

World Journal of *Clinical Cases*

World J Clin Cases 2022 October 6; 10(28): 9970-10390



REVIEW

- 9970 COVID-19 and the heart
Xanthopoulos A, Bourazana A, Giamouzis G, Skoularigki E, Dimos A, Zagouras A, Papamichalis M, Leventis I, Magouliotis DE, Triposkiadis F, Skoularigis J
- 9985 Role of short chain fatty acids in gut health and possible therapeutic approaches in inflammatory bowel diseases
Caetano MAF, Castelucci P

MINIREVIEWS

- 10004 Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation
Yang Y, Hong M, Lian WW, Chen Z

ORIGINAL ARTICLE**Clinical and Translational Research**

- 10017 Effects of targeted-edited oncogenic insulin-like growth factor-1 receptor with specific-sgRNA on biological behaviors of HepG2 cells
Yao M, Cai Y, Wu ZJ, Zhou P, Sai WL, Wang DF, Wang L, Yao DF

Retrospective Study

- 10031 Analysis of the successful clinical treatment of 140 patients with parathyroid adenoma: A retrospective study
Peng ZX, Qin Y, Bai J, Yin JS, Wei BJ
- 10042 Efficacy of digital breast tomosynthesis combined with magnetic resonance imaging in the diagnosis of early breast cancer
Ren Y, Zhang J, Zhang JD, Xu JZ
- 10053 Prevention and management of adverse events following COVID-19 vaccination using traditional Korean medicine: An online survey of public health doctors
Kang B, Chu H, Youn BY, Leem J
- 10066 Clinical outcomes of targeted therapies in elderly patients aged ≥ 80 years with metastatic colorectal cancer
Jang HR, Lee HY, Song SY, Lim KH
- 10077 Endovascular treatment vs drug therapy alone in patients with mild ischemic stroke and large infarct cores
Kou WH, Wang XQ, Yang JS, Qiao N, Nie XH, Yu AM, Song AX, Xue Q

Clinical Trials Study

- 10085** One hundred and ninety-two weeks treatment of entecavir maleate for Chinese chronic hepatitis B predominantly genotyped B or C

Xu JH, Wang S, Zhang DZ, Yu YY, Si CW, Zeng Z, Xu ZN, Li J, Mao Q, Tang H, Sheng JF, Chen XY, Ning Q, Shi GF, Xie Q, Zhang XQ, Dai J

Observational Study

- 10097** Dementia-related contact experience, attitudes, and the level of knowledge in medical vocational college students

Liu DM, Yan L, Wang L, Lin HH, Jiang XY

SYSTEMATIC REVIEWS

- 10109** Link between COVID-19 vaccines and myocardial infarction

Zafar U, Zafar H, Ahmed MS, Khattak M

CASE REPORT

- 10120** Successful treatment of disseminated nocardiosis diagnosed by metagenomic next-generation sequencing: A case report and review of literature

Li T, Chen YX, Lin JJ, Lin WX, Zhang WZ, Dong HM, Cai SX, Meng Y

- 10130** Multiple primary malignancies - hepatocellular carcinoma combined with splenic lymphoma: A case report

Wu FZ, Chen XX, Chen WY, Wu QH, Mao JT, Zhao ZW

- 10136** Metastatic multifocal melanoma of multiple organ systems: A case report

Maksimaityte V, Reivytyte R, Milaknyte G, Mickys U, Razanskiene G, Stundys D, Kazenaite E, Valantinas J, Stundiene I

- 10146** Cavernous hemangioma of the ileum in a young man: A case report and review of literature

Yao L, Li LW, Yu B, Meng XD, Liu SQ, Xie LH, Wei RF, Liang J, Ruan HQ, Zou J, Huang JA

- 10155** Successful management of a breastfeeding mother with severe eczema of the nipple beginning from puberty: A case report

Li R, Zhang LX, Tian C, Ma LK, Li Y

- 10162** Short benign ileocolonic anastomotic strictures - management with bi-flanged metal stents: Six case reports and review of literature

Kasapidis P, Mavrogenis G, Mandrekas D, Bazerbachi F

- 10172** Simultaneous bilateral floating knee: A case report

Wu CM, Liao HE, Lan SJ

- 10180** Chemotherapy, transarterial chemoembolization, and nephrectomy combined treated one giant renal cell carcinoma (T3aN1M1) associated with Xp11.2/TFE3: A case report

