateral paresis of the sixth cranial nerves were present. Findings from the chest examination were within normal limits.

**Laboratory Results**

Routine laboratory data were within normal limits. The chest x-ray film was unremarkable (Fig 1). The results of bilateral pulmonary tomographic studies, two bronchoscopic examinations, five sputum cytologic studies, an intravenous pyelogram, and a complete gastrointestinal series were unremarkable.

A brain scan showed multiple areas of increased radioisotopic uptake present bilaterally. These findings were compatible with metastatic carcinoma.

A carotid arteriogram showed several defects, including a deep mass in the posterior parietal occipital area (Fig 2).

An electroencephalogram was abnormal, showing mild generalized slowing, suggestive of a diffuse process; there was focal slowing in the right temporal region, indicative of a structural lesion in this area. The spinal fluid was clear, with a high opening pressure (manometric reading considered unreliable due to poor cooperation of the patient).

**Hospital Course**

With steroid and radiation therapy, a reasonably good response of the central nervous system (CNS) symptoms was observed.

*Pulmonary Fellow, Veterans Administration Hospital and Indiana University School of Medicine, Indianapolis; and Nangrahar Medical School, Jalalabad, Afghanistan.
**Chief, Nontuberculous Pulmonary Disease Section, Department of Medicine, Veterans Administration Hospital, Indianapolis, and Professor of Medicine, Indiana University School of Medicine, Indianapolis.
On July 23, the patient developed respiratory symptoms, with cough, fever, and left-sided pleuritic chest pain. Physical examination at that time revealed findings of consolidation over the left lower lobe. The progression of the x-ray films with the respective dates is shown in Figures 3 to 5. It should be noted that there was no history of any kind of chest trauma prior to or during the recent respiratory illness.

On the basis of the previously mentioned clinical and laboratory findings, the diagnosis of acute Pseudomonas pneumonia with bronchopleural fistula was made. Pseudomonas aeruginosa was cultured on several occasions from the left pleural space.

**QUESTIONS**

1. In respect to the acute respiratory illness:
   a. Would you agree with the diagnosis?
   b. What else would you consider in the differential diagnosis?
   c. Can you relate the chest disease to the original neurologic syndrome?

2. In reference to this patient's hospitalization in May 1974:
   a. Would you agree with the diagnosis of metastatic brain tumor and the way it was managed?
   b. Do you think this patient should have had further neurologic procedures, including craniotomy?
   c. Would you have done anything else to ascertain the primary site of the suspected malignant neoplasm?
Comments by
Piero Serra, M.D.†

Briefly, this 46-year-old man, a chronic alcoholic for 20 years, was admitted for neurologic symptoms, which were thought to be due to metastatic lesions on the basis of a brain scan, carotid arteriogram, and electroencephalographic findings. During the course of his hospitalization, the patient developed respiratory symptoms related to the changes illustrated in the series of x-ray films.

The diagnosis of pneumonia due to P aeruginosa with bronchopleural fistula cannot be questioned for several reasons: (1) P aeruginosa was cultured on several occasions from the left pleural space, in the absence of trauma and thoracocentesis; (2) pneumonia due to P aeruginosa has a great propensity to develop in hospitalized patients with debilitating disease, such as alcoholism or cancer; and (3) the presence of an air-fluid level in the pleural space indicates that the infection has gone across the pleura, a common complication of pulmonary infection with Pseudomonas.

The relationship between the chest disease and the neurologic syndrome is uncertain. One wonders about the pathogenesis of the infection. Was the proved Pseudomonas pneumonia the result of an aspiration pneumonia or secondary to the neurologic damage, or was the pneumonia facilitated by a cancer of the lung, whose neurologic syndrome is a secondary manifestation? The multiplicity of the infiltrates in many areas, particularly while the neurologic syndrome was improving, argues against the former hypothesis.

The presence of a cancer of the lung is more likely. Carcinoma is known to predispose to infection with Pseudomonas, and the fact that this patient had a history and findings compatible with metastatic disease must call our attention to a primary lung tumor. The appearance of the left hilum accords well with this suspicion.

