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Pleural endometriosis

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CASE PRESENTATION

DR. BOWMAN: A 24-year-old black woman, who had never been pregnant, was in her usual state of good health until 4 months before hospital admission when she was diagnosed with "pneumonia" and treated with azithromycin. Her symptoms completely resolved.

About 3 weeks before hospital admission, she developed dyspnea and mild pleuritic chest pain on the right side. Dyspnea was neither exertional nor positional, and she denied cough, hemoptysis, fever, and chills.

She was admitted to the Baylor Medical Center at Irving where a chest radiograph showed a completely opacified right hemithorax. A chest tube was immediately placed in the right pleural space and 4 liters of grossly bloody fluid evacuated; lactate dehydrogenase (LDH) was 981 U/L and protein was 4.9 g/dL, findings consistent with bloody exudate. The right lung failed to expand completely despite replacement of the chest tube.

Chest computed tomography (CT) showed a persistent right pleural effusion, a small pneumothorax on the right side, normal bilateral lung parenchyma, and ascites. Abdominal ultrasonography demonstrated a 3.7-cm simple left ovarian cyst and ascites. Abdominal CT demonstrated a moderate amount of ascites and several cystlike structures in the pelvis. Laparoscopy was initiated and converted to a full laparotomy. In addition to the ascites and simple left ovarian cyst, diffuse omental and small-bowel implants were noted. These masses were biopsied. Another right chest tube, the third, was placed in the operating room. The right lung again failed to expand completely. The patient was then transferred to Baylor University Medical Center (BUMC).

When the patient was 16 years old, a simple right ovarian cyst was removed laparoscopically. A recent Pap smear had been normal. She never had dyspareunia, unusual menstrual pain, or a sexually transmitted disease. She never had diabetes mellitus, systemic hypertension, heart disease, or cancer. Several family members, however, had diabetes mellitus and hypertension. There was no family history of sickle-cell disease or cancer.

She did not smoke cigarettes, drink alcohol, or use illicit drugs. She was employed as a corrections officer.

Her weight had been stable. There was no change in her energy level, and she had no fever. Review of systems disclosed no positive or abnormal findings. She had no known allergies. She was not taking any prescription or over-the-counter drugs. She used barrier contraceptives.

On examination, her blood pressure was 115/65 mm Hg; heart rate, 83 beats per minute; respiratory rate, 21 breaths per minute; and temperature, 36.8?C (98.2?F). She was alert and oriented and in no distress. Examination of her eyes, ears, mouth, pharynx, teeth, and neck disclosed no abnormalities. The breath sounds over the entire right side of the chest were decreased, and the right hemithorax was dull to percussion. The left side of the chest was normal. Precordial examination disclosed no abnormalities. The abdomen was soft and nontender. Surgical staples were in place in the lower midabdomen. No organs were enlarged. Neurologic examination disclosed no abnormalities. Her legs and arms and their arterial pulses were normal.

The laboratory data were sodium, 140 mEq/L; potassium, 4.1 mEq/L; chloride, 103 mEq/L; CO_2, 30 mEq/L; blood urea nitrogen, 8 mg/dL; creatinine, 0.8 mg/dL; and glucose, 84 mg/dL. The white blood cell count (WBC) was 7.8 x 10^3/?L; hemoglobin, 11.2 g/dL; hematocrit, 34%; and platelets, 592 x 10^3/?L. The blood smear differential showed 10% lymphocytes, 5% monocytes, 82% segmented neutrophils, and 3% eosinophils. Prothrombin time was 12 seconds, and partial thromboplastin time was 22 seconds. Alpha-fetoprotein was 0.7 ng/mL. The patient also tested negative for human immunodeficiency virus.

CT scan of the chest showed the right hemithorax almost completely filled with fluid and the right lung almost completely collapsed. There was a small pneumothorax on the right side. A chest tube was in place. Free fluid was seen in the upper abdomen.

At BUMC, a right thoracotomy was done: 500 mL of serosanguineous fluid was removed, and multiple adhesions between the right lung and pleura were divided by electrocautery. Three brownish-green masses (0.6 X 0.2 X 0.2 cm, 3 X 1 X 0.5 cm, and 1.5 X 0.6 X 0.2 cm) were noted in the pleural space, and all were resected.

CASE DISCUSSION

DR. ROSENBLATT: The important findings in this case relate to the differential diagnosis of a bloody pleural effusion in a young woman. Bloody effusions most commonly are associated with trauma to the chest, pulmonary emboli, malignancy, clotting abnormalities, ruptured aortic aneurysms, or ovarian pathology.

