Pulmonary Tumor Microembolism

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Patients with cancer have a high risk of thromboembolism. Less frequently, embolism of tumor tissue itself can cause occlusion of the main pulmonary artery or its large segmental branches. The risk of pulmonary tumor microembolism in cancer patients is considered to be extremely low but may be poorly recognized. To appropriately diagnose pulmonary tumor microembolism and avoid aggressive treatment in terminally ill patients, it is essential to recognize the clinical features and available diagnostic modalities. This review focuses on the presentation, clinical features, and management of patients who may have pulmonary tumor microembolism.

The likelihood of pulmonary tumor microembolism depends on the underlying malignancy and its propensity to embolize. Even in patients with a known cancer, the correct diagnosis of tumor embolism is made in fewer than 6% of cases.[1] Two retrospective studies that reviewed autopsies over a several-year period reported the incidence to be 0.9%[2] and 2.4%.[3] Prospectively, Soares and colleagues[4] studied 222 consecutive autopsies of patients with carcinoma, excluding tumors of the lung and central nervous system, and found pure tumor emboli in 8.5% of cases. Reviews focusing on specific malignancies have reported an incidence rate of tumor embolism of 1.5% for non–small cell lung cancer[5] and 26% collectively for patients with choriocarcinoma and carcinomas of the breast, stomach, liver, or kidney.[6]

Pulmonary tumor microembolism is characterized by the occlusion of the small pulmonary arteries, arterioles, and alveolar septal capillaries by aggregates of tumor cells accompanied by platelet-fibrin thrombosis.[2] Pulmonary tumor embolism is a well-described cause of morbidity and mortality in patients with malignancy. However, failure to recognize this condition antemortem is unfortunately common, and many patients either have no diagnosis established or are misdiagnosed as having pulmonary embolism or metastasis to the lung.

As with all forms of metastatic disease, malignant cells usually reach the lung via the hematogenous route; most circulating malignant cells neither cause symptoms nor establish metastatic foci because they are destroyed by local defense mechanisms.[7] In a small number of cases, impaction of tumor cells in the pulmonary vascular bed, coupled with the local reaction to their presence, results in substantial obstruction of the pulmonary vascular bed that can be associated with significant dyspnea and may progress to respiratory failure.[2] Respiratory failure is a frequent complication of malignancy and is often noted near death. Common causes of respiratory failure in patients with cancer are shown in **Table 1**.

The diagnosis of pulmonary tumor microembolism is difficult to make even in known cases of malignancy, but it becomes more difficult if the patient has no known malignancy. Cancer patients presenting with respiratory symptoms and a clear chest radiograph often are mistakenly diagnosed with pulmonary thromboembolism. It is therefore important to recognize this condition in patients with cancer and unexplained dyspnea to avoid unnecessary work-up and treatment.

PATHOPHYSIOLOGY

Pathologically, tumor embolism is defined as the presence of isolated cells or clusters of tumor cells within the pulmonary arterial system, including the alveolar septal capillaries (**Figure**). The proximal segmental and tertiary arteries are infrequently involved. Four basic types of involvement of pulmonary vessels by tumor cells occur[2]: (1) large tumor emboli occluding either the

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Table 1. Common Causes of Respiratory Failure in Cancer Patients

Acute cor pulmonale
Acute respiratory distress syndrome
Infection
Lymphangitic spread
Metastatic tumor embolism
Pleural effusion
Primary or metastatic endobronchial tumor
Pulmonary vascular disease secondary to chemotherapy or radiation therapy
Restrictive lung disease secondary to chemotherapy or radiation therapy
Thromboembolism

main pulmonary arteries or the large segmental branches, (2) generalized lymphatic obstruction, (3) pure microscopic tumor emboli involving the small arteries or arterioles, and (4) combination of all of the above. In addition, Abbondanzo et al[8] described a diffuse septal capillary embolization by tumor microemboli as a fifth type of tumor embolization.

