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Tumor Markers in Undiagnosed Pleural Effusions

Patients with pleural effusions are a common occurrence in the practice of pulmonologists. The annual incidence of pleural effusion in the United States is estimated to be 1.5 million, and approximately 200,000 are due to malignancy.[1] The etiology of an effusion can be established in the majority of cases with a careful history, a physical examination, and an evaluation of the pleural fluid obtained by thoracentesis including fluid cultures, cytology, and testing for tuberculosis, such as the measurement of adenosine deaminase levels.[2]

What approach should be taken if the pleural effusion remains undiagnosed following this initial evaluation? The article by Porcel and associates in this issue of *CHEST* (see page 1757) concludes by suggesting that the measurement of a panel of tumor markers is useful in guiding the selection of patients who might benefit from further invasive procedures. Although many previous articles have been published concerning the utility of tumor markers in the differential diagnosis of pleural effusions, this is the most comprehensive. This series included a total of 416 patients, including 166 with definite malignant effusions, 77 with probable malignant effusions, and 173 with benign effusions. When cutoff levels were selected such that none of the 173 benign effusions had levels above the cutoff value, at least one of the four tumor markers (*ie*, carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 15-3, or cytokeratin 19 fragments) was elevated in 54% of the patients.

Can an elevated tumor marker level (as defined in the article by Porcel et al) be used to establish the diagnosis of pleural malignancy? Certainly, an elevated tumor marker level defined in this manner is very suggestive that the effusion is due to malignancy. However, I am hesitant to use elevated levels of tumor markers to definitively establish the diagnosis of malignancy. The consequences of incorrectly making the diagnosis of pleural malignancy would be devastating. Such a diagnosis is essentially a sentence of death with a median life expectancy of about 90 days. In contrast to the use of tumor markers for making the diagnosis of malignant pleural effusions, it should be noted that I am a strong advocate of using pleural fluid levels of adenosine deaminase to make the diagnosis of tuberculous pleuritis.[3] The consequences of wrongly diagnosing pleural tuberculosis are far less severe than those of wrongly diagnosing a pleural malignancy. If the patient has a malignant pleural effusion, the effusion will not improve with therapy, and additional diagnostic procedures, such as thoracoscopy, can be performed. Since the presence of a pleural effusion with malignancy indicates inoperable disease, probably little is lost if the diagnosis is delayed. The treatment of a pleural effusion that has been misdiagnosed as pleural tuberculosis places the patient at risk of toxicity from unnecessary exposure to antituberculous medications.

I, therefore, agree with Porcel and coworkers that the presence of elevated levels of tumor markers in the pleural fluid can serve as an indicator for a more invasive procedure to establish the diagnosis of malignant pleural effusion but, in itself, should not

be used to establish the diagnosis. The key question is whether we need the tumor markers for this guidance. The first procedure I recommend for a patient with an undiagnosed pleural effusion after undergoing thoracentesis is a spiral CT scan. The spiral CT scan will demonstrate the presence or absence of pulmonary emboli. Additionally, it will demonstrate the presence of pleural, parenchymal, or mediastinal lesions, which should be approached invasively.

If the finding of the spiral CT scan is negative for pulmonary emboli, and for pleural, parenchymal, and mediastinal lesions, and if the patient is improving, I believe observation is the best course of action. Patients with malignancy rarely improve spontaneously. If the patient is not improving or is getting worse, attempts should be made to obtain a diagnosis. Since the panel of tumor markers, as outlined by Porcel and associates, will identify only 54% of the patients with tumor, a negative finding on a panel of tumor markers does not rule out malignancy. Therefore, an invasive procedure is indicated to determine the etiology of the pleural effusion.

The invasive procedure generally recommended in this situation is thoracoscopy. It should be emphasized, however, that the only two diagnoses established by thoracoscopy are pleural malignancy and pleural tuberculosis, both of which are established in $> 95\%$ of cases.[4–6] If the patient has pleural thickening, a CT-guided cutting needle biopsy is a reasonable alternative.[7] If thoracoscopy is not available, a needle biopsy of the pleura is recommended. Needle biopsy is not generally recommended in patients with a suspected malignant pleural effusion as findings are frequently negative in patients with pleural malignancy and negative cytology findings. In one series from the Mayo Clinic,[8] the pleural biopsy findings were positive in only 20 of 118 patients (17%) with pleural malignancy and negative cytology findings.

Some clinical characteristics may also be useful in identifying patients with pleural effusions that are likely to be malignant. Ferrer and associates[9] reviewed 93 patients who were referred for diagnostic thoracoscopy, of whom 54 were shown to have pleural malignancy. They found that the following four characteristics were predictive of malignancy: a symptomatic period of > 1 month; the absence of fever; the presence of serosanguineous pleural fluid; and chest CT scan findings suggestive of malignancy. All 30 patients who had all four criteria had malignancy, while all 20 patients with one or no criteria had a nonmalignant disease.[9] These results are somewhat better than those obtained with a panel of tumor markers.

In conclusion, the article by Porcel and coworkers in this issue of *CHEST* demonstrates that one can identify about 50% of patients with pleural malignancy with a panel of tumor markers. However, I do not recommend the routine use of such a panel since the clinical characteristics of the patients are at least as predictive as the panel of tumor markers.

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Use of Therapeutic Drug Monitoring in Tuberculosis Patients

In this issue of *CHEST* (see page 1770), Li and colleagues describe their experience using therapeutic drug monitoring (TDM) in the management of patients with multidrug-resistant (MDR) tuberculosis (TB). The authors are to be commended for quantifying their experience.

In clinical settings, and especially in outpatient clinic settings, there are a number of logistical difficulties related to TDM to overcome. In the