Wang P, Zhang X, Shao SH, Wu F, Du FZ, Zhang JF, Zuo ZW, Jiang R

- 10186** Tislelizumab-related enteritis successfully treated with adalimumab: A case report

Chen N, Qian MJ, Zhang RH, Gao QQ, He CC, Yao YK, Zhou JY, Zhou H

- 10193** Treatment of refractory/relapsed extranodal NK/T cell lymphoma with decitabine plus anti-PD-1: A case report
Li LJ, Zhang JY
- 10201** Clinical analysis of pipeline dredging agent poisoning: A case report
Li YQ, Yu GC, Shi LK, Zhao LW, Wen ZX, Kan BT, Jian XD
- 10208** Follicular lymphoma with cardiac involvement in a 90-year-old patient: A case report
Sun YX, Wang J, Zhu JH, Yuan W, Wu L
- 10214** Twin reversed arterial perfusion sequence-a rare and dangerous complication form of monochorionic twins: A case report
Anh ND, Thu Ha NT, Sim NT, Toan NK, Thuong PTH, Duc NM
- 10220** Potential otogenic complications caused by cholesteatoma of the contralateral ear in patients with otogenic abscess secondary to middle ear cholesteatoma of one ear: A case report
Zhang L, Niu X, Zhang K, He T, Sun Y
- 10227** Myeloid sarcoma with ulnar nerve entrapment: A case report
Li DP, Liu CZ, Jeremy M, Li X, Wang JC, Nath Varma S, Gai TT, Tian WQ, Zou Q, Wei YM, Wang HY, Long CJ, Zhou Y
- 10236** Alpha-fetoprotein-producing hepatoid adenocarcinoma of the lung responsive to sorafenib after multiline treatment: A case report
Xu SZ, Zhang XC, Jiang Q, Chen M, He MY, Shen P
- 10244** Acute mesenteric ischemia due to percutaneous coronary intervention: A case report
Ding P, Zhou Y, Long KL, Zhang S, Gao PY
- 10252** Persistent diarrhea with petechial rash - unusual pattern of light chain amyloidosis deposition on skin and gastrointestinal biopsies: A case report
Bilton SE, Shah N, Dougherty D, Simpson S, Holliday A, Sahebjam F, Grider DJ
- 10260** Solitary splenic tuberculosis: A case report
Guo HW, Liu XQ, Cheng YL
- 10266** Coronary artery aneurysms caused by Kawasaki disease in an adult: A case report and literature review
He Y, Ji H, Xie JC, Zhou L
- 10273** Double filtration plasmapheresis for pregnancy with hyperlipidemia in glycogen storage disease type Ia: A case report
Wang J, Zhao Y, Chang P, Liu B, Yao R
- 10279** Treatment of primary tracheal schwannoma with endoscopic resection: A case report
Shen YS, Tian XD, Pan Y, Li H
- 10286** Concrescence of maxillary second molar and impacted third molar: A case report
Su J, Shao LM, Wang LC, He LJ, Pu YL, Li YB, Zhang WY

- 10293** Rare leptin in non-alcoholic fatty liver cirrhosis: A case report
Nong YB, Huang HN, Huang JJ, Du YQ, Song WX, Mao DW, Zhong YX, Zhu RH, Xiao XY, Zhong RX
- 10301** One-stage resection of four genotypes of bilateral multiple primary lung adenocarcinoma: A case report
Zhang DY, Liu J, Zhang Y, Ye JY, Hu S, Zhang WX, Yu DL, Wei YP
- 10310** Ectopic pregnancy and failed oocyte retrieval during *in vitro* fertilization stimulation: Two case reports
Zhou WJ, Xu BF, Niu ZH
- 10317** Malignant peritoneal mesothelioma with massive ascites as the first symptom: A case report
Huang X, Hong Y, Xie SY, Liao HL, Huang HM, Liu JH, Long WJ
- 10326** Subperiosteal orbital hematoma concomitant with abscess in a patient with sinusitis: A case report
Hu XH, Zhang C, Dong YK, Cong TC
- 10332** Postpartum posterior reversible encephalopathy syndrome secondary to preeclampsia and cerebrospinal fluid leakage: A case report and literature review
Wang Y, Zhang Q
- 10339** Sudden extramedullary and extranodal Philadelphia-positive anaplastic large-cell lymphoma transformation during imatinib treatment for CML: A case report
Wu Q, Kang Y, Xu J, Ye WC, Li ZJ, He WF, Song Y, Wang QM, Tang AP, Zhou T
- 10346** Relationship of familial cytochrome P450 4V2 gene mutation with liver cirrhosis: A case report and review of the literature
Jiang JL, Qian JF, Xiao DH, Liu X, Zhu F, Wang J, Xing ZX, Xu DL, Xue Y, He YH
- 10358** COVID-19-associated disseminated mucormycosis: An autopsy case report
Kyuno D, Kubo T, Tsujiwaki M, Sugita S, Hosaka M, Ito H, Harada K, Takasawa A, Kubota Y, Takasawa K, Ono Y, Magara K, Narimatsu E, Hasegawa T, Osanai M
- 10366** Thalidomide combined with endoscopy in the treatment of Cronkhite-Canada syndrome: A case report
Rong JM, Shi ML, Niu JK, Luo J, Miao YL
- 10375** Thoracolumbar surgery for degenerative spine diseases complicated with tethered cord syndrome: A case report
Wang YT, Mu GZ, Sun HL

