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Case report

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A case of localized peritoneal malignant mesothelioma with ovarian metastasis and literature review

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Summary

Peritoneal malignant mesothelioma (PMM) is a rare mesothelial cell-derived malignant tumor, which is clinically distinguished into a localized and diffuse forms, the latter being more common. The onset of PMM is insidious, so it is not easy to make a preoperative diagnosis of PMM. Clinicians must pay more attention to this disease in view of its poor prognosis. In order to improve the understanding of PMM, a case of patient with localized PMM metastasizing to the ovary is reported and discussed, along with a review of relevant literature to further explore the etiology, epidemiology, clinical manifestations, examination methods, diagnosis, treatment and prognosis of PMM.

Keywords: localized peritoneal malignant mesothelioma; ovarian tumor; diagnosis; case report

1. Case Report

A 35-year-old female patient with intermittent right upper middle abdominal pain for more than half a year was admitted to our hospital on September 17, 2020. The pain was tolerable without reflex pain. Nor was it associated with other symptoms, such as diarrhea, nausea, and vomiting. Owing to its intermittent onset, dull pain in the right upper abdomen was substantially ignored until its frequency increased to about once every 2-3 days. The hepatitis B surface antigen was negative, and enhanced CT of pelvic and abdominal cavity showed an abundant blood supply nodule with size of 3×2 cm in the anterior edge of the lower pole of the liver, an enhanced nodule with size of 1.4 cm on the right side of the uterus and a small amount of fluid. Enhanced MRI of the liver revealed a rich blood supply nodule in the abdominal cavity of the right upper abdomen and a small amount of fluid in the abdominal cavity, thus suggesting either a hemangioma or a neuroendocrine tumor. The patient had no chills, fever, nausea, vomiting, obvious abdominal distension, hematemesis, melena, or jaundice. She showed a good mental state, normal appetite, good sleep, normal urine and bowel movements, and normal body weight.

1.1. Past health history

The patient had cesarean section in 2014 and underwent subtotal thyroidectomy in 2015 but the postoperative pathology showed a benign nodule. Thyroid hormones turned out to be in the reference range. She denied any history of chronic disease and drug allergy.

1.2. Occupational history

The patient lived in Zhouzhuang Town, Jiangyin City, Jiangsu Province, Shanghai, China, where she was employed as an ordinary office clerk. Therefore, she was not occupationally exposed to asbestos, silica, or radioactive substances. Her home was located

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near chemical fiber factory, though any possible environmental exposure remains unidentified.

1.3. Physical examination

The vital signs were stable. Cardiopulmonary auscultation was normal, and the abdomen was flat and soft. There were no gastrointestinal peristaltic waves, and no varicose veins on the abdominal wall. An abdominal lump of about 3 cm in diameter, with flat surface and suboptimal mobility, could only be palpable in the right upper abdomen. There was no tenderness and rebound pain. Liver, gallbladder, and spleen were not touched. Moreover, both Murphy's sign and mobile voiced were negative. There was no restriction of movement of the limbs, no deformities and edema. Pathological reflex was not elicited. Gynecological examination: vulva, no abnormalities; vagina, no obvious abnormal discharge, no peculiar smell; cervix, smooth, except for a 2 mm-sized intracervical polyp; uterus, normal without tenderness; bilateral adnexa, no abnormal masses were touched, no tenderness.

