Refractory Pleural and Peritoneal Effusion– A Case of Atypical Malignant Mesothelioma (Postprint)

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Abstract

This article reports a case of atypical malignant mesothelioma (MM) involving the pleura and peritoneum, describes its atypical clinical and pathological features, reviews the relevant literature, and aims to enhance clinicians' awareness of atypical presentations of MM.

Full Text

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Abstract

This article reports a case of atypical malignant mesothelioma involving both pleura and peritoneum. The aim is to strengthen clinicians' understanding of the atypical manifestations of malignant mesothelioma by illustrating its clinical and pathological characteristics and reviewing related literature.

Keywords: pleural effusion, peritoneal effusion, malignant mesothelioma

Case Presentation

A young-to-middle-aged female patient presented with a chronic course of disease and relatively slow progression. She developed pleural effusion followed by peritoneal effusion, both with similar characteristics and both exudative in nature. The patient reported a 5 kg weight loss over several months and denied any history of tuberculosis or contact with TB patients. She had a history of occupational exposure to asbestos-containing materials while working in waste recycling in Xinjiang from 2007 to 2015.

Physical examination revealed no enlarged superficial lymph nodes, clear lungs without rales, and normal cardiac findings. A peritoneal drainage tube was present in the left lower abdomen, draining clear yellow fluid. The abdomen was soft and non-tender with no palpable masses. Shifting dullness was positive. There was no pitting edema in the lower extremities.

Initial Evaluation and Differential Diagnosis

Exudative serous cavity effusions should prompt consideration of infectious diseases, immune-mediated diseases, or malignant tumors. Regarding infectious etiologies, the patient had a chronic course with predominantly mononuclear cells in both pleural and peritoneal fluids, raising suspicion for tuberculosis. The purified protein derivative (PPD) test was (++), and the enzyme-linked immunospot assay for TB infection was positive (10 spot-forming cells per 10 peripheral blood mononuclear cells). However, after four months of regular quadruple anti-tuberculosis therapy, the pleural effusion showed minimal improvement, making TB infection unlikely. Screening for drug-resistant TB or other special pathogens was still necessary, though routine cultures of pleural and peritoneal fluid had been negative. Given the fastidious growth requirements or short survival time of certain pathogens, measures to improve culture yield could include bedside inoculation, culture of tissue homogenates, use of special media, and extended culture duration. Meanwhile, special staining of the previous pleural biopsy specimens from the outside hospital could be performed for further pathogen evaluation.

Autoimmune diseases such as systemic lupus erythematosus can cause exudative multi-serous cavity effusions and predominantly affect young-to-middle-aged women. However, this patient had no involvement of other organ systems and autoimmune antibodies were negative, making this diagnosis unlikely.

Malignant tumors, including primary tumors of the pleura/peritoneum and metastatic disease, remained a consideration. Despite multiple negative cytology examinations and pleural/peritoneal biopsies, malignancy could not be definitively excluded, and repeat cytology or laparoscopic biopsy might be necessary.

Additionally, given the patient' s long-term waste recycling work with potential exposure to heavy metals such as lead and mercury from waste batteries, chronic intoxication was considered. However, acute and chronic heavy metal poisoning typically manifests with renal, neurological, and hematological involvement rather than serous cavity effusions, making this unlikely. Blood and urine toxicology screening could be performed to rule this out.

Laboratory Findings

Admission laboratory tests showed: hemoglobin 94 g/L, RBC count 5.16 × 10^{12}/L, MCV 69.2 fL, MCH 20.8 pg, serum iron 10.9 g/dl, total iron binding capacity 255 g/dl, transferrin saturation 4.0%, serum ferritin 79 ng/ml, and ESR 97 mm/h.

Pleural fluid analysis (2015) revealed: clear yellow fluid, Rivalta test weakly positive, nucleated cell count 1140 × 10 /L with neutrophils predominating, total protein 53.5 g/L, LDH 9140 U/L, ADA 14.8 U/L, and glucose 6.59 mmol/L. Repeated tumor cell searches in pleural fluid were negative.

Peritoneal fluid analysis showed: slightly turbid yellow fluid, total cell count 2262 × 10 /L, nucleated cell count 106 × 10 /L with mononuclear predominance, Rivalta test positive, total protein 48 g/L, albumin 21 g/L, LDH 200 U/L, ADA 9.9 U/L, glucose 1.66 mmol/L, and chloride 0.13 mmol/L. Serum-ascites albumin gradient was <11 g/L. Peritoneal fluid TB-DNA, cultures for aerobic/anaerobic bacteria, actinomycetes, and Nocardia, as well as acid-fast staining, were all negative. Parasite examinations of peripheral blood and stool were negative. Blood and urine toxicology screens were negative. Autoimmune antibody panels were negative.

Imaging Studies

Chest imaging [Figure 1: see original paper] showed right pleural effusion (2015). Follow-up CT [Figure 2: see original paper] demonstrated right middle lobe subpleural linear opacities and bilateral lower lung subpleural ground-glass opacities. No active or old TB lesions were identified in both lung fields.

Enhanced CT and PET/CT scans revealed a soft tissue mass anterior to the left kidney measuring 28 mm × 31.7 mm with arterial blood supply, SUVmax 8.4. Multiple nodules were seen in the greater omentum and mesentery, with multiple pelvic lymph nodes showing partial calcification and mild metabolic activity, suspected to be inflammatory. Gastroscopy and colonoscopy showed no abnormalities.