Because the neoplastic cells induce local coagulation, vascular occlusion often is attributable to obstruction by both thrombus and tumor cells,[2] and a continuum ranging from predominantly thrombosis to predominantly tumor cells has been observed. In addition to the obstructive effects of intravascular emboli within small muscular arteries, mural changes of pulmonary hypertension also may develop. These changes include medial hypertrophy of small arteries and arterioles, prominent intimal fibrosis, and disruption of the internal elastic lamina by fibrinoid necrosis with endarteritis. The intimal fibrosis induced by the tumor cells is irreversible and complete, in contrast to thromboembolic disease in which recanalization of the vessel usually occurs.[4]

Because of this irreversible occlusion of the vessels, cor pulmonale tends to develop earlier in tumor embolism than in thrombotic embolism. Acute cor pulmonale may result from large tumor emboli[2] and, rarely, from tumor cell microemboli.[9] Subacute cor pulmonale associated with tumor embolism may stem from several factors, including mechanical obstruction of pulmonary flow by intravascular tumor or associated thrombi, obstruction of pulmonary flow by obliterative endarteritis, and vasoconstriction associated with microemboli.[2] Owen and colleagues[10] noted myocardial hypertrophy of the right ventricle secondary to pulmonary hypertension in a high number of cases. They also observed dilatation of the right ventricle and right atrium with relatively normal-sized left ventricles. Soares et al[4] suggested that the most important event in the pathogenesis of subacute cor pulmonale is the arrest of circulating tumor cells injuring the endothelium layer, thereby producing pulmonary endarteritis.

Microvascular emboli are thought to be the source of lymphangitic carcinomatosis.[11] Pulmonary lymphangitic carcinomatosis refers to tumor growth in the bronchovascular, interlobular septal, and subpleural lymphatic vessels. Because the pulmonary vascular bed receives the entire cardiac output and clears any cell with a diameter of 10 μm or greater, most tumor cells are destroyed either by mechanical and shear forces of the microcirculation or by the immune system. Fewer then 1% of tumor cells that enter the circulation survive the passage through the lungs.[11] The route by which tumor cells reach the pulmonary lymphatic vessels is either by emboli traversing the pulmonary arterioles or capillaries or through the thoracic duct and hilar lymph nodes and thence by retrograde flow into the lungs.

Pulmonary microembolism can increase lung vascular permeability.[12] This process involves fibrin deposition and neutrophil sequestration. These activated neutrophils produce free oxygen radicals and proteases, leading to vascular endothelial injury.[13]

CLINICAL PRESENTATION

Progressive dyspnea (ranging from a few days to 6 months in duration) with tachycardia and tachypnea is the most common presentation of tumor embolism. Other symptoms include cough, pleuritic chest pain, and hemoptysis. Syncope, fatigue, weight loss, and sudden death also have been reported. Acute[14] and subacute cor pulmonale[15] both have been reported. Pulmonary tumor embolization after peritoneovenous shunting for the alleviation of malignant ascites also has been reported.[16] Although tumor embolization rarely is the initial presentation of underlying malignancy,[17] most patients with tumor embolism have well-established malignancies at the time the emboli become symptomatic. In many instances, metastases to other organs were documented prior to the onset of respiratory failure.[6] The risk of pulmonary tumor microembolism appears greatest for patients with mucin-secreting adenocarcinomas. Malignancies associated with tumor microembolism are shown in **Table 2**.