1.4. Auxiliary examination

Examination by transvaginal ultrasonography on September 13, 2020 showed an 18 mm×17 mm medium echo mass in the right ovary and pelvic effusion about 4 cm. Thinprep cytology test (TCT) revealed that no intraepithelial diseased cells or malignant cells were found, and HPV was negative. The pelvic fluid collected by posterior fornix puncture was yellow, and the bacterial examination was negative. PET-CT showed that an irregular soft tissue mass (35 mm×26 mm) in the mesenterium of hepatic flexure of colon, which was multi-nodular fusion. Fluorodeoxyglucose (FDG) metabolism was increased, and the maximum of standardized uptake value (SUV) was 7.1. Scanning of FDG metabolism also increased after a delay of one hour and the maximum of SUV turned out to be 6.2. The diameter of the soft tissue nodule in the right appendage area was 19 mm and the FDG metabolism was increased with a maximum of SUV 5.2. Scanning of FDG metabolism also increased after a delay of one hour with a maximum of SUV 6.5 and pelvic effusion. The above images suggested malignant tumors and possible metastasis, so a laparoscopic biopsy was recommended. Color Doppler flow imaging showed linear dotted color blood flow and an anechoic area about 46 mm×21 mm in pelvic cavity without other obvious abnormalities. Routine blood tests were all within the reference values as were all tumor markers (CA125 33.3 U/ml, CA199 4.0 U/ml, CA724 <1.5 U/ml, CA153 6.65 U/ml, CA242 2.7 IU/ml, NSE 10.20 ng/ml, CEA 0.8 μg/L, AFP 3.1 μg/L). The electrocardiogram showed sinus rhythm, short P-R interval, and normal QRS complex. The chest radiograph showed no obvious abnormalities in the heart, lung, and diaphragm. Abdominal B-ultrasound showed that no obvious masses in the liver, gallbladder, pancreas, and spleen. Colonoscopy suggested that the colorectum was normal.

Since the PET-CT examination showed adnexal mass and increased FDG metabolism, a laparoscopy was performed, and a biopsy was taken for pathological examination. Intraoperative findings are shown in Figure 1: a small amount of faint yellow ascites about 100 ml in the abdominal cavity was taken out and sent for routine and exfoliated

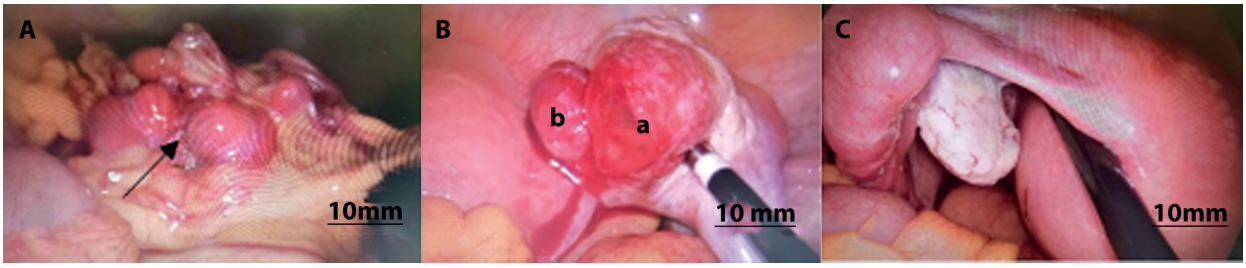

Figure 1. Pelvic and abdominal cavity observed intraoperatively.
A: Omentum mesothelial tumor; **B:** Right ovary (a, luteal cyst; b, mesothelial tumor); **C:** Left ovary.

cell examination. The liver was dark red, soft, with sharp edges, and no obvious space-occupying lesions or cirrhosis. The size of the gallbladder with smooth wall was 7 cm×3 cm×2 cm, and there was no obvious incrassation or edema. The common bile duct had no obvious bolding. There was no obvious abnormality in the stomach, duodenum, pancreas, etc. A dark red nodular fusion tumor with tortuous blood vessels, about 3 cm×2 cm in size, was seen on the omentum majus in the colon and liver flexure of the right upper abdominal. The tumor was free, and there was no obvious adhesion to the surrounding organs and abdominal wall. No clear lesions were seen on the abdominal wall, pelvic cavity, or mural peritoneum. There were no abnormalities in the bilateral fallopian tubes, left ovary and uterus. Two dark red masses about 1.5 cm in diameter were seen on the right ovary, one of which was partially ruptured. After exploration, it was decided to perform the resection of tumor in the omentum majus of right upper abdomen + the resection of the right ovarian mass. The patient was discharged on d 5 after surgery.