The classical definition of a hemothorax is a hematocrit >50% of the peripheral blood hematocrit (1). However, a bloody effusion is only a descriptive term, and small amounts of blood in the pleural space can cause the effusion to appear bloody. This patient was described initially as having a bloody effusion, as 4 liters of fluid were removed, yet her admitting hemoglobin was 12 mg/dl. Thus, a true hemothorax is unlikely, as the hemoglobin should have been much lower with this amount of “blood” in the pleural space. The fluid may have been bloody, but it was unlikely secondary to true blood loss. This is

further confirmed by the description of serosanguineous-appearing fluid draining from the chest tubes later in her course.

The right lung, despite drainage of the fluid, failed to expand completely. This failure to expand suggests that the lung was trapped or that a pleural leak was present. Should the latter have occurred, the chest tube should have continuous bubbling. The “trapped lung,” or incomplete expansion of the lung with nonbubbling drainage of the pleural space, suggests that the effusion is related to a chronic process.

Her history was significant for the lack of fever, cough, hemoptysis, or weight loss, all characteristic findings of chronic granulomatous diseases or neoplastic processes. The findings, at the laparotomy, of ascites, diffuse omental and small-bowel implants, and a left ovarian cyst were compatible with ovarian pathology but unlikely to be ovarian cancer because more aggressive surgical therapy was not performed. The brownish-green masses resected from the pleural space at the time of her thoracotomy were similar in description to the peritoneal findings and, in all likelihood, also were related to nonneoplastic ovarian disease.

A diagnosis of “pneumonia” was made 4 months prior to her hospital admission. The clinical manifestations relating to that diagnosis are not available but are probably not related to the pleural space abnormalities seen at this admission. A *bacterial process* as a cause of her pneumonia certainly would not explain a bloody effusion 3 to 4 months after an apparent clinical recovery. The infiltrates of *sarcoidosis* can spontaneously resolve, but the pleural effusions that are noted in this process are usually small (2). *Tuberculosis*, which will be discussed later, rarely causes bloody effusions in the presence of normal lung parenchyma, especially with no other systemic symptoms. Radiographically, *malignancy* can be mistaken for pneumonia, but usually the clinical manifestations are not similar.

Thus, the clinical information given and the implants found in the pleural space at the time of surgery would suggest the possibilities of malignancy, endometriosis, or granulomatosis.

Prior to discussing these diagnoses, let us review the mechanism of pleural fluid formation and the diagnostic tests used to evaluate pleural effusions.

The pleural space is a dynamic space with movement of fluid. This movement is based on Starling's Law, which relates the fluid's movement to the hydrostatic and oncotic forces in the capillaries and pleural space (*Figure 1*). The hydrostatic pressure in the parietal pleural capillaries is approximately 30 cm H_2O in contrast to 24 cm in the visceral pleural capillaries. The pleural pressure is usually approximately –5 cm.

The oncotic forces counterbalance these hydrostatic forces. Assuming a normal albumin, the oncotic pressure in both the visceral and parietal capillaries is approximately 34 cm. The pleural space has an oncotic pressure of –5 cm. Thus, normal pleural space dynamics reflect a pressure gradient of 6 cm from the parietal pleura to the pleural space (3).

Pleural effusions are seen only in disease states. Fluid accumulation in the pleural space is

prevented by the presence of lymphatic vessels in the parietal pleura which communicate with the pleural space. Since there are no lymphatics in the visceral pleura, the fluid in the pleural space is absorbed by these parietal lymphatics which prevent pleural fluid accumulation in the normal individual. The mean lymphatic flow in this situation is 0.2 to 0.4 cc/kg/h (4). Fluid accumulates in the pleural space only when the lymphatics are affected, the hydrostatic forces change, or the oncotic forces decrease.

Classifying the pleural fluid into exudates and transudates allows for a simplification of the diagnostic possibilities. Unfortunately, there is no “gold standard.” The criteria published by Light et al in 1972 have been commonly used to distinguish exudates from transudates and include any one of the following: a pleural fluid protein to serum protein ratio >0.5, a pleural fluid LDH to serum LDH ratio >0.6, or a pleural fluid LDH more than two thirds of the upper normal serum LDH (5).