LETTER TO THE EDITOR

- 10384** Are pregnancy-associated hypertensive disorders so sweet?
Thomopoulos C, Ilias I
- 10387** Tumor invasion front in oral squamous cell carcinoma
Cuevas-González JC, Cuevas-González MV, Espinosa-Cristobal LF, Donohue Cornejo A

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Malignant peritoneal mesothelioma with massive ascites as the first symptom: A case report

Xi Huang, Yu Hong, Si-Ya Xie, Hui-Li Liao, Hao-Ming Huang, Jian-Hong Liu, Wen-Jie Long

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Abstract

BACKGROUND

Malignant peritoneal mesothelioma (MPM) is an extremely rare tumor with nonspecific clinical manifestations, which is extremely difficult to diagnose. Herein, we reported a case of MPM in the abdominal cavity with massive short-term ascites as the first symptom.

CASE SUMMARY

A 65-year-old woman presented to the hospital with abdominal pain, distention, and shortness of breath that persisted for 15 d. The serum CA-125 level was 1075 U/mL. The abdominal computed tomography showed massive ascites and no obvious tumor lesions. The pathological examination of the ascitic fluid showed numerous heterotypic cells with some papillary structures. The immunohistochemistry and fluorescence *in situ* hybridization showed the deletion of CDX2 (-), WT-1 (-), Ki-67 (about 10% +), CEA (-), Glut-1 (+++), desmin (-), PD-L1 (-), and CDKN2A (P16). The final diagnosis was MPM. The patient refused tumor cytoreductive surgery and received two cycles of cisplatin plus pemetrexed bidirectional chemotherapy. In the second cycle, she received an additional cycle of hyperthermic intraperitoneal chemotherapy and immune checkpoint inhibitor therapy due to massive recalcitrant ascites. She died of disease progression 2 mo after diagnosis.

CONCLUSION

In case of massive unexplained ascites, the possibility of MPM should not be excluded to avoid misdiagnosis and delay in treatment.

Key Words: Malignant peritoneal mesothelioma; Ascites; Immunohistochemistry; Chemotherapy; Immunotherapy; Case report

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Core Tip: Malignant peritoneal mesothelioma (MPM) is an extremely rare tumor with nonspecific clinical manifestations, which is extremely difficult to diagnose. Herein, we reported a case with massive ascites as the first symptom. The patient was diagnosed with MPM based on a combination of histological, immune, and imaging findings. The patient refused tumor cytoreductive surgery and then received bidirectional chemotherapy, hyperthermic intraperitoneal chemotherapy, and immune checkpoint inhibitor therapy. Unfortunately, she died of disease progression two months after diagnosis. This case report aims to provide clinical evidence for the diagnosis, treatment, and prognosis of rare MPM.

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INTRODUCTION

Mesothelioma is a rare malignancy of serosal membranes. It commonly appears in the visceral pleura but may also be seen in the peritoneum[1]. Patients with malignant peritoneal mesothelioma (MPM) may have different symptoms, including abdominal distention, abdominal pain, early satiety, weight loss, nausea, new hernias, unexplained fever, night sweats, and so forth[2,3]. In addition, acute abdominal symptoms due to malignant intestinal obstruction or perforation have also been reported[4]. At present, there is no specific diagnosis for abdominal mesothelioma[5].

Herein, we reported a case of MPM in the abdominal cavity with massive short-term ascites as the first symptom. The patient was diagnosed by the pathological examination of ascites and exfoliated cells and genetic testing.

