The Spectrum of Diffuse Pulmonary Infiltration in Malignant Disease

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The development of diffuse pulmonary infiltration in patients with known malignant disease represents a difficult diagnostic problem for the clinician. Although the lung biopsy is the only means to make a definite clinical diagnosis, it is our opinion that a correct clinical diagnosis can be made in a large majority of cases. The diffuse infiltrates may represent a manifestation of involvement of the lungs by the malignant disease, a complication of the management of the disease, or a superimposed infectious process. There are certain clinical and laboratory features which are characteristic of each of the three major categories. Attention to these features will usually imply specific diagnosis or will suggest appropriate diagnostic studies to differentiate between the various entities under consideration.

The development of diffuse pulmonary infiltration in patients with known malignant disease is not uncommon. Accurate diagnosis of the etiology of the diffuse infiltration is one of the most challenging problems that confronts the clinician. The diffuse infiltrates may be a manifestation of involvement of the lungs by the malignant disease, a complication of the management of the malignant disease, or a superimposed infectious process. The various entities which are included in each of these three major groups are outlined in Table 1. There are certain clinical and laboratory features which are characteristic of each of the three major categories in the differential diagnosis. Careful attention to these features will usually imply specific diagnosis or will suggest appropriate diagnostic studies to differentiate between the various entities under consideration. It is the purpose of this paper to review the various entities which may cause diffuse pulmonary infiltration in patients with malignant disease and to emphasize their salient clinical and roentgenologic features.

**Manifestations of Malignant Disease**

Diffuse malignant involvement of the lungs results in a characteristic syndrome. The major clinical feature is dyspnea. Although cough is frequently present, sputum production is uncommon. Cor pulmonale may be evident.

**Table I—Diffuse Pulmonary Infiltration in Malignant Disease**

<table>
<thead>
<tr>
<th>I. Manifestations of Malignancy</th>
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<tbody>
<tr>
<td>A. Primary</td>
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<tr>
<td>1. Alveolar cell carcinoma</td>
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<tr>
<td>2. Lymphoproliferative disorders</td>
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<tr>
<td>B. Metastatic</td>
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<tr>
<td>1. Lymphangitic carcinomatosis</td>
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<td>2. Miliary metastases</td>
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<td>3. Bronchiolo-alveolar metastases</td>
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**II. Complications of Management**

| A. Lipid embolization   |
| B. Radiation pneumonitis |
| C. Pulmonary hemorrhage |
| D. Leukoagglutinin reaction |
| E. Fluid overload      |
| F. Drug-induced pneumonitis |

**III. Superimposed Infections**

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monale and respiratory insufficiency are frequent sequelae. With the exception of the rare occurrence of diffuse infiltration of the lungs by leukemia or lymphoma, acute systemic symptoms suggestive of an infectious process are absent. In addition, the pulmonary infiltrates do not evolve as rapidly as those associated with an infectious process or with many of the complications of management. The malignant diseases which may cause diffuse pulmonary infiltrates are alveolar cell carcinoma, leukemia, lymphoma, and metastatic carcinoma.

Alveolar cell carcinoma of the lung has been demonstrated by electron microscopy to originate from the alveolar type 2 cell. Unlike the more commonly occurring bronchogenic carcinomas, there is no sex predominance or relationship to cigarette smoking. Although metastases outside the thorax are demonstrable in 15-20 percent of cases at autopsy, clinically apparent metastatic disease is uncommon. The clinical presentation of patients with alveolar cell carcinoma is quite varied. The disease may initially present as a well circumscribed peripheral pulmonary mass, a chronic unresolving pneumonia, or a diffuse parenchymal infiltration. In patients with the diffuse form of the disease, progressive dyspnea is the predominant symptom. While weight loss, anorexia, weakness and nonproductive cough are usually present, only a small percentage of patients will have production of large quantities of mucoid sputum. The chest roentgenogram in the diffuse form of alveolar cell carcinoma reveals the characteristic pattern of acinar filling (Fig 1). In those cases in which the disease initially present in a more localized fashion, progression to the diffuse stage may occur.