More recently, Heffner et al reexamined these criteria in a desire to eliminate the necessity to obtain concomitant serum values and to simplify the diagnosis. Their criteria for an exudate were any one of the following: pleural fluid protein >2.9 g/dL, pleural fluid cholesterol >45 mg/dL, or pleural fluid LDH >45% of the upper normal serum level. The criteria of Light and Heffner have similar sensitivities and specificities (*Table*) (6).

Table. Diagnostic criteria for an exudate

Light et al (5):	
	Pleural fluid protein to serum protein ratio >0.5
	Pleural fluid LDH to serum LDH ratio >0.6
	Pleural fluid LDH > / of upper normal serum LDH
Heffner et al (6):	
	Pleural fluid protein >2.9 g/dL
	Pleural fluid cholesterol >45 mg/dL
	Pleural fluid LDH >45% of upper normal serum LDH

Several pathologic conditions are associated with characteristic protein findings in the pleural space. Although congestive heart failure usually is associated with transudative effusions, the protein level in the fluid will be falsely elevated after acute diuresis. A very high pleural fluid protein (range, 7–8 g/dL) suggests conditions such as Waldenstr?m's macroglobulinemia or multiple myeloma (7, 8). Patients with *Pneumocystis carinii* pneumonia may have small effusions. The pleural fluid to serum protein ratio is characteristically <0.5 in these individuals, but the pleural fluid to serum ratio of LDH exceeds 1.0 (9). Very high values of LDH (>1000 U/L) are suggestive of empyema, rheumatoid arthritis, or malignancy (10).

Low glucoses in the pleural fluid (<60 mg/dL) are nonspecific but suggest an infected pleural space, rheumatoid arthritis, or malignancy (11).

Pleural fluid pH measurements have prognostic, diagnostic, and management implications. The pH of normal pleural fluid is approximately 7.6. A low pH (<7.3) is associated with the same diagnoses as seen in effusions associated with low glucoses (12). Patients with a low pleural fluid pH and a malignancy have a poor response to chemical pleurodesis in an attempt to prevent further accumulation of pleural fluid. The low pH in a parapneumonic

effusion indicates a complicated effusion that will require drainage of the pleural space (12).

The cell count in the pleural fluid is never diagnostic in itself but may be helpful in suggesting certain diagnoses. A high WBC (>50,000/mm^3) suggests a parapneumonic process. Lupus pleuritis, acute pancreatitis, and bacterial pneumonia typically have WBC >10,000/mm^3, whereas chronic exudates caused by tuberculosis or malignancy have WBC <5000/mm^3 (13). Eosinophils in the pleural space generally result from a pneumothorax or from air introduced into the pleural space at the time of a thoracentesis (14).

Tuberculosis should always be considered in patients who present with a chronic effusion. A tuberculous empyema is rare and represents the failure of a primary tuberculous effusion to resolve. The fluid is purulent and contains many tuberculous organisms. In contrast, a tuberculous effusion is thought to be the sequelae of a hypersensitivity reaction to tuberculous antigens, which probably enter the pleural space after a rupture of a subpleural focus (15).

Patients with tuberculous effusions typically present with an acute febrile illness with a nonproductive cough (94%) and pleuritic chest pain (78%) (16). The purified protein derivative tuberculin test is usually positive but not uniformly so, as older studies suggested. False-negative skin test results initially occur in 7% to 31% of patients but will be positive 2 months later with repeat testing (16).

The tuberculous pleural fluid is usually straw-colored, exudative (high protein level of >5.0 g/dL in 50%–70%), and lymphocyte predominant with cell counts of 1000/mm^3 to 6000/mm^3. Neutrophils, however, can be seen in acute effusions, as has been demonstrated in experimental animals. Having more than 5% mesothelial cells is rare, and more than 10% eosinophils usually excludes the diagnosis of tuberculosis unless a prior thoracentesis has been performed (1).

Radiographically, tuberculous effusions are unilateral in 95% of the cases. Chest x-rays do reveal parenchymal disease as well as the pleural effusion in 50% of the proven cases; and, as expected, CT scans are more sensitive in revealing parenchymal disease, approximately 80% of the time (17).

Diagnostically, older studies suggest that sputum cultures are positive for *Mycobacterium tuberculosis* in 20% to 25% of patients with a tuberculous effusion. However, in a more recent study of 70 patients with tuberculous effusions, 31 of 35 patients with parenchymal disease and a pleural effusion on a chest x-ray had a positive sputum culture in contrast to only 4 of 35 patients without parenchymal changes on a chest x-ray or CT scan (18). Pleural fluid cultures are positive approximately 40% of the time (19).