Postoperative pathology (Figures 2 and 3): Delivery of right ovarian cysts with intraoperative frozen section (as shown in Figure 1B a) suggested corpus luteum cyst. Postoperative pathology demonstrated both abdominal tumor and right ovarian lesion (as shown in Figure 1B b) that was a localized malignant mesothelioma (MM) of the epithelial type. Immunohistochemical indicators prompted that mesothelioma cells were positive for CD99, CK5/6, Cam5.2, CK, Ki-67 (+5%), EMA, Vim, CK7, CK19, WT-1, D2-40, p53 (+40%) and calrentin, and negative for myogenin, A103, HMB45, PNL.2, bcl.2, STAT6, TTF-1, CD34, CD31, S-100, SMA, desmin and Gly-3. Postoperative pathological sections were sent to Fudan University Shanghai Cancer Center for consultation. The results of immunohistochemical assessment indicated that mesothelioma cells were positive for AE1/AE3, calrentin, CK5/6, D2-40, WT-1, BAP1 and Ki67, and negative for Ber-EP4, Moc31 and PAX8, and molecular test using FISH method to detect the deletion of P16 gene turned out to be negative.

Outcome and prognosis: the patient continued chemotherapy in Shanghai Cancer Center. The therapeutic schedule was cisplatin intraperitoneal hyperthermic perfusion chemotherapy with three courses of treatment. As of the writing of this article, the patient is still alive. The tumor markers are normal after re-examination, and there is no obvious recurrence or metastasis in the imaging examination of the pelvic and abdominal cavity.

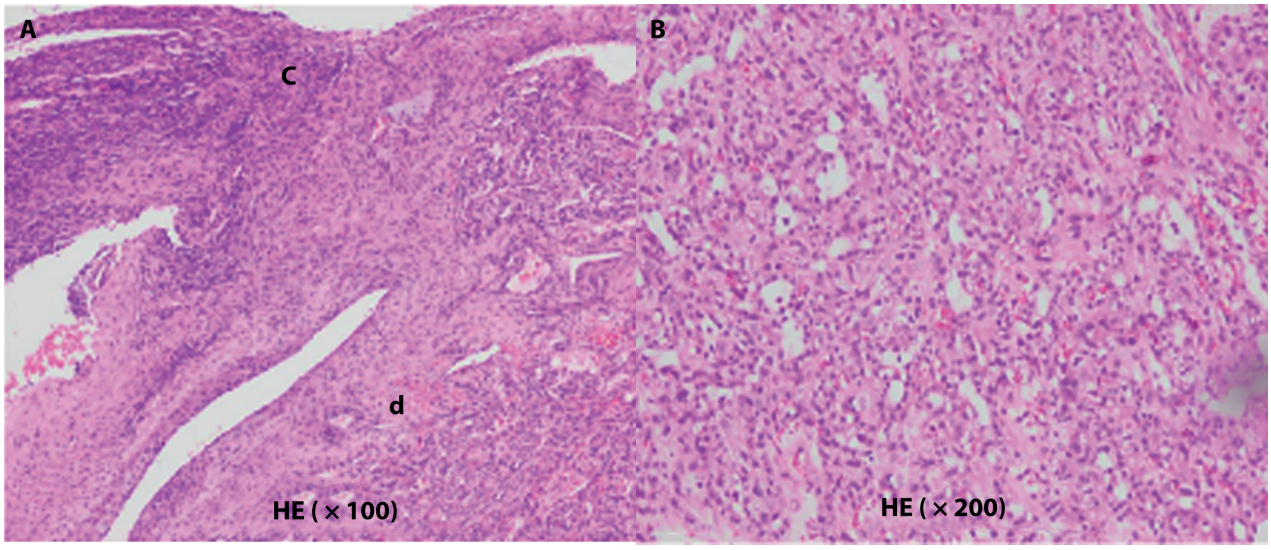

Figure 2. HE staining observation of the right ovarian tumor tissue.
A: c and d represent ovarian tissue and tumor tissue, respectively, ×100; **B:** Tumor tissue, ×200.