In reference to this patient's hospitalization in May, I think that enough evidence was available to make the diagnosis of metastatic lesions and that the management, therefore, was appropriate. If one does not accept the diagnosis of multiple foci from the combined tests, ie, brain scan, carotid angiogram, and EEG, then one would be obliged to proceed to other diagnostic procedures, such as craniotomy. Under these latter circumstances, one would then be considering a primary curable tumor of the brain. Moreover, some physicians recommend surgery on isolated metastatic lesions of the brain.

Nevertheless, I don't think that we need to consider these possibilities, because my impression is that there were multiple lesions in the brain; secondly, in the case of metastatic disease, even when studies indicate the presence of an isolated brain lesion, at surgery we usually find multiple nodules.

I would not have recommended other diagnostic procedures to ascertain the primary site of the suspected malignant neoplasm. In the case of the respiratory tract, this would mean mediastinoscopic examination or thoracotomy, procedures with certainly high risk and almost certainly low yield in the presence of an unremarkable chest x-ray film and tomograms. Clearly, demonstrating the presence of a primary lung tumor in this patient would affect neither his management nor his clinical course.

If, from the limited information given, my reconstruction of this patient's clinical course is correct, this case report does have significant educational value, since it illustrates several points that are generally not fully appreciated.

Given an adult male patient who, in the absence of well-recognized factors (such as chronic pulmonary diseases, surgical trauma to the airways of the lungs, immunosuppressed state, etc.), develops an acute pulmonary infection complicated by a bronchopleural fistula, pneumonia due to Pseudomonas should be suspected. The other two organisms (or groups of organisms) that should be in the etiologic differential diagnosis are Staphylococcus and anaerobes. Pseudomonas aeruginosa was, in fact, cultured from the pleural space.

If one accepts this diagnosis, in patients like ours, with previous evidence of metastatic disease, a primary bronchogenic cancer should be highly suspected. Neither the inability to support this diagnosis radiologically (in the presence of such a massive infiltrate) nor the negative smoking history should divert one too far from this suspicion.

If, as I suspect, a primary bronchogenic cancer is the underlying pathologic mechanism for the acute disease in the left lower lobe, it is interesting that this tumor had manifested itself with metastases to the brain almost three months earlier. At that time, the chest x-ray film and other diagnostic procedures directed (I believe appropriately) at discovering a primary lung tumor, failed to yield positive results. The message from this consideration is that in the adult male population the presence of multiple metastases to the brain should make the physician highly suspicious of a bronchogenic cancer, since this is statistically the most common primary site. It is not terribly unusual for the routine laboratory studies (x-ray film, bronchoscopic examination, and cytologic studies) to fail to demonstrate its presence.

†III Clinica Medica, Universita di Roma; Policlinico Umberto I, Rome.

72 SERRA, HOPPES

CHEST, 71: 1, JANUARY, 1977
at the time the metastatic symptoms bring the patient to the physician's attention. On many occasions, the clinical and laboratory evidence of a primary lung tumor may lag behind the metastatic manifestations by as long as three to six months.

Comments by
William L. Hoppes, M.D.†

This 46-year-old man was admitted to the hospital following the insidious onset of neurologic symptoms. Although the primary tumor site was never determined, a diagnosis of carcinoma metastatic to the brain was made, and the patient was treated with steroids and radiation therapy. He subsequently developed a necrotizing pneumonia with an apparent bronchopleural fistula. I will address my initial comments to the questions regarding his first admission.

The insidious onset of CNS symptoms over a period of weeks puts brain tumor high on the list of diagnostic possibilities. Ten percent of patients with metastases to the brain may have CNS symptoms as either the first indication of neoplasm or concomitantly with symptoms referable to the site of the primary tumor. The brain scan showing multiple lesions makes a malignant neoplasm or an infection most likely, but it does not distinguish between the two. The lack of fever or acute symptoms would be in favor of the diagnosis of a malignant neoplasm (the white blood cell count is not mentioned, but we may probably assume that this was included in the "normal routine laboratory data"). The classic "tumor blush" on the arteriogram essentially confirms the diagnosis.