The pleural biopsy is a useful adjunct in the diagnosis of tuberculous effusions. Pleural biopsy cultures are positive in 64% of cases, granulomas are seen in 70% of cases (providing at least 4 biopsies are done), and the combination of both pleural biopsy culture and granulomas is positive in 90% of cases (19).

Tuberculous effusions should resolve 2 months after treatment. Thus, in this young woman, the bloody effusion without fever and cough makes the likelihood of tuberculosis as the etiology of the effusions and implants very unlikely.

As discussed earlier, *malignancy* is a common cause of bloody effusions. Lung cancer is the most common cause (36%), and breast cancer is the second most common cause (25%). Ovarian cancer accounts for 5% of malignant effusions (20). This patient probably did not have ovarian cancer because of the type of treatment she received.

Pleural effusions can also occur in the presence of other ovarian pathology. Meigs' syndrome refers to ovarian fibromas, teratomas, or granulosa cell tumors that are associated with pleural effusions. Pseudo-Meigs is associated with benign ovarian cysts, uterine leiomyomas, or teratomas. In an early report of 130 pleural effusions in patients with ovarian masses, 10 were described as hemorrhagic (21). The peritoneal and serum calcium 125 (^{125}Ca) may be elevated in these nonmalignant conditions (22) and are thought to arise from the mesothelial expression of the antigen rather than from the fibroma itself. Although our patient had an ovarian cyst removed at age 16 and elevated ^{125}Ca, the multiple implants described at the time of her thoracotomy and laparotomy make Meigs' syndrome a less tenable diagnosis.

The most likely explanation for the findings in our patient is *endometriosis*, which is ectopic endometrial glands and stroma located outside the uterus. It is quite frequent, occurring in 3% to 10% of the female population and in 25% to 35% of infertile women. The ^{125}Ca assay is increased in these patients and correlates with the degree of disease and the response to treatment. Metastases, which appear on the pleural surface as well as in the lung, may be secondary to vascular or lymphatic transport of fragments. The effusions and pleural implants may, in turn, be secondary to fluid movement through the normal fenestrations in the diaphragm. A review of pleural and parenchymal pulmonary endometriosis in 1981 reported on 65 published cases. Fifty-four patients had pleural involvement, and 11 patients had parenchymal lesions. The right side was involved 93% of the time (23). About 70% of the reported patients with pleural endometriosis were young (average age 32 years), black females.

I suspect that she was treated with attempts at hormonal manipulation or gonadotropic-releasing agonists.

PATHOLOGY

DR. MYERS: Several biopsies of tan, maroon, hemorrhagic pleura were received. Histological sections showed fibrosis, inflammation, degeneration, and dystrophic calcifications. Organizing hemorrhage was present in association with numerous hemosiderin-laden macrophages and multinucleated giant cells (*Figure 2*). Focal collections of endometrial-type glands and stroma also were present (*Figures 3* and *4*), leading to the diagnosis of *pleural endometriosis* (24). Review of omental tissue, obtained from outside BUMC, showed abdominal endometriosis.

FOLLOW-UP DISCUSSION

DR. BOWMAN: *Endometriosis* is defined as an extrauterine growth of endometrial tissue, and it is estimated that it affects 10% to 15% of women of reproductive age (25). It is usually limited to the pelvis but can occur elsewhere, including the thoracic cavities. Thoracic endometriosis was first recognized by O. H. Swartz in 1938 (26). Less than 100 cases have been reported in English-language publications.

Two types of thoracic endometriosis have been described: pleural and parenchymal (25). Pleural endometriosis is the more common of the 2 forms. It usually causes chest pain and dyspnea and may be associated with catamenial pneumothorax, catamenial hemothorax, or both. "Catamenial" means simultaneous with menses. Parenchymal endometriosis usually results in catamenial hemoptysis, but it may be discovered as asymptomatic pulmonary nodules on chest radiograph. There are 3 main theories of pathogenesis for thoracic endometriosis:

1) Sampson theorized that menstrual blood with endometrial fragments could regurgitate from the fallopian tubes into the pelvis (23). This blood could find its way to the subphrenic space and pass through diaphragmatic fenestrations. Studies have shown that there are more fenestrations in the right hemidiaphragm (27). When researchers placed radioactive tracers into the peritoneum and watched the flow of peritoneal fluid, the fluid flowed into the right hemithorax and into the thoracic duct. Similarly, during peritoneal dialysis, fluid that leaks into the thoracic cavity ends up on the right side more often than the left.