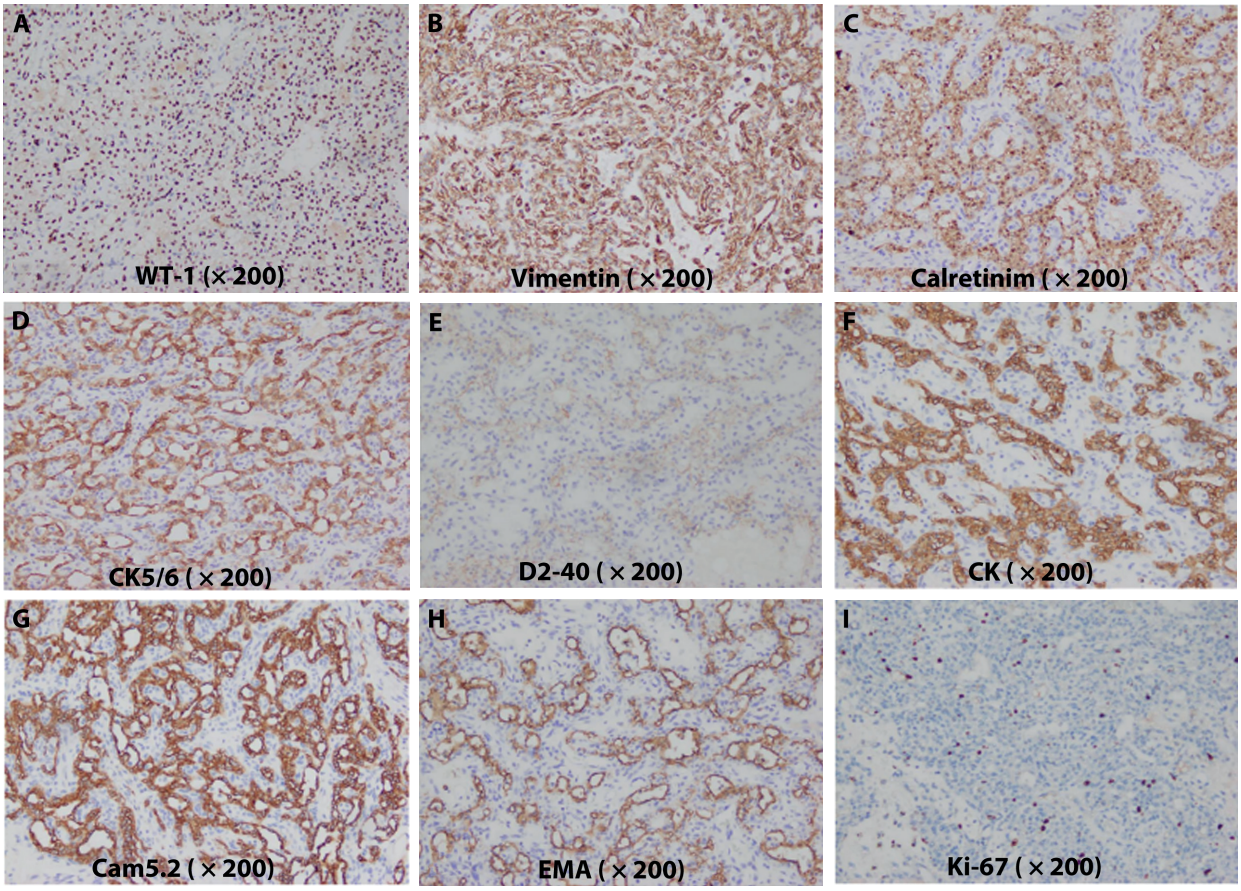

Figure 3. Immunohistochemical observation of the right ovarian tumor tissue**.**
A: Nuclear positive for WT-1, ×200; **B:** Cytoplasmic positive for vimentin, ×200; **C:** Cytoplasmic positive for calretinin, ×200; **D:** Cytoplasmic positive for CK5/6, ×200; **E:** Cytoplasmic positive for D2-40, ×200; **F:** Cytoplasmic positive for CK, ×200; **G:** Cytoplasmic positive for Cam5.2, ×200; **H:** Cytoplasmic positive for EMA, ×200; **I:** Proliferation index for Ki-67 is about 5%, ×200.