Diffuse infiltration of the lungs by lymphomas or leukemias is uncommon but occurs most frequently in Hodgkin’s disease. The chest roentgenogram may reveal multiple discrete nodules or diffuse fibronodular infiltration. A recent review of Hodgkin’s disease of the lungs suggested that diffuse pulmonary involvement is an accompaniment of progressive systemic disease and is associated with a very poor prognosis. In essentially all cases of pulmonary involvement in Hodgkin’s disease, hilar adenopathy is present on the chest roentgenogram at the time of diagnosis unless the patient has received prior mediastinal radiation. This observation can be very useful in differentiating infiltration of the lung by Hodgkin’s disease from other causes of pulmonary infiltration in patients with this disease. Although diffuse leukemic infiltration of the lungs may be observed in 25 percent of cases at autopsy, premortem radiographic changes are unusual. Radiographic evidence of pulmonary infiltration by leukemic cells occurs most commonly in patients with chronic lymphocytic leukemia (Fig 2). Clinical and laboratory evidence of active leukemia is usually present when pulmonary involvement becomes apparent. Significant pulmonary and systemic symptoms usually indicate an infectious process in these patients rather than a manifestation of a leukemic infiltration.

Diffuse metastatic involvement of the lungs is probably the most common cause of diffuse pulmonary infiltration caused by the malignant diseases. It is not necessary to consider diffuse metastases which take the form of multiple large discrete nodules since this roentgenographic pattern will not be confused with the diseases being considered in the differential diagnosis of diffuse infiltration. Nevertheless, there are three roentgenographic patterns of metastases to the lungs which do present as
Diffuse infiltration: lymphangitic carcinomatosis, diffuse miliary metastasis, and diffuse bronchioloalveolar metastasis. Lymphangitic carcinomatosis most commonly arises from adenocarcinoma of the breast, prostate, pancreas, lung and stomach. The chest roentgenogram reveals diffuse linear and nodular interstitial infiltrates (Fig 3). Hilar adenopathy, Kerley's lines, and pleural effusion may also be noted. The diagnosis of lymphangitic metastasis may occasionally be substantiated by demonstrating involvement of submucosal lymphatics of the bronchi by blind biopsy at the time of bronchoscopy. Miliary metastases and bronchioloalveolar metastases are also manifestations of metastatic adenocarcinomas. Miliary metastases are seen most frequently with tumors originating from the thyroid or kidneys, while alveolar metastases arise most frequently from tumors of the pancreas and breast. The specific diagnosis of thyroid metastases may occasionally be made by demonstrating diffuse uptake in the lungs after administration of radioiodine (Fig 4, 5). Roentgenographically, bronchioloalveolar metastases appear as diffuse acinar filling. Although specific diagnosis of diffuse metastases requires lung biopsy, in most cases it is unnecessary to progress to that point in the evaluation. In the absence of systemic symptoms suggesting a superimposed infection or a clinical history suggesting a complication of therapy, a correct clinical diagnosis may usually be made.

Complications of Management

There are a number of complications stemming from diagnostic tests and therapeutic modalities in patients with malignant disease which may result in diffuse pulmonary infiltration. It is mandatory to accurately diagnose these entities since they are reversible and if unrecognized, may result in significant morbidity and mortality. The clinical presentation of these complications may either occur acutely and be temporally related to the offending form of management or may occur in a more chronic manner. Likewise, the spectra of the roentgenographic pattern observed in this group of entities are quite

Figure 3. Lymphangitic carcinomatosis. Chest roentgenogram demonstrating mediastinal and hilar adenopathy and diffuse interstitial infiltrates.

Figure 4. Miliary thyroid metastasis. Chest roentgenogram demonstrating multiple small nodules.

Figure 5. Metastatic thyroid carcinoma. Radioactive iodine scan demonstrating diffuse uptake over the lungs.
diverse. The clinical and roentgenographic manifestations of these complications may be confused with a fulminating superimposed infectious process or with diffuse malignant involvement of the lungs. This differentiation can be made if one is aware of the potential complications which can occur in the management of malignant diseases.