CASE PRESENTATION

Chief complaints

A 65-year-old female patient sought medical attention for abdominal distention and shortness of breath that persisted for 15 d.

History of present illness

The aforementioned symptoms appeared half a month ago with no apparent cause, and the patient felt as if her symptoms were worsening.

History of past illness

She had a history of high blood pressure and type 2 diabetes but no history of asbestos exposure.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

On admission to the hospital, she had a distended abdomen, with an abdominal circumference of 111 cm, slight tension in the abdominal muscles, mild tenderness, and mobile dullness. She reported a weight gain of 5 kg in 1 mo.

Laboratory examinations

The findings of blood tests and routine examination of ascites are shown in Table 1. After collection,

Table 1 Blood test and routine examination of ascites

Specimen	Item	First diagnosis (November 8)	Before the first chemotherapy (November 27)	After the first chemotherapy (December 9)	Before the first immunotherapy (December 13)	After the first immunotherapy (December 26)
Blood	CEA (ng/mL)	1.18		1.38		
	PLT (E+9/L)	598	527	235	312	290
	CA125 (U/mL)	1075	395.2	314.7	354.6	
	CA199 (U/mL)	23.77	-	45.47	38.57	
	HE4 (pmol/L)	235.5	-	-	207.6	
	ALB (g/L)	34.3	36.1	33.7	27.2	30.7
	T-SPOT	Negative				
Ascites	TP (g/L)	50.4	-	26.7		
	ADA (U/L)	11	-	7		
	Color	Yellow	-	Yellow		
	RBC (E+6/L)	5000	-	1000		
	WBC (E+6/L)	2149	-	209		
	CEA (ng/mL)	0.73				

CEA: Carcinoembryonic antigen; PLT: Platelet count; CA125: Carbohydrate antigen 125; CA199: Carbohydrate antigen 199; HE4: Human epididymis protein 4; ALB: Albumin; TP: Total protein; ADA: Adenosine deaminase; RBC: Red blood cell; WBC: White blood cell.

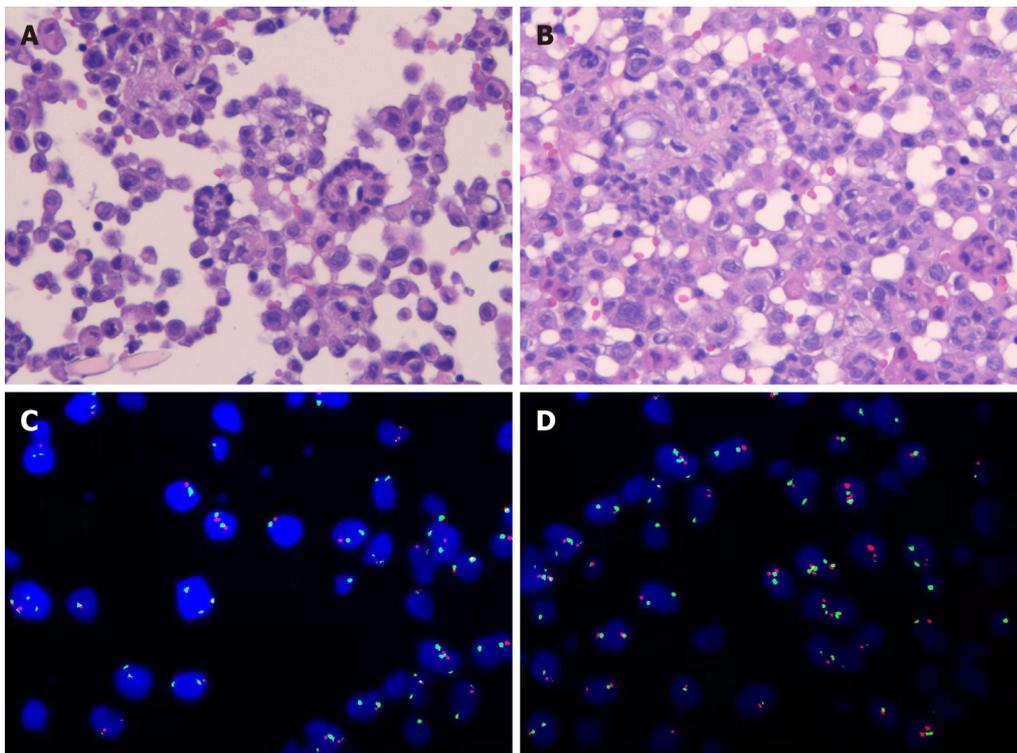
ascitic fluid was sent for pathological examination and immunohistochemistry. The final report of liquid-based cell preparation and cell-block hematoxylin and eosin (HE)-stained section indicated numerous atypical cells, some of which had papillary structures. The immunohistochemical (IHC) markers were as follows: CK (+), CK20 (-), Villin (-), CDX2 (-), CR (+), WT-1 (-), SATB-2 (scattered +), Ki-67 (about 10% +), TTF-1 (-), CEA (-), Pax-8 (-), P16 (individual +), M-mell (-), and Glut-1 (+++), and desmin (-). fluorescence *in situ* hybridization (FISH) detected CDKN2A (P16) gene deletion and PD-L1 (-) (Figure 1).