2. Literature Review

2.1. Etiology and Epidemiology

MM is a type of highly malignant tumor that originates from mesothelial cells on the surface of serous membrane. PMM refers to MM that originates in the visceral and parietal layers of peritoneum. The etiology of PMM is not yet fully understood. Early studies showed that PMM was closely related to asbestos exposure [1], but this patient has no obvious correlation with asbestos exposure. In recent years, some scholars believed that localized PMM has nothing to do with the history of asbestos exposure and asbestos exposure is not a necessary condition for the diagnosis of PMM [2]. PMM may be related to many factors: (i) certain minerals, such as silica dust, asbestos-like fibers; (ii) chronic inflammatory stimuli; (iii) radioactive substances; (iv) viruses: for example, simian virus 40; (v) genetics factors; (vi) other factors, such as organic chemicals, drug factors, etc. [3].

2.2. Clinical and Histological Findings

PMM generally has an insidious onset, and its clinical manifestations are diverse and non-specific: There are no obvious clinical manifestations in the early stage, and it is difficult to diagnose in time. After the organs are involved, abdominal pain, bloating, abdominal mass, and ascites are often present with symptoms such as nausea, vomiting, diarrhea,

and fever. In the late stage of PMM, extensive adhesions between the abdominal cavity and intestinal walls may occur, which may cause intestinal obstruction. If the lesion infiltrates the deep part of the cavity, it may cause ulcers or perforation. PMM can be divided into diffuse type and localized type according to the scope of the disease, and the diffuse PMM is more malignant and more common, whose manifestations include diffuse and irregular/nodular thickening of the peritoneum, omentum and mesenteric, accompanied by extensive invasion of the abdominal cavity and varying amounts of abdominal effusion. The localized PMM is rare and manifests as localized cystic, cystic solid or solid irregular mass, and most of them are cystic solid. The localized PMM can invade the surrounding structures, but its malignant degree is relatively low and distant metastasis, abdominal and pelvic effusion are rare.

According to the WHO histopathological classification method, PMM has the characteristics of bidirectional differentiation in histopathology. It can be divided into three types: (i) epithelial type, (ii) sarcoma type and (iii) mixed type [4]. The epithelial type is the most common and accounts for about 75% to 90% of PMM. Tumor cells in epithelial type PMM can be arranged into glandular tube, papillary, cord-shaped, nest-shaped, and trabecular-shaped with various morphologies and obvious atypia. Pathological mitotic phenomenon is often noticed, interstitial cells are filled with denatured mucus, and the prognosis is the best. In the sarcoma type PMM, most tumor cells are fusiform, arranged in bundles, and may be accompanied by collagen fibrosis and ossification. The sarcoma type PMM is rare and has the worst prognosis, with an overall survival period less than 6 months. The mixed type is also named the two-way type, accounting for about 25% of PMM, and cells have both epithelial and sarcoma forms [5, 6]. Most cases of PMM are diffuse, whereas localized PMM is very rare [7]. It has been reported that the rate of extra-abdominal metastasis of PMM is about 50%, and the pro-strate growth along the serosal layer and submesothelial tissue of the peritoneum is an important biological characteristic of PMM, but it can also be metastasized by local infiltration, implantation, lymphatic and hematological transfer [8]. This case is an epithelial localized PMM metastasized to the surface of the ovary, but the lesion did not grow along the serous layer and submesothelial tissue of the peritoneal surface, which is significantly different from previous reports in the literatures.

2.3. Examination Methods and Diagnosis

Tumor markers: A study of serum osteopontin (OPN) and sugar chain antigen 125 (CA125) in 20 female patients with PMM [9] found that the combined detection of OPN and CA125 could improve the sensitivity, specificity, and positive predictive value of PMM diagnosis. OPN had a higher negative predictive value for the diagnosis of PMM, and combined detection with CA125 could improve the diagnosis rate of PMM. Immunohistochemistry (such as calretintin, CK5/6, TTF, WT-1, etc.) in ascites has a certain prompting role in the diagnosis of PMM. If a large number of mesothelioma cells are found in the patient's ascites test, it is highly indicative of PMM. However, this patient did not have a large amount of ascites, therefore, neither the first visit nor the doctors in our hospital considered the possibility of PMM. Also, detailed ascites immunohistochemical test had not been performed.