Clinical features commonly identified on physical examination are shown in **Table 3**. The most common presentation of pulmonary tumor microembolism consists of significant pulmonary hypertension and right

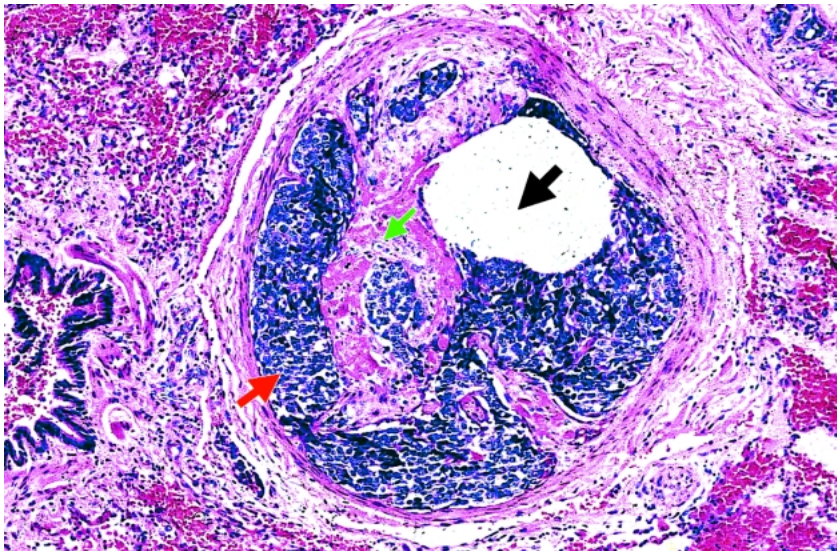

Figure. Microscopic section of the lung showing a partially occluded small pulmonary artery with fibrin (*green arrow*) intermixed with tumor cells (*red arrow*). The vessel lumen is narrowed (*black arrow*). These pathologic findings may explain the gradual development of subacute cor pulmonale in patients with tumor embolism and lymphangitic carcinomatosis.

ventricular overload with tachycardia and tachypnea. This classic presentation is reported in only 15% to 20% of cases, however.[23]

DIAGNOSTIC METHODS

Laboratory Evaluation and Initial Diagnostic Testing

Arterial blood gas analysis in patients with pulmonary tumor microembolism usually reveals hypoxemia and respiratory alkalosis. PaO_2 is usually less than 50 mm Hg. The alveolar-arterial oxygen gradient is increased in almost all cases. The electrocardiographic findings include sinus tachycardia, nonspecific ST-T segment abnormalities, and, rarely, an S_1Q_3 pattern. Right ventricular hypertrophy or overload also may be observed. The chest radiograph usually appears normal,[3] although radiographic findings may include a prominent pulmonary artery, right ventricular enlargement, focal atelectasis, pleural effusion, and bilateral infiltrates.[2,24,25] Rarely, features suggestive of miliary tuberculosis may be seen.[26] Doppler echocardiographic findings are nonspecific and may include dilated chambers on the right side and other evidence of pulmonary hypertension.[15] Mean pulmonary arterial pressures, as measured by Doppler echocardiography, are usually higher than 50 mm Hg, suggesting a subacute process with accommodation of the right ventricle to high pulmonary arterial pressures.

Lung Biopsy

Open lung biopsy or video-assisted thoracoscopic surgery remains the gold standard method for diagnosis of pulmonary tumor microembolism. Transbronchial biopsy is generally contraindicated in patients suspected of having severe pulmonary hypertension. Some patients may be too hypoxemic to undergo lung biopsy, and, in these circumstances, other modalities (eg, pulmonary wedge aspiration cytology) may be attempted to establish the diagnosis.

Table 2. Malignancies Associated with Tumor Embolism

Atrial myxoma[18]
Breast[1,6]
Choriocarcinoma[6]
Colon[19]
Gallbladder[20]
Gynecologic[1]
Hepatoma[6]
Lung[1]
Melanoma[1]
Mesothelioma[1]
Pancreas[19]
Parotid[1]
Peritoneovenous shunting for malignant ascites[16,21]
Prostate[1]
Renal[1,6,22]
Stomach[6]
Thyroid[6]
Urinary bladder[14]

Ventilation-Perfusion Radionuclide Scanning

Sostman et al[27] described breast cancer patients with tumor emboli and lymphangitic carcinomatosis who