Lipid embolization to the lungs occurring as a complication of lymphangiography is the only complication of a diagnostic technique which may result in diffuse pulmonary infiltration. It occurs as an acute syndrome, becoming manifested within hours following the procedure. Nonproductive cough, dyspnea, and fever may be present. The chest roentgenogram characteristically reveals a diffuse ground-glass appearance, and the syndrome resolves within days without therapy. In an extremely symptomatic patient, treatment with steroids will usually be of benefit.

Diffuse pulmonary infiltrates related to volume overload by fluids or blood occurs during or shortly after fluid administration. In an occasional patient, pulmonary symptomatology will not be pronounced, and evidence of infiltration will be detected only on the chest roentgenogram. Unless the clinical setting is appreciated, this may be confused with other forms of diffuse infiltration. Another complication of blood transfusion that may result in diffuse pulmonary infiltration is the immune mediated leukoagglutinin reaction. This syndrome also presents as an acute reaction during transfusion. Fever, chills, cough, and dyspnea are commonly present. Peripheral eosinophilia may be detected at the time of the reaction. This syndrome can be differentiated from volume overload by the absence of cardiomegaly and a normal venous pressure.

Spontaneous intrapulmonary hemorrhage may occur as a manifestation of drug-induced thrombocytopenia. Hemoptysis, bleeding from other sites, and demonstration of severe thrombocytopenia help to substantiate the diagnosis. Fever and cough may be present, and in the absence of hemoptysis this entity is easily confused with a primary pulmonary infectious process.

Three drugs used in the therapy of malignant disease have caused diffuse pulmonary disease. Busulfan was the first of these drugs to be implicated in the pathogenesis of diffuse interstitial pneumonitis and fibrosis. Progressive dyspnea, the clinical hallmark of this complication, is accompanied by the development of diffuse interstitial infiltrates on the chest roentgenogram. Patients who develop this complication have generally been receiving the drug for at least one year. Discontinuation of the drug and the use of steroids has been beneficial in several cases.

More recently, methotrexate has also been demonstrated to cause diffuse lung disease. In all but one of the reported cases, the patients had been receiving intermittent methotrexate therapy, and the syndrome appeared within the first six months of treatment. Most commonly, an acute syndrome characterized by cough, dyspnea, fever and chills has been observed. The chest roentgenogram during the acute reaction usually reveals bilateral confluent infiltrates. Eosinophilia has been observed in approximately 50 percent of the patients. The pneumonitis has been shown to respond dramatically to steroid therapy, with rapid resolution of the clinical syndrome and clearing of the chest roentgenogram. A chronic presentation manifested by dyspnea and diffuse interstitial infiltrates has also been observed. Bleomycin therapy has also been reported to cause diffuse interstitial pneumonitis. Experimental studies in dogs have demonstrated the ability of bleomycin to cause pathologic changes similar to those seen with busulfan.

Radiation therapy may result in an acute radiation pneumonitis or chronic interstitial fibrosis. The acute reaction may occur from two weeks to six months following completion of therapy and is characterized by fever, cough, and dyspnea. Although the roentgenographic changes are usually observed in the field of radiation, abnormalities may also be seen in other areas of the lung producing a diffuse pneumonitis, resulting in partial resolution of the infiltrative process. The chronic fibrotic stage usually evolves without an antecedent acute stage, and the patient presents with a nonproductive cough and progressive dyspnea. The chest roentgenogram demonstrates interstitial infiltrates and volume loss. If the fibrotic reaction becomes widespread or is superimposed on pre-existent lung disease, respiratory insufficiency may result.

Superimposed Infections

The most common pulmonary complication experienced by patients with malignant disease is infectious. There are three major characteristics of diffuse infectious pneumonias which are generally present and which assist in differentiating these processes from the noninfectious causes of diffuse pulmonary infiltration. The patients are usually receiving cytotoxic drug therapy. Systemic symptoms of fever, chills and prostration accompany the pulmonary symptoms, and the clinical course and roentgenographic abnormalities evolve in a rapid fashion. This combination of clinical and roentgenographic findings makes an infectious process of prime consideration, despite the fact that they may also occur with some of the acute complications of management or
diffuse lymphomatous or leukemic involvement of the lung. With few exceptions, it is not possible to make a specific etiologic diagnosis of diffuse infectious pneumonia without bacteriologic or histopathologic demonstration of the pathogen.