Imaging examinations: Although ultrasound and CT can be used as common clinical diagnostic methods, the positive detection rate for PMM is low. The value of ultrasound examination mainly lies in the early detection of ascites and solid masses in the abdominal cavity. A retrospective analysis on 112 cases of diffuse PMM [10] showed that ultrasound examination of PMM manifested as diffuse thickening of the peritoneum and omentum majus with hard touch. It is believed that ultrasound-guided needle biopsy of the peritoneal thickened area is an effective way to diagnose PMM. In addition, some studies on PMM [11] considered that CT manifestations often displayed with diffuse thickening, irregular and (or) nodular thickening of the omentum majus and mesenteric. Owing to mesothelioma cells often creep along the surface of the peritoneum and can expand locally. Then it grows to form a cystic solid mass or expands along the serosal layer of the organ to form a mass, which infiltrates the parenchymal organ, so it is easy to confuse with the primary tumor of the organ. It has been reported that according to

the imaging characteristics of CT, PMM is usually divided into 3 types [12]: (i) wet type, mainly manifested as diffuse peritoneal nodules, ascites, intestinal obstruction; (ii) dry type, mainly manifested either as a single or multiple large masses in the abdominal cavity without ascites; (iii) mixed type, manifested with both the above-mentioned two kinds of CT imaging characteristics. Although ultrasound examination and CT scans lack specificity and cannot be used as a direct diagnostic basis for PMM, they can detect the location and extent of omental lesions and lesions in time, and provide a certain basis to help for later peritoneal puncture positioning. MRI and PET-CT examinations play an important role in the clinical staging of tumors, evaluation of curative effect, especially the evaluation of potentially operable lesions. Studies have shown that [13] MRI and PET-CT can detect early space-occupying lesions, and preliminarily determine whether the lesions are benign or malignant with metastasis, which could guide to adopt appropriate clinical treatment plans.

Immunohistochemistry: The current diagnosis of MM is ultimately based on pathological diagnosis such as immunohistochemistry analysis. The diagnosis of PMM lacks specific antibodies, and combined detection of multiple antibodies is often required for comprehensive diagnosis in clinical practice. Sensitive positive markers comprise AE1/AE3, calretinin, CK5/6, vimentin, WT-1, D2-40 and IMP-3 [14]. The most specific marker is calretinin, and AE1/AE3 and vimentin are the most sensitive. Negative indicators include CEA, ER, Moc31, Ber-Ep4, LeuM1 and Bg8 [15]. Because the sensitivity and specificity of a single index have not reached 100%, so the current method used in the internationally universal "Guidelines for Pathological Diagnosis of Malignant Mesothelioma" is the combined diagnosis of two positive markers and two negative markers [2]. In this case, AE1/AE3, calretinin, WT-1, CK5/6, and D2-40 of the patient were all positive, while Ber-EP4 and Moc31 were negative, and this case also expressed the mesenchymal marker vimentin and epithelial marker CK, Cam5.2 and EMA, so this patient is in line with the diagnosis of MM. Some scholars have discovered genetic abnormalities in MM, among which the most common is P16 gene. Some literatures showed that detection of P16 gene deletion by using FISH was an effective method to distinguish between reactive mesothelioma and MM with extremely high sensitivity and specificity [16-17]. However, research in this area is currently mainly focused on pleural malignant mesothelioma, and there are very few domestic reports on the deletion and expression of P16 gene in PMM. The pathology consultation report of the patient outside the hospital indicated that there was no deletion of the P16 gene in this case.

2.4. Treatment and Prognosis

PMM is a highly malignant tumor. Because of its non-specific early symptoms, most patients have an advanced disease when the clinical symptoms are obvious. Now specific therapy of PMM is deficient, except for surgery and subsequent comprehensive treatment. Surgery leading to complete removal of the tumor and involved organs is the first choice for patients with localized lesions. If the lesions are extensive, palliative resection should be sought, so that surgical resection can be performed again when recurrence occurs [18]. The more recognized treatment plan for PMM is CRS/HIPEC [19]: CRS removes the lesions and separates the abdominal adhesions to achieve the best drug exposure for the small residual lesions and improve the efficacy of HIPEC. According to the research of Swedish scholars, diffuse PMM receiving CRS/HIPEC treatment had a good long-term survival rate, and the overall survival rate was improved [20].

