CASE REPORT

Pleural Endometriosis: An Exceptional Cause of Hemorrhagic Pleural Effusion

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Introduction

The differential diagnosis of bloody pleural effusions is relatively narrow. Trauma, iatrogenic or otherwise, represents the most common cause of hemothorax. Other common causes of bloody pleural effusion include malignancy (primary or metastatic), tuberculosis, pulmonary embolism, and serositis from collagen vascular diseases such as rheumatoid arthritis and systemic lupus erythematosus.

Clinical history along with pathologic, microbiologic, and biochemical evaluation pleural fluid evaluations confirm the

diagnosis in most cases. However, if repeated pleural fluid examination reveals only hemorrhagic effusion without corroborative history or mass lesion in lung, or evidence of microorganisms, then a search for uncommon etiology is necessary.

Endometriosis most commonly occurs in the ovaries, uterine ligaments, rectovaginal septum, Cul-de-sac, and the surrounding peritoneum of pelvic organs [1]. Thoracic endometriosis syndrome (TES) is an exceptional condition. There were reported only 38 pathologically documented cases of TES (pleural–21 cases, and parenchymal–17 cases) in the literature till the year 2000 [1].

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One such rare case of pleural endometriosis which created an enormous diagnostic dilemma and ultimately confirmed by histopathologic study is being described.

Case Report

A 27-year-old lady presented with history of intermittent, sharp, pleuritic chest pain radiating from the right subscapular region, across the anterior chest, and down the right arm during the last 2 years. Symptoms developed gradually, beginning with heaviness of right side of chest. It was followed by dull aching chest pain, having occasional exacerbation along with abdominal pain which was relieved by analgesics. Patient could not name any exacerbating factors. She also complained of loss of appetite, headache, dizziness, and difficulty of swallowing. Patient denied weight loss, fevers, dyspnoea, palpitations, gastrointestinal complaints, or a history of easy bruising or bleeding.

History of cough or hemoptysis (which indicates parenchymal involvement) was not obtained. There was history of trauma to chest wall at ages 7 and 15 years. The case was subsequently investigated, and a right-sided loculated pleural effusion was identified both by clinical and radiologic examination (chest X-ray) (Fig. 1). Routine blood examination revealed a mild degree of anemia (Hb–10.2 gm/dL), normal total ($7.600/\text{mm}^3$) and differential WBC counts (N-71, E-04, B-00, L-22, M-03), and mild increase of ESR (28 mm/h). She underwent therapeutic as well as diagnostic thoracentesis. Physical observation of pleural fluid revealed a deep red-colored hemorrhagic appearance, which closely mimicked color of blood. Hematocrit of pleural fluid was more than 50 % of blood. Total cell count of pleural fluid was $650/\text{mm}^3$, and 60 % were lymphocytes, with plenty of RBCs. Increased ADA (46.19 U/L) level was noted in the

fluid (>70 IU/L suggestive of tubercular effusion, and ADA between 40 and 60 IU/L suspected to be of tubercular effusion). Later, the patient underwent repeated pleural taps for six more times over a period of 15 months repeatedly after commencing ATD. No AFB was detected in the pleural fluid as well as in sputum. Mantoux test with ten tuberculin units PPD produced an induration of 8-mm diameter.

A category III ATD regimen (as formulated in RNTCP of India [2]) was applied after careful evaluation of clinical details and results of various investigations. However, even after 6 months of ATD (from 16/05/2006 to 16/11/2006; cat-III ATD), the loculated pleural effusion did not resolve (Fig. 2).

A pleural fluid examination now revealed similar physical and cytologic characteristic was noted 6 months ago. No malignant cell or AFB was identified, but ADA was 58 U/L. A fiber-optic bronchoscopy under local anesthesia revealed no endobronchial growth. Broncho alveolar lavage (BAL) fluid also showed a fair number of WBCs without any malignant cell or AFB. A CT scan of thorax detected gross right-sided pleural effusion, normal mediastinum, no lung parenchymal lesion, and no lymphadenopathy (Fig. 3).

