CHEST

A Woman in Her 30s With a History of Cervical Cancer Presents With Shortness of Breath and Pleuritic Chest Pain

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A woman in her 30s presented to the ED with a 3-month history of shortness of breath on exertion, dry cough, and pleuritic chest pain. A month ago, the patient was seen at an internal medicine clinic and was found to have a right pleural effusion. A thoracentesis revealed straw-colored fluid, a total nucleated cell count of 1,260 $\times$ 10^6/L, and a differential with neutrophils of 0.15, lymphocytes of 0.55, macrophages/monocytes of 0.19, and eosinophils of 0.10. Fluid cytology and culture were negative. The patient was presumed to have a parapneumonic effusion and treated empirically with antibiotics. However, she continued to have progressive symptoms, prompting her current visit to the ED. The patient was diagnosed with stage IIIB invasive cervical squamous cell carcinoma (SCC) approximately 7 months ago. MRI of the pelvis demonstrated a cervical mass with invasion of the right parametrial fat, but there was no evidence of uterine, vaginal, or lymph node involvement. A CT scan of the chest, abdomen, and pelvis was negative for distant metastases. The patient completed treatment with external beam radiation therapy and cisplatin chemotherapy 6 months ago. Three weeks prior to presentation to the ED, a repeat MRI pelvis showed no evidence of tumor progression and features consistent with posttreatment fibrotic changes.

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Physical Examination Findings

The patient had normal vital signs. There was no cervical lymphadenopathy. Cardiovascular examination revealed normal heart sounds, no murmurs, no jugular venous distention, and no peripheral edema. Respiratory examination revealed decreased breath sounds to the right mid and lower zones and no pleural friction rub.

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Diagnostic Studies

Initial laboratory investigations revealed a white blood cell count of 8.1 $\times$ 10^9/L, hemoglobin of 104 g/L, and platelet count of 608 $\times$ 10^9/L. Serum protein was 81 g/L (normal, 60-80 g/L), and serum lactate dehydrogenase was 195 units/L (normal, 140-280 units/L). A thoracentesis revealed markedly bloody fluid with glucose of 1.5 mmol/L, protein of 51 g/L, and lactate dehydrogenase of 2,212 units/L. The total nucleated cell count was 2,100 $\times$ 10^6/L, and the differential showed neutrophils of 0.10, lymphocytes of 0.60, macrophages/monocytes of 0.15, and eosinophils of 0.15. Fluid cytology, Gram stain, and culture were negative.

A chest radiograph is shown in Figure 1. Select images from the patient's CT pulmonary angiogram are shown in Figure 2.

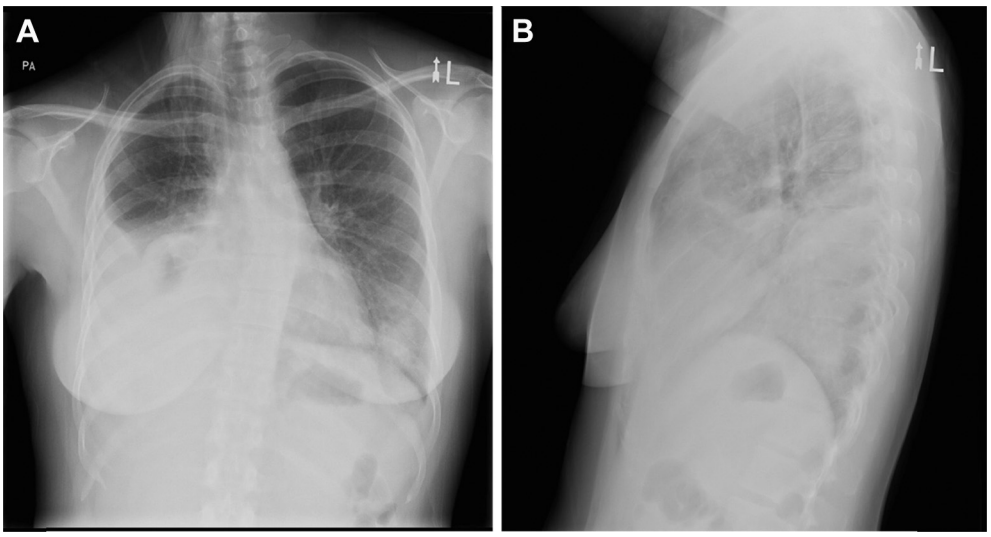

Figure 1 – *A, B, Chest radiograph with posterior-anterior (A) and lateral (B) views showing a large right pleural effusion with associated atelectasis.*