Neurosurgical procedures on metastatic tumors of the brain are limited almost exclusively to slow-growing solitary lesions in accessible areas, where surgical removal would not make the resultant prolongation of existence more miserable. This patient had multiple lesions, including at least one large deep lesion in an inaccessible area; therefore, surgery was not indicated.

The demonstration of the type of tumor would have been useful for predicting the response to therapy. The solid tumors most commonly metastasizing to the brain are bronchogenic and breast carcinomas and malignant melanoma. In this man, an undetected bronchogenic carcinoma would be the most likely diagnosis. The initial chest x-ray film (Fig 1) indeed shows an irregular mass with surrounding fibrotic strands in the right apex, which could be a granulomatous or neoplastic process. A fairly extensive series of studies was performed in an attempt to demonstrate the site of the primary tumor. The only additional test I might have suggested would have been a gallium scan. If a suspicious area had been demonstrated, for instance, in the thorax, a medias-

In the absence of the tissue type and in the presence of demonstrated CNS lesions, a trial of steroid and radiation therapy is certainly indicated, and such therapy was described as resulting in a reasonably good response.

I will now turn to a consideration of the acute respiratory illness. A probable pulmonary infection exists when a patient has fever, leukocytosis, and a new or progressive infiltrate or purulent secretions or both. We are told that the patient has a fever, and the chest x-ray films show a new infiltrate.

Most bacterial pneumonias begin with aspiration of bacteria from the pharynx. Patients with abnormalities of the swallowing mechanism or who suffer periods of disturbed consciousness due to any cause are at increased risk. This man's neurologic disorder and his history of alcoholism might make him especially prone to aspiration. If the primary tumor were bronchogenic in origin, the local mechanisms of pulmonary clearance might be impaired.

The serial roentgenograms are most compatible with a necrotizing pneumonia and demonstrate the most common complications of that disorder, empyema and a bronchopleural fistula. This clinical picture may be caused by Staphylococcus aureus, facultative gram-negative organisms including P. aeruginosa, Nocardia, or the opportunistic fungi, such as Candida or Aspergillus; however, the most frequent cause of necrotizing pneumonia and empyema are the normal anaerobic flora of the upper airway.

The question of whether P. aeruginosa is the causative organism cannot be answered by the limited information provided in the protocol. Gram-negative bacilli cultured in a hospital setting may be spurious contaminants, harmless commensal organisms, or pathogens, depending on circumstances associated with the specific patient and with the method of collection and processing of specimens for culture.

Determination of the etiologic agent in a specific case of bacterial pneumonia may be very difficult. In some studies the only acceptable criteria for diagnosis are positive cultures of blood, pleural fluid (if available), or secretions obtained by transtracheal or possibly transtracheal aspiration. We do not know the results of cultures of blood or sputum. We are told that "Pseudomonas aeruginosa was cultured on

†Department of Medicine, Indiana University School of Medicine, Indianapolis.
several occasions from the left pleural space.” If Pseudomonas organisms were cultured from an initial specimen from thoracentesis, which also revealed polys and gram-negative rods on Gram stain, this is valid information. However, if Pseudomonas organisms were isolated only from a chest tube which had been in place for several days, the Pseudomonas could be a contaminant. The demonstration of antipseudomonas antibodies in the patient’s serum would have been indicative of true infection, as opposed to colonization or contamination.

If Pseudomonas were the infecting organism, answer to three additional questions would permit a better understanding of why this patient became infected. (1) Was the patient hospitalized for the entire 10% weeks, or was he discharged following therapy and readmitted when his respiratory symptoms developed? (2) Had the patient received antibiotic therapy prior to the onset of the infection? (3) Was the patient still receiving steroid or radiation therapy or both; and if not, how long prior to the infection were they discontinued?