Pathological Examination

Initial right thoracoscopic pleural biopsy showed fibrous tissue with papillary-arranged mesothelial cells and small clusters of suspicious histiocytoid and plasmacytoid cells. Immunohistochemistry was atypical: EMA (+), GLUT-1 (-), calretinin (-), D2-40 (-), Desmin (-), CK (-), CD34 (-), ERG (-), LCA (+), CD68 (-), TTF-1 (-), Ki-67 (2%+), P53 (-).

Laparoscopic exploration was subsequently performed due to the unclear nature of the peritoneal effusion and suspicion of malignancy. Intraoperative findings [Figure 4: see original paper] showed diffuse white miliary nodules distributed on the parietal peritoneum and uterine surface. The soft tissue mass anterior to the left kidney was excised along with greater omentum tissue [Figure 5: see original paper].

Final pathology [Figure 6: see original paper] revealed epithelioid malignant tumor cells in fibrous and lymphoid tissue with papillary formation. Immunohistochemistry showed: AE1/AE3 (+), CAM5.2 (+), MC (+), WT-1 (+), Ki-67 index 10%, while CR, B72.3, P53, EMA, Ber-EP4, CK20, CK5/6, CK7, CDX-2, CEA, Vimentin, PAX-8, ER, and PR were all negative.

Discussion

Atypical Clinical Features

This case exhibited several atypical features. First, simultaneous involvement of both pleura and peritoneum is rare, with only a few case reports documented in the literature. Second, the pleural and peritoneal effusions were yellow and slightly turbid, 不同于 the typically bloody exudates reported in mesothelioma. Third, the disease course was prolonged with slow progression, contrasting with the highly aggressive nature usually associated with mesothelioma.

The patient had a history of asbestos exposure, and the similar nature of pleural and peritoneal effusions suggested that the initial pleural effusion might have been associated with pleural mesothelioma. Although the initial pleural biopsy was non-diagnostic, this could be attributed to small sample size, non-representative tissue sampling, or early-stage atypical pathological changes.

The temporal relationship between intrapleural injection of elemene for pleural effusion and subsequent development of peritoneal malignancy appears coincidental. Elemene is commonly used for malignant pleural effusion with minimal side effects, primarily local pain, and no reported association with secondary tumor development.

Atypical Pathological Features

Malignant mesothelioma demonstrates heterogeneous histology and immunophenotype. Histologically, it can be classified as epithelioid, sarcomatoid, or mixed (biphasic) types, with epithelioid being most common. Immunohistochemical marker selection varies based on histological type, tumor location, and differential diagnostic considerations.

Typical positive markers for mesothelioma include calretinin, CK5/6, WT-1, and D2-40, while negative markers include CEA, Ber-EP4, and B72.3. Differentiation from reactive mesothelial hyperplasia may utilize GLUT-1 and IMP3, which are positive in 73% and 67% of mesotheliomas respectively, but typically negative in benign hyperplasia. Differentiation from metastatic tumors requires

organ-specific markers: TTF-1 and Napsin-A for lung adenocarcinoma, p63 and CK5/6 for squamous cell carcinoma, PAX-8 for renal cell carcinoma, ER/PR for breast cancer, and CDX-2 for gastrointestinal tumors.

In this case, the immunohistochemical profile was atypical: WT-1 was positive while calretinin, CK5/6, and D2-40 were negative. However, diagnosis requires integration of clinical features, histology, and immunohistochemistry. The papillary epithelioid morphology, negative organ-specific markers, and exclusion of other primary malignancies by imaging and endoscopy supported the diagnosis of malignant mesothelioma.

Treatment and Prognosis

After definitive diagnosis, the patient received treatment at a local hospital with pemetrexed combined with cisplatin chemotherapy plus hyperthermic intraperitoneal chemotherapy. After 2 cycles, peritoneal effusion markedly decreased and the patient' s general condition improved. Bevacizumab was not administered due to economic constraints.

Surgical treatment remains controversial and is generally reserved for early-stage disease in good-performance-status patients. Chemotherapy is the only evidence-based treatment shown to improve survival, with pemetrexed plus cisplatin being the first-line regimen. The optimal number of chemotherapy cycles remains undefined. Vascular endothelial growth factor (VEGF) plays a role in angiogenesis and tumor growth in mesothelioma, and the addition of bevacizumab to chemotherapy has been shown to prolong overall and progression-free survival compared to chemotherapy alone. Radiotherapy is used only as palliative or adjuvant therapy.

Conclusion

This case highlights several important lessons. When serous cavity effusions present with atypical clinical and laboratory features that pose diagnostic challenges, malignant mesothelioma must remain in the differential diagnosis. Due to its clinical heterogeneity and variable disease progression, some patients may lack typical tumor consumption symptoms and have negative early imaging findings, leading to delayed diagnosis. Therefore, for diagnostically challenging serous effusions, aggressive pursuit of thoracoscopic or laparoscopic biopsy is crucial, sometimes requiring repeat procedures to avoid missed diagnosis. The heterogeneity and atypical features of mesothelioma can create significant diagnostic confusion and warrant heightened clinical vigilance.

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Note: Figure translations are in progress. See original paper for figures.