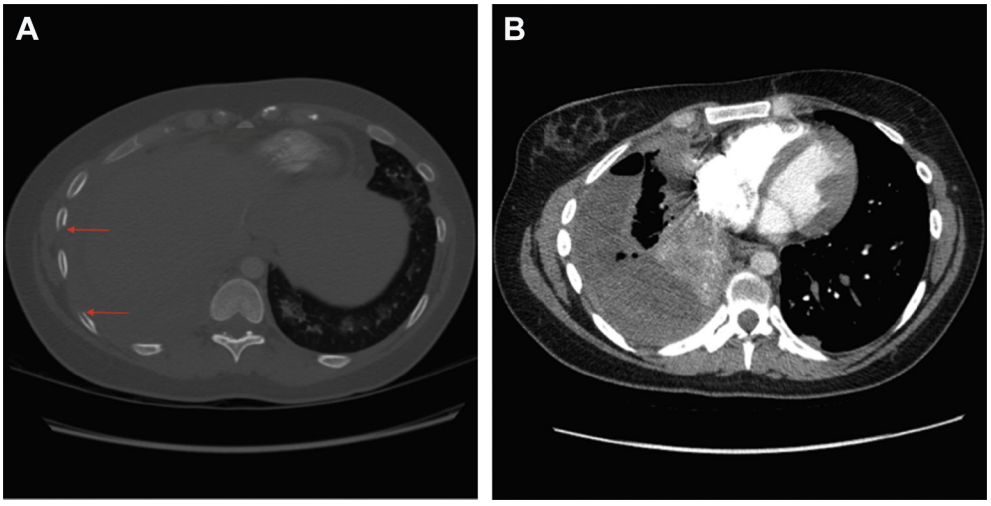

Figure 2 – *A, B, CT pulmonary angiogram was negative for pulmonary embolism. However, it demonstrates pleural thickening and nodularity with extension into the intercostal spaces (A) and associated osseous destruction (arrows in A). A large right-sided pleural effusion with significant atelectasis of the right middle and lower lobes is shown (B).*

What is the most probable diagnosis?

Diagnosis: Poorly differentiated invasive cervical SCC metastatic to the ribs and pleura.

Discussion

Although the incidence of cervical cancer has decreased in developed countries because of extensive screening programs with the Papanicolaou test, cervical cancer remains the third most common gynecologic malignancy to cause death in the United States. Despite recent advances in treatment, approximately 30% of women with invasive cervical cancer die because of recurrent or persistent disease.

Cervical cancer recurrence is defined as regrowth of local tumor or evidence of distant metastases discovered $\geq$ 6 months after treatment and regression of the primary lesion. Although pelvic recurrence is typical of cervical cancer, atypical manifestations such as thoracic metastases have been reported. Pulmonary nodules and mediastinal or hilar lymphadenopathy are the most frequent thoracic manifestations of cervical SCC metastases. The overall rate of thoracic metastases for cervical SCC ranges from 4% to 10%. Of those with thoracic metastases, osseous rib and pleural involvement are uncommon, with rates of 6% and 8% to 27%, respectively.

Clinical manifestations that should increase the suspicion for a malignant pleural effusion (MPE) include hemoptysis, cachexia, lymphadenopathy, and a prior history of malignancy. CT scan is often helpful in identifying radiographic features suggestive of malignancy. These features include pleural lesions such as thickening or nodules, unilateral hilar adenopathy, or a pulmonary mass. Nodular or irregular pleural enhancement along with a pleural thickness $>$ 1 cm have been reported to have a sensitivity $>$ 80%, with high specificity in the diagnosis of suspected malignancy.

When MPE is suspected, a diagnostic thoracentesis should be performed. Over 95% of MPEs are exudative, and approximately one-half are hemorrhagic. Hemorrhagic effusions are macroscopically bloody in appearance and require the presence of at least 5,000 to 10,000 RBCs per cubic millimeter.