Chemotherapy is the primary choice in cases who cannot receive surgical treatment. Refer to the treatment of pleural mesothelioma, platinum combined with pemetrexed was the first choice for systemic chemotherapy [21], of which the effective rate and disease control rate were 26.0% and 71.2%, respectively [22]. Radiotherapy is often used as a palliative treatment, which can improve symptoms without control of MM development.

Other treatment options such as molecular targeted therapy (nintedanib, bevacizumab), gene

therapy (BAP1, TP53, NF2, ALK), immune checkpoints inhibitor combined chemotherapy (CTLA-4, PD-1) are still in the research stage, and their clinical effects need to be further verified [23]. Most MM patients are diagnosed at an advanced stage, and the overall prognosis is poor with an average survival time of only 1 year and 5-year survival rate being 20% [24].

The literatures indicated that poor prognostic factors related to MM mainly included male, PS score> 2 points, age> 60 years, mixed or sarcoma type, incomplete resection and deep tissue infiltration, and the patients with extensive lesions of the small intestine and its mesentery prompted by preoperative CT and elevated platelets before surgery, have a higher rate of disease recurrence and a poor prognosis [25]. Some scholars have studied the expression of COX-2, NF-κB, WT-1 and PTEN in PMM, and found that the high expression of COX-2 and NF-κB indicated poor prognosis, and PTEN and WT-1 were independent prognostic factors affecting PMM [26, 27].

3. Discussion

At present, PMM is difficult to diagnose early in clinical practice for its infrequence, hidden onset and lack of specific clinical manifestations, sensitive laboratory indicators and obvious imaging features, and thus is easy to be misdiagnosed. The literatures about MM mainly focused on the pleura and peritoneum, while the metastasis of mesothelioma from peritoneum to ovary was rare. Among the PMM patients reported in the literatures, their clinical manifestations were all vast stubborn ascites and ovarian mass, the malignant tumor had been clearly diagnosed before the operation, and the radical resection of malignant tumor had been performed during the operation (total uterus + bilateral adnexa + omentum resection + pelvic lymph node dissection). In this case, the symptoms of the patient were mild, and the clinical manifestations were atypical. Although the ultrasound examination in other hospital and our hospital showed pelvic effusion, the ascites exfoliated cells examination and immunohistochemical assessment were not performed due to the lack of relevant knowledge. In addition, no malignant cells were found in the abdominal irrigation fluid collected during the operation, which may be related to less ascites. Although PET-CT examination found abnormal FDG uptake in the peritoneum and the right adnexal area, suggesting a malignant tumor, it is not possible to diagnose accurately for that positioning punctures under ultrasound B-scans could not be performed before operation owing to the peculiar location of the tumor. Removement of ruptured ovary cyst and local resection of omentum lesions were first received during the operation to send for frozen examination, and ovarian surface mesothelioma lesions were sent for postoperative pathology. Unfortunately, routine rapid freezing could not fully understand the pathological features of the disease, and thus missed the best time to the initial complete removal of the tumor and involved organs. The postoperative pathological report suggested PMM, and the ovarian lesion was caused by the metastasis of peritoneal mesothelioma. Taking into account that these two lesions are localized, without other diffuse lesions and massive ascites, the second expansion surgery, which would cause great damage, was not performed. At the same time, in consideration of the poor prognosis of MM and possible replantation and metastasis in the pelvic and abdominal cavity, intraperitoneal hyperthermic perfusion chemotherapy was given to reduce the recurrence rate.

MM is rare in clinical, and it is easy to be misdiagnosed due to atypical initial symptom of localized lesions, low imaging specificity and no sensitive tumor markers. At present, MM can only be diagnosed by immunohistochemical analysis of a series of related markers, and is difficult to make a definitive diagnosis before surgery. Therefore, the possibility of MM should also be considered in addition to common diseases when female patients with abdominal pain were encountered in clinical practice. The differential diagnosis should be carefully performed, relevant examinations should be performed in time, and the diagnosis should be made as soon as possible to improve the prognosis and reduce misdiagnosis and mistreatment.

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