Imaging examinations

The contrast-enhanced computed tomography (CT) showed a large volume of ascites in the abdominal cavity, but no abdominal wall thickening or intra-abdominal soft-tissue shadow was observed (Figure 2). However, subsequent pelvic enhancement magnetic resonance imaging (MRI) revealed mild peritoneal thickening (Figure 3).

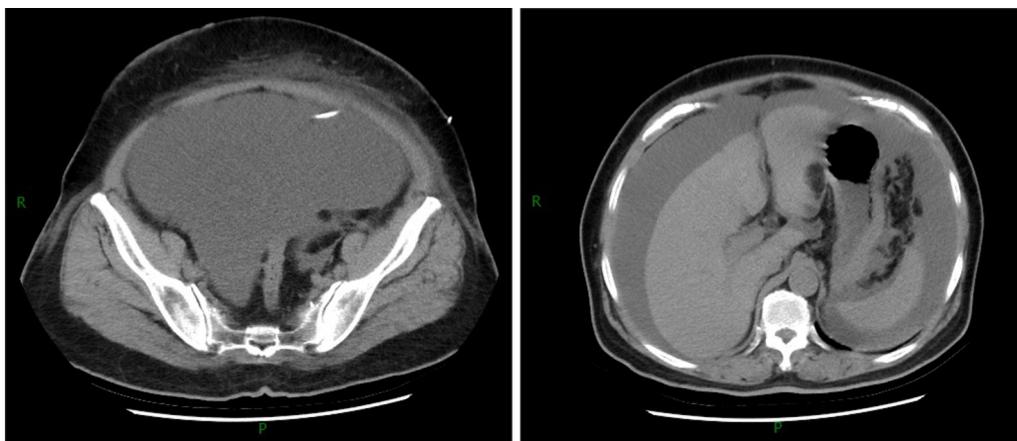
MULTIDISCIPLINARY EXPERT CONSULTATION

Cases of MPM are rare, and their diagnosis is difficult. A pathological analysis indicated that ascitic fluid contains numerous proliferating cells with papillary structure formation and a few scattered atypical proliferating cells with SATB2 positivity. However, the results could not distinguish between epithelial-derived tumors and mesothelial-derived lesions. Thus, the recommendations were as follows: (1) Perform immunohistochemistry for BerEP4, CDX2, BAP1, EMA, SATB2, and P53 to assist in the diagnosis; and (2) Provide a comprehensive assessment of the detailed clinical picture (any history of gastrointestinal disease, any thickening of the pleura and peritoneum, *etc.*). However, the patient and her family refused further immunohistochemistry and laparoscopy.



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Figure 1 Histopathological and fluorescence *in situ* hybridization features. A and B: A large number of heterozygous cells, some of which are papillary structures, increased nucleocytoplasmic ratio, hyperchromatic nuclei, and obvious atypia (hematoxylin and eosin stain; scale bar: 100 μ m); C and D: Fluorescence *in situ* hybridization detection results: CDKN2A (P16) probe (+), number of missing cells/total counted cells = 41%.