Table 3. Common Clinical Signs in Pulmonary Tumor Microembolism

Accentuated pulmonic component of second heart sound
Ascites
Cyanosis
Fever (rare)
Hypotension
Increased respiratory rate
Jugular venous distension
Pedal edema
Pleural effusion, pleural rub, crackles, wheezes
Respiratory failure
Right-sided gallop

had normal results on ventilation scanning, but the perfusion scan revealed numerous small defects that outlined the pulmonary fissures and bronchopulmonary segments. This pattern was termed the segmental contour pattern. Although this pattern is strongly suggestive of tumor microembolism, it may be seen in various other conditions, including pulmonary vasculitis, primary pulmonary hypertension, fat or oil embolism, septic emboli, and intravenous drug abuse.[28] Rarely, a high-probability perfusion scan may be observed.[29]

Pulmonary Angiography and Computed Tomography Scanning

The role of pulmonary angiography is to exclude the alternative diagnosis of venous thromboembolic disease. In tumor microembolism, the sites of embolic involvement are confined to the capillary bed and small arterioles, which are beyond the resolution limits of conventional angiography. However, features that may occasionally be seen in patients with tumor emboli include delayed filling of segmental arteries, pruning and tortuosity of the third- to fifth-order vessels, and subsegmental filling defects measuring 1 to 2 mm in diameter.[30,31] Arterial occlusions 1 mm or less in diameter are difficult to visualize. A distinct thrombus usually is not seen.

Because pulmonary angiography carries a substantial risk, the availability of computed tomography (CT) angiography makes it easier to perform this study safely and effectively. Similar to pulmonary angiography, CT angiography may not be able to demonstrate occlusion secondary to tumor microembolism because the tumor emboli are below the resolution limit of the technique.[32] Findings of dilated and beaded peripheral pulmonary arteries on CT scan are highly suggestive of metastatic intravascular tumor emboli.[33] Beaded arteries should not be confused with the beaded septa seen in lymphangitic carcinomatosis, which are produced by thickening of the peribronchovascular interstitium and fissures. Although CT scan may prove valuable in the diagnosis of tumor embolism, further studies are needed to establish its efficacy.

Right Heart Catheterization and Pulmonary Wedge Aspiration Cytology

Right heart catheterization in patients with pulmonary tumor microembolism typically reveals high right ventricular systolic pressures of approximately 50 to 60 mm Hg, with mean pulmonary arterial pressures of approximately 50 to 100 mm Hg. Pulmonary capillary wedge pressures are usually normal.[25]

Most cases of lymphangitic carcinomatosis are thought to result from tumor microembolism with subsequent spread into the interstitial lymphatics and eventual parenchymal involvement.[7,11] Pulmonary microvascular cytology (PMVC) for the diagnosis of lymphangitic carcinomatosis and tumor embolism can be obtained by placing a pulmonary artery catheter in a wedge position and slowly aspirating blood from the pulmonary arterial port.[34] After the first 10 to 13 mL of blood are discarded, the next 5 to 10 mL are withdrawn into a heparin-treated tube for cytologic analysis. In the original report, results were positive for malignant cells in 7 of 8 patients with pulmonary tumor microembolism and were normal in 16 of 17 patients with cancer but without pulmonary metastasis.[34] Two false-positive results occurred, one in a patient with extensive pulmonary infarction and the other in a patient with extensive tumor in hepatic veins. The presence of malignant cells in PMVC preparations in patients with cancer and unexplained dyspnea constitutes presumptive evidence of lymphangitic carcinomatosis and tumor embolism. One of the advantages of this procedure is that it can be performed at the time of pulmonary angiography with no additional morbidity and with little added cost. Lukl[35] described 2 caveats in the interpretation of PMVC specimens. First, megakaryocytes obtained in a PMVC specimen can assume a variety of bizarre forms and can be misinterpreted as malignant cells, hence expert interpretation is needed to identify the cells correctly. Secondly, the significance of the presence of malignant cells in the circulation should be assessed with caution because mere presence of these cells may not indicate a significant tumor burden.