Bacterial infections of the lung rarely cause diffuse infiltration. In most cases bacterial pneumonia presents as confluent infiltrates, localized to one or several lobes or as multiple areas of patchy involvement characteristic of hematogenous spread. In either case, the roentgenographic pattern would not be confused with a diffuse pattern.

Viral infections may cause diffuse involvement of the lungs. With the exception of characteristic skin lesions, which may be observed in infections with viruses from the zoster group, there are no clinical or roentgenographic features which help to distinguish these diseases. Current laboratory techniques for identifying viruses are not clinically useful during the acute stage of illness. Fungal or tuberculous infection may also occur in these patients. In contrast to the other diffuse infectious pneumonias, the clinical course may not demonstrate rapid progression. In addition to the clinical differences, the chest roentgenogram may also be helpful in suggesting the etiology of the lung disease. The presence of true miliary infiltration is generally indicative of disseminated fungal or tuberculous infections. The clinical course may be quite variable, and chest roentgenograms may reveal nonspecific diffuse alveolar and interstitial infiltration. Since therapy is available for the granulomatous infections, it is important that vigorous attempts be made to isolate the organism. Histopathologic and bacteriologic examination of material obtained from skin lesions, liver or bone marrow biopsy, and bacteriologic examination of the sputum and urine are helpful in making the diagnosis of disseminated granulomatous infection. If these measures fail, serious consideration should be given to lung biopsy.

The clinical and roentgenographic features of Pneumocystis carinii infection have been adequately reviewed in the literature. It is important to consider this infection in all cases of diffuse infectious pneumonia, since it also represents a potentially curable disease. A great majority of these patients have a rapidly progressive clinical course with a diffuse acinar pattern evident on the chest roentgenogram. The patients are extremely dyspneic and have a nonproductive cough. Lung biopsy or bronchial brush biopsy is generally required to make an accurate diagnosis. If the patient's condition is too grave to permit diagnostic biopsy, therapy with pentamidine isethionate should be instituted empirically until a specific diagnosis is made.

**Comments**

The diagnosis of the etiology of diffuse pulmonary infiltration in patients with malignant disease is a most difficult clinical problem. Although lung biopsy is the only means available to make an absolute diagnosis in many of these conditions, it is our opinion that a correct clinical diagnosis can be made in the great majority of cases. Careful attention to the clinical features clearly separates those acute syndromes caused by superimposed infections and some of the management complications from the more subacute and chronic syndromes caused by diffuse malignant involvement of the lungs or interstitial pneumonitis induced by various forms of therapy.

The entities in the more chronic group are distinguishable on the basis of the history and the roentgenographic manifestations of the disease. Knowledge of the specific malignancy the patient has and review of the patient's therapy usually allows the diagnosis to be made by exclusion. If the patient has not received radiation or any of the drugs which have been implicated in the pathogenesis of interstitial pneumonitis, then the etiology of the diffuse infiltration is most likely involvement of the lungs by malignant disease. In addition, in many cases the roentgenographic manifestations of diffuse metastases to the lungs and primary alveolar cell carcinoma are quite characteristic and are unlikely to be confused with the diffuse changes observed with radiation fibrosis or drug-induced interstitial pneumonitis.

Identification of the specific pathogen responsible for diffuse pneumonia requires histopathologic or bacteriologic techniques. Because of the inherent delay in most techniques for accurately identifying a pathogen, empiric therapy frequently must be considered because of the gravity of the clinical situation. This is a most unsatisfactory approach in dealing with this situation because of the spectrum of drugs which must be used on an empiric basis to cover the potentially curable causes of diffuse infectious pneumonias. As a result, lung biopsy or bronchial brush biopsy for specific diagnosis should be performed on an emergent basis in order to direct specific therapy.

If a logical approach to the diagnosis of the etiology of diffuse infiltration in patients with malignant disease is undertaken by careful attention to the clinical and roentgenologic features of each case, a correct clinical diagnosis can be made in the majority of cases. Diagnostic biopsy can be reserved for the selected case in which an acute infectious pneumonia seems most probable.
REFERENCES

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