On further query, the patient revealed that there was increased chest pain in the right side during menstrual cycle, which was missed previously when she had been admitted in our hospital. Hence, estimations of CEA of pleural fluid (5 $\mu\text{g/dL}$) and CA-125 level of blood (55.1 U/L) were performed. Both CEA and CA 125 were increased. At this point, the presumptive diagnosis was malignant mesothelioma or metastatic adenocarcinoma, but to determine the definite underlying condition responsible for the effusion, the patient underwent a pleural biopsy. Hematoxylin & Eosin (H&E)-stained paraffin section showed similar looking glandular structures lined by cuboidal cells, separated by uniform, round-shaped stromal cells with foci of hemorrhagic

Fig. 1 Initial chest X-ray showing a right-sided loculated pleural effusion

Fig. 2 Chest X-ray taken after 6 months of ATD—showing failure of resolution of loculated pleural effusion

Fig. 3 CT scan of thorax (non contrast) detected gross right-sided pleural effusion, without any lung parenchymal and mediastinal lesion, or lymphadenopathy

(Fig. 4a). No cellular atypia or necrosis was seen. Foci of mesothelial hyperplasia were noted. Considering the clinical features, results of various investigations and histomorphology, an immunohistologic study for the presence of endometrial tissue (estrogen and progesterone receptor) was performed, which produced a positive result (Fig. 4b).

A definitive diagnosis of pleural endometriosis was made. On diagnostic laparoscopy, dense adhesions were noted in the pelvis. Pelvic peritoneum, lateral pelvic wall, and surface of the gut were all covered with minute, reddish endometriotic spots. A laparoscopic biopsy of pelvis with immunohistologic study confirmed these lesions as foci of endometriosis.

Treatment and Follow Up

Patient was treated with injection depot medroxyprogesterone acetate 150 mg IM every 3 months with calcium supplement resulting in complete remission of clinical

signs and radiologic evidence of pleural effusion. She is under regular follow up for the last 2 years. Latest chest X-ray of chest confirmed complete resolution of pleural effusion (Fig. 5) without any recurrence.

Discussion

Prevalence of endometriosis in women of childbearing age is estimated to be 5–10 %. Only a small proportion of cases occur in extrapelvic sites [3]. Endometriosis involving pleura or lung is rare, and its prevalence remains unknown because of a lack of well-defined studies [3]. The most consistent, albeit retrospective, series on TES included 110 patients and showed that the mean age at presentation was 35 ± 0.6 years, with a range from 15 to 54 years. Interestingly, the peak incidence for pelvic endometriosis is between 24 and 29 years, whereas the peak incidence for TES is approximately 5 years later [4].

Fig. 4 **a** Uniform glandular structures lined by cuboidal cells, in a stroma containing uniform, round cells with areas of hemorrhage (H&E, $\times 100$). **b** Positive immunohistologic staining for estrogen receptors

The most common clinical manifestation of pleural endometriosis is the recurrent catamenial shortness of breathing-related recurrent unilateral right-sided pneumothorax [5]. Less frequent presentations include recurrent hemorrhagic effusion, hemoptysis, or catamenial pain. In the present case, the patient had no features of pneumothorax or did not reveal any history of significant chest pain which produced a considerable diagnostic dilemma. In contrast, patient with lung parenchymal endometriosis typically present with catamenial hemoptysis or blood-tinged cough (which were absent in the present case), or even asymptomatic. Catamenial hemothorax represents the second-most common manifestation of TES, occurring in 14 % of known cases, and affects the right side in about 80 % of the time. Wilkins et al. [6] described 15 cases of TES presenting with hemothorax wherein every case was present only in the right hemithorax. Concomitant pelvic endometriosis was found in 100 % of cases [4].