Tumor-Associated Monoclonal Antibody Imaging

Tumor embolism is one of the many clinical settings in which this experimental radionuclide imaging technique may be beneficial.[25] The radiolabeled antibodies are injected intravenously into patients with cancer. Radiolocalization of tumor masses at the primary site and local metastases is achieved by external scintigraphy 3 minutes to 18 hours after injection. The main advantages of this technique are that it is easy to perform and the results are available quickly; however, its utility has not been established in the setting of tumor microembolism.

MANAGEMENT

The majority of patients with pulmonary tumor microembolism have widespread metastatic disease by the time they present with pulmonary symptoms. Although their disease is rarely curable, selected patients may be capable of achieving a sustained remission with the use of appropriate chemotherapy. There have been no prospective trials of chemotherapy in patients with tumor microembolism because of the infrequency with which the diagnosis is made antemortem. The most important consideration in a patient suspected of having tumor embolism is how aggressively to pursue the diagnosis. The simple verification of the presence of tumor embolism may avoid unnecessary anticoagulation, thrombolytic therapy, interruption of the inferior vena cava, and unnecessary investigation, and occasionally points to the recurrence of the tumor.

Definitive Therapy

Tumor-directed therapy is the treatment of choice. Complete resection of the primary tumor may lead to resolution in a few cases. Surgical resection has been effective in treating large tumor emboli originating from renal cell carcinomas and atrial myxomas.[18,22] Successful emergent tumor embolectomy and inferior vena cava filter placement have been employed in unusual patients suffering from large, central emboli from infradiaphragmatic tumors.

The value of chemotherapy has been disputed. Successful improvement has been reported in chemotherapy-responsive tumors such as choriocarcinoma,[24] breast cancer, and prostate cancer. In addition to chemotherapy, hormonal therapy may play a definitive role in alleviating symptoms of tumor microembolism in patients with these malignancies.

Although treatment modalities can be used in attempts to control the underlying malignancy, a fatal outcome usually is not altered. As new chemotherapeutic agents are developed, an early diagnosis may become more important.

The benefit of using corticosteroids has not yet been demonstrated, although transient response to corticosteroids may be observed because most patients with tumor microembolism also have lymphangitic spread. Anticoagulation therapy has no documented role in the management of pulmonary tumor microembolism.

Palliative Therapy

As patients with pulmonary tumor microembolism are invariably hypoxemic, oxygen therapy usually is required. Other supportive therapies include administration of fluids and vasopressors and should be tailored to the clinical situation. Palliative measures such as the use of opiates and the control of pleural effusions also may be recommended.

CONCLUSION

Pulmonary tumor microembolism is a well known but uncommon sequela of a variety of common malignancies, notably breast, stomach, and lung. It should be considered whenever a patient with a known malignancy presents with unexplained progressive dyspnea or pulmonary hypertension. Patients also may present with signs and symptoms suggestive of pulmonary embolism. The chest radiograph is usually negative but may show an interstitial pattern with streaky micronodular mottling. Recognition of the clinical picture and the characteristic ventilation-perfusion scan pattern of contour mapping may lead to a rapid diagnosis. Rapid deterioration marked by progressive respiratory impairment is the usual course of the illness. Using PMVC may lead to earlier detection of malignant cells in pulmonary microvasculature.

Except in cases of chemosensitive tumors, the major utility of the antemortem diagnosis of pulmonary tumor embolism is sparing the patient aggressive and unnecessary interventions and preventing morbidity related to anticoagulation therapy or the placement of an inferior vena cava filter. Because the diagnosis often portends a short-term survival and because definitive therapy options are few, palliative measures such as the use of opiates and the control of pleural effusion are encouraged. Rarely, definitive treatment in the form of removal of the tumor and use of appropriate chemotherapy may result in increased long-term survival. **HP**

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