The question of whether or not the patient was in the hospital at the onset of his pneumonia is important for two reasons. First, if he were ill enough to require indwelling intravenous catheters for a prolonged period of time, a septic phlebitis could have lead to septic emboli to the lung with initiation of infection by the vascular route. Alternatively, if the infection followed aspiration of pharyngeal flora, the following statistics become of interest. Only 2 percent of nonhospitalized normal persons have gram-negative bacilli in their pharynx. In hospitalized patients who are not seriously ill, the rate of gram-negative pharyngeal colonization jumps to 30 to 40 percent. In hospitalized patients with serious or chronic illnesses, gram-negative bacilli become the prevalent oropharyngeal flora. Several sites of origin of these bacteria have been incriminated, including nebulizers and other parts of inhalation apparatus, nurses’ hands, food, water, sinks, flower vases, solutions, medication, and unsterile suctioning technique. That all patients do not become colonized from exogenous sources is suggested by the fact that approximately 20 percent of the patients ill enough to enter an intensive care unit will have gram-negative bacilli in their pharynx at the time of admission to the hospital. Therefore, patients not infrequently may become infected by their own indigenous flora. Broad-spectrum antibiotics tend to suppress a patient’s normal flora and enhance colonization by more unusual and antibiotic-resistant organisms, including Pseudomonas.

The final consideration in the question of why this patient should develop a pneumonia due to Pseudomonas is the status of his immune system. We have a patient with a metastatic malignant neoplasm who has been treated at least with steroid and radiation therapy, and the interval between therapy and the onset of his respiratory infection is not known. Patients with terminal cancer may develop deficiencies in their cell-mediated immunity and become anergic. Radiation may lead to depressed function of B-lymphocytes and T-lymphocytes. Therapy with steroids may result in multiple immunologic defects, including (1) inhibition of macrophagic function and possible impairment of antigenic processing, (2) occasional inhibition of B-lymphocytic or antibody responses, (3) inhibition of cellular (T-lymphocytic) immune response and the “helper” function of T-lymphocytes in the humoral response, and (4) suppression of the normal inflammatory response, including vascular reactions and exudation of plasma and polymorphonuclear leukocytes. Infections with Pseudomonas are more prone to occur in patients with depressed levels of γ-globulins or decreased levels of circulating neutrophiles. We know neither the white blood cell count and differential count nor the immunoglobulin level of this patient at the time of onset of his respiratory disease.

In summary, the question of whether Pseudo-

Figure 6. Posteroanterior chest x-ray film. Pathologic findings in left hemithorax have almost completely resolved. On right, there is new infiltrate in midlung field, as well as pleura effusion with pneumothorax and large air-fluid level.
monas is the cause of this patient's pneumonia cannot be answered in the absence of further information. Factors in this case which might lead to this complication are discussed.

**DEPARTMENT EDITOR'S COMMENT**

Several weeks later, the patient was hospitalized again for acute respiratory symptoms (Fig 6). Three samples of sputum and two samples of pleural fluid were then reported as diagnostic of a malignant neoplasm, morphologically most consistent with adenocarcinoma. Bronchoscopic examination, pleural biopsy, and percutaneous lung biopsy of the right lower lobe failed to provide more definitive evidence of neoplastic disease in the right side of the chest. Treatment was for relief of symptoms, directed primarily at controlling the accumulation of fluid in the right pleural space, ie, chest-tube drainage with instillation of mechlorethamine (nitrogen mustard). Shortly thereafter, the patient died. Autopsy was performed and revealed a fairly well-differentiated adenocarcinoma involving the lower lobe of the right lung. Metastases were found in the pleura, pericardium, peritoneum, mesentery, heart, pancreas, brain, and liver. There was residual evidence of an empyema in the left side of the chest.

---

**ANNOUNCEMENTS**

**Recent Advances in Cardiopulmonary Care — III**

The Sarasota Memorial Hospital will present the course, Recent Advances in Cardiopulmonary Care (III) at the Holiday Inn, Lido Beach, Sarasota, February 25-26. For information, contact the Sarasota Memorial Hospital, 1901 Arlington Street, Sarasota 33579.

**Acute Respiratory Failure — in Black and White**

The California Thoracic Society will present the annual course, Acute Respiratory Failure—in Black and White, March 2-4 at the Sir Francis Drake Hotel, San Francisco. For information, contact Mrs. Betty Rhodes, CTS Program Assistant, 424 Pendleton Way, Oakland 94621.