Fig. 5 Chest X-ray revealed complete resolution of pleural effusion after specific therapy for endometriosis

Chest X-rays in cases of pleural endometriosis usually reveal a pneumothorax or occasionally a pleural effusion or pleural lesion [1]. Spiral CT may show pleural or diaphragmatic thickening in involved areas [7]. In the present case, radiologic investigations revealed a right-sided loculated pleural effusion and diaphragmatic thickening. In contrast, chest X-ray of parenchymal endometriosis shows nodular infiltrates or opacification of an entire lobe [8].

Pleural endometriosis is almost invariably confined to right side [1, 6]. The lesions are characteristically multiple, dark red or blue nodule, or cyst, commonly on the diaphragmatic pleura. Parenchymal endometriotic lesions are not exclusively right-sided and morphologically are solitary, tan to gray, focally hemorrhagic nodules or thin-walled cyst located subpleurally, or may involve bronchial wall or lumina [1]. Microscopically, typical endometriosis consists of a typical presence of both endometriotic glands and stroma. The glands usually have an endometrioid appearance ranging from inactive to proliferative (or occasionally, secretory) to hyperplastic. The endometriotic stroma characteristically resembles eutopic inactive or proliferative endometrial stroma [9]. Immunohistochemically, in the series reported by Flieder and associates, most glands showed cytoplasmic positivity with broad spectrum cytokeratin, cytokeratin 7, and BER-EP4, and strong nuclear staining for estrogen and progesterone receptors [8]. Estrogen and progesterone receptors are present in endometriotic glands and stroma in a lower concentration than in eutopic endometrium [10, 11]. Like normal and neoplastic endometrial stromal cells, endometriotic stromal cells are typically immunoreactive for CD10 [9]. Most stromal cells showed strong cytoplasmic staining for vimentin, and approximately 30 % stained for actin, smooth muscle actin, and desmin. Neither epithelial nor neuroendocrine markers expressed in the stromal cells.

Endometriosis is frequently accompanied by mesothelial hyperplasia of the pelvic or even extrapelvic peritoneum, which in some cases may be striking [9]. In the present case, we have noticed focal hyperplasia of mesothelium. This feature may produce a false categorization as lesion originating from mesothelium. However, careful clinico-pathologic correlation and immunohistologic study helps to detect the appropriate nature of the lesion. Pathogenesis of TES is not yet well understood. There are three theories of the pathogenesis of endometriosis: implantation, vascular or lymphatic metastasis, and coelomic metaplasia [12, 13].

Diagnosis is frequently delayed until several episodes have occurred as patient fails to associate symptoms with menstruation. Pleural fluid cytology is usually not helpful. Level of CA-125 may be elevated in the serum and body cavity fluid of patient with endometriosis [14]. The concentration of CA-125 correlates with both the severity and the clinical course of the disease [1].

Therapy for TES includes the suppression of endometrial tissue and the prevention of further pelvic seeding. Medical therapy should be considered as the first line of treatment [15]. Ghio et al., [16] reported a case of catamenial pneumothorax with chest pain and used medroxy-progestation acetate as therapy. According to Light [17], hormonal therapy (progestational agents, danazol and leuprolide acetate, fail in at least 50 % cases. Medical treatment for endometriosis symptoms (with or without surgery) is generally needed for longer periods of time because of the chronic and recurrent nature of the disease; progestins may be an appropriate alternative for the medical management of endometriosis, given that these agents are relatively well tolerated, have a more limited metabolic impact than other agents, and are also inexpensive [18]. Treatment with GnRH analogs, such as leuprolide, is limited to only 6 months, because these agents induce a hypoestrogenic state that substantially decreases BMD. Poor tolerability represents the major drawback of danazol as a treatment for endometriosis: this agent has both androgenic and anabolic properties. Pleurodesis may be considered as a means of preventing the recurrence of hemothorax [3].

Pleural endometriosis is a rare, unusual lesion that may mimic various conditions. Thorough observation of different symptoms and signs along with appropriate investigations are essential for appropriate diagnosis in such cases.

Therefore, our learning message was always enquiring about detailed menstrual history in every case of hemorrhagic pleural effusion in young female, and a good history taking is of paramount importance in clinical medicine.

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