2) Ivanoff theorized that irritant or neoplastic agents could pass through such fenestrations and produce metaplasia of the pleural surface, which is histologically similar to that of the peritoneum (23). However, these 2 theories do not explain parenchymal disease as well as they do pleural disease.

3) Some theorize that large cells, including endometrial cells, could pass from the peritoneum into the lymphatics (28). These cells could then travel through the thoracic duct and hilar lymph glands to spread retroperitoneally into the lungs, causing parenchymal disease (28).

Treatment of thoracic endometriosis includes immediate intervention followed by more long-term control of symptoms. Immediate treatment of a significant pneumothorax or a large hemothorax is lung reexpansion with chest tube drainage (29). Smaller effusions can be drained by thoracentesis alone. After the immediate treatment, 2 options exist for women who wish to remain fertile. First, thoracotomy for surgical removal of intracavitary endometriotic tissue, abrasion of the pleura surfaces, or both can be performed (29). Hormonal suppression of ovulation can be employed, for example, with a gonadotropin-releasing hormone analog (29). For women who do not wish to have children, a bilateral oophorectomy can be performed.

Our patient, during the hospital period, had recurring pleural effusions and multiple thoracenteses. She was advised to have monthly injections of the gonadotropin-releasing

hormone analog leuprolide acetate to control her peritoneal and pleural endometriosis. On her ninth hospital day, drainage from the tubes was minimal; they were removed. She was discharged to home the next day. Over the next few months, she had 2 subsequent admissions to BUMC for recurrent hydropneumothorax. She underwent adhesion lysis during the first repeat admission and eventually received pleurodesis on the last admission.

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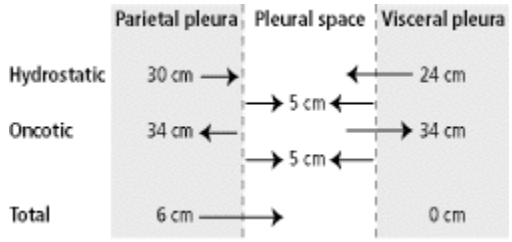

Figure 1

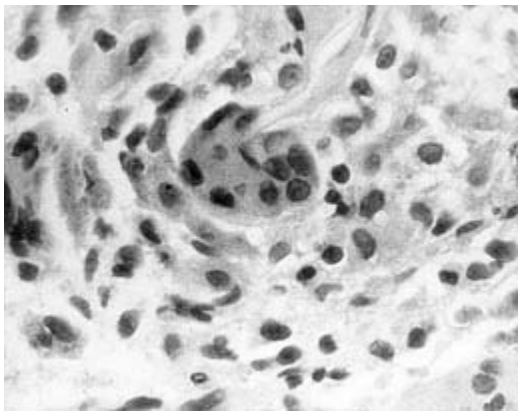

Figure 2

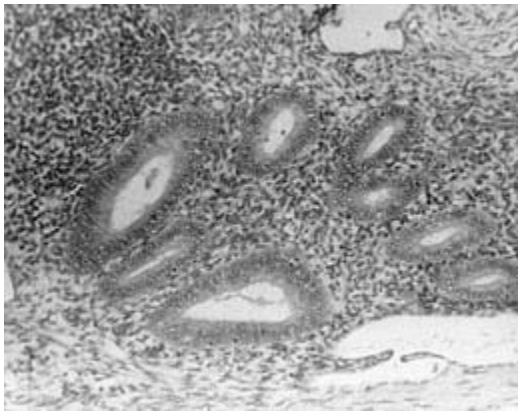

Figure 3

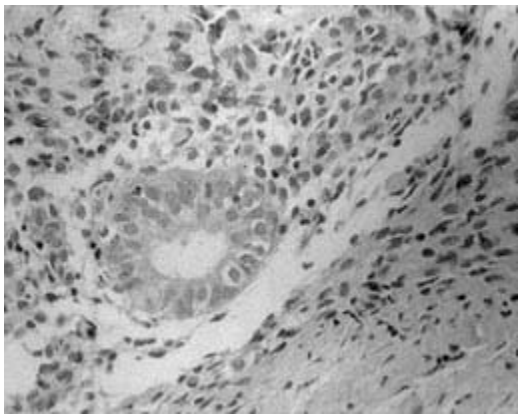

Figure 4