Pleural fluid cytology using standard cytomorphologic analysis is the simplest means of detecting pleural malignancy. However, it has a sensitivity of 40% to 87% and therefore cannot be used to rule out malignancy. Several ancillary cytologic studies have been proposed. Cytogenetic analysis by fluorescence in situ hybridization allows the detection of chromosomal abnormalities, with a reported sensitivity of 60% in detecting MPEs. Compounded with standard cytology, sensitivity for detection of malignancy was increased by almost 20%. Flow cytometry has been used to identify cells with abnormal DNA content (DNA aneuploidy), a characteristic exhibited more commonly, but not exclusively, in malignant cells. Measuring levels of certain tumor markers, such as carcinoembryonic antigen, cancer antigen 15-3, and carbohydrate antigen 19-9, may have a role in detecting malignancy. Using individual tumor markers yielded a high specificity of 83% to 98%, but a low sensitivity of 21% to 58%. High levels of a combination of tumor markers increased the sensitivity to 56% to 90%. Although not definitively diagnostic, ancillary studies may have a role as an adjunct to standard cytology in identifying patients with a higher likelihood of underlying malignancy who warrant further testing.

CT-guided percutaneous pleural biopsy is a reasonable next step (sensitivity of 87%, specificity of 100%) when pleural cytology is negative for malignancy, but clinical suspicion for MPE remains high. Although more invasive than CT-guided percutaneous pleural biopsy, medical thoracoscopy has a sensitivity of 95% for detecting malignancy in undiagnosed pleural effusions. This procedure enables biopsy of the pleura, diaphragm, lung, and mediastinum and also has a therapeutic role through facilitation of talc pleurodesis. In the few cases where medical thoracoscopy is inconclusive despite high clinical suspicion for malignancy, video-assisted thoracic surgery or exploratory thoracotomy may be indicated. Bronchoscopy is not routinely recommended in the diagnosis of MPE because of low diagnostic yield, but it may be useful diagnostically when an endobronchial lesion is suspected.

Clinical Course

The patient in our study initially refused a CT-guided percutaneous biopsy of the pleura, given severe pleuritic chest pain with thoracentesis. As a result, bronchoscopy was performed first. Although chest pain is an atypical presentation in MPEs, malignant involvement of parietal pleura and rib may have caused the patient's pleuritic chest pain. Bronchoscopy revealed two nonobstructing nodular densities extending into the right lower lobe bronchus. Brush and bronchial wash samples were negative for malignancy, and the endobronchial biopsy

was nondiagnostic. The patient then consented to a CT-guided percutaneous biopsy of the right ninth rib and associated region of pleural thickening. This yielded an invasive, poorly differentiated carcinoma consistent with SCC and immunohistochemistry compatible with a cervical origin.

The patient in our study developed evidence of pleural metastases with extension into the ribs seemingly without radiographic evidence of nodal metastases or local tumor progression. This may have been caused by micrometastatic disease in the pleura, initially undetectable radiographically, but in time progressing to clinically evident disease despite treatment.

After discharge, the patient completed one cycle of salvage chemotherapy before returning to hospital with hypoxic respiratory failure requiring intubation. Her family elected to withdraw life support, and the patient passed away the next day.

Clinical Pearls

1. *Approximately 4% to 10% of invasive cervical SCCs can metastasize to the thoracic cavity, even in the absence of regional radiographic recurrence or progression. Metastases to the thoracic cavity can manifest as pulmonary nodules, mediastinal or hilar lymphadenopathy, MPEs, or osseous rib lesions.*
2. *Ancillary cytologic studies such as chromosomal analysis and identifying tumor markers may improve the diagnostic sensitivity of standard pleural fluid cytology; however, further large-scale studies are required before routine clinical use. Their current role may be adjunctive to clinical and radiographic suspicion for underlying malignancy, identifying patients who should proceed to more invasive testing.*
3. *CT-guided percutaneous pleural biopsy is an efficient and sensitive procedure for the diagnosis of underlying malignancy in suspected MPE, and negative pleural fluid cytology.*

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Suggested Readings

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