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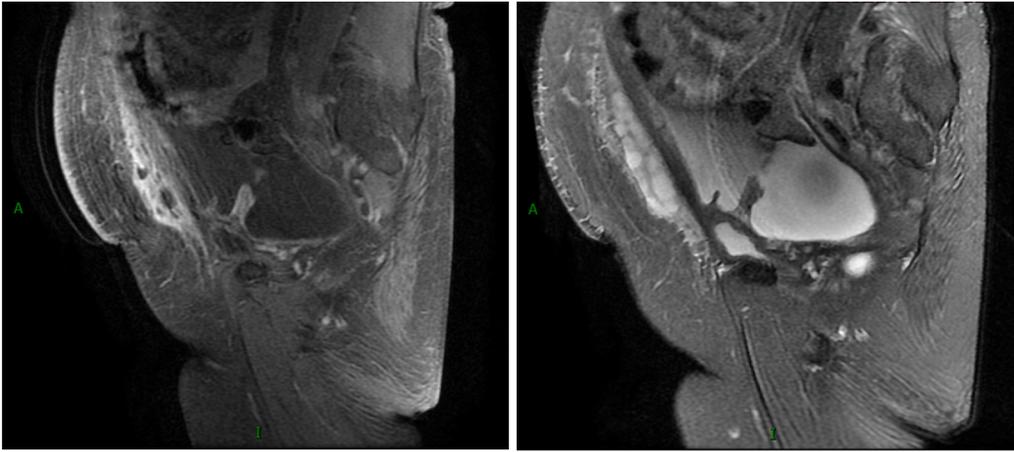
Figure 2 Abdominal computed tomography showed massive ascites without parenchymal lesions.

FINAL DIAGNOSIS

The patient was diagnosed with MPM based on a combination of cytological, immune, and imaging tests.

TREATMENT

The patient refused cytoreductive surgery (CRS) and only received two cycles of cisplatin plus pemetrexed bidirectional chemotherapy. She received an additional cycle of hyperthermic intraperitoneal chemotherapy (HIPEC) and immune checkpoint inhibitor therapy in the second cycle of chemotherapy because of massive recalcitrant ascites.



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Figure 3 Enhanced magnetic resonance imaging showed massive peritoneal fluid accumulation and mild peritoneal thickening.

OUTCOME AND FOLLOW-UP

The patient was scheduled to return for the third course of chemotherapy on January 13, 2022, but she passed away at home on January 12, 2022, due to disease progression.

DISCUSSION

MPM is a rare tumor that originates from mesothelioma cells on the surface of the peritoneum. The incidence of MPM in the population is about 1-2/100 million. Peritoneal mesothelioma is more common in women than pleural mesothelioma, and its association with asbestos exposure is weak. It often manifests as nonspecific symptoms such as abdominal pain, bloating, ascites, abdominal mass, gastrointestinal symptoms, and so forth. Therefore, MPM may be easily confused with peritonitis and peritoneal neoplastic lesions, such as tuberculous peritonitis, mesenteric lipid membrane inflammation, peritoneal pseudomyxoma, peritoneal metastasis, lymphoma, primary peritoneal serous carcinoma, mesenteric fibromatosis, *etc.*[5]. As observed in our patient, thrombocytosis was previously reported in some patients with malignant abdominal mesothelioma, but the specific pathogenesis is unclear[6].

No uniform criteria exist for diagnosing MPM. We propose a combination of clinical manifestations, imaging, and pathological features. The patient in this case presented with complaints of massive ascites and abdominal distention, which are common but nonspecific presentations of MPM.

CT is currently recommended as the first-choice examination. In intravenous contrast-enhanced CT images, soft-tissue shadows with irregular margins and large omental nodules or peritoneal thickening are often seen[5,7]. No solid tumor signs were seen on the mesentery, omentum, and peritoneum in this patient. However, a large amount of ascites and fatty edema of the abdominal wall were observed. The pelvic enhancement MRI showed mild peritoneal thickening, and the left lower abdominal wall subcutaneous fascia was in the shape of a mass with segmentation shadows. The enhancement scan was not uniformly enhanced, and the adjacent abdominal muscle was swollen. Because of the aggressive nature of MPM, the possibility of peritoneal lesions combined with abdominal wall infiltration could not be excluded. Notably, a slightly thickened pleura was seen bilaterally on enhanced CT images, but no pleural effusion and mediastinal lymph node enlargement were found. The patient had no respiratory symptoms such as dyspnea, chest pain, cough, and expectoration and lacked the pathological examination results of the pleura. Therefore, we could not determine whether pleural metastasis occurred. In a series of 33 MPM cases based on CT scans, nearly a quarter of the patients with peritoneal mesothelioma had pleural abnormalities[8].

Confirming mesothelioma diagnosis requires histopathologic analysis, with the fine-needle aspiration of biopsies and laparoscopy being the common means of performing tests. The histological analysis can identify the histological subtype, grade, and degree of infiltration of mesothelioma. However, our patient refused tumor CRS.

Diagnostic paracentesis is the primary means of obtaining ascites for evaluation, and some epithelioid carcinomas can release malignant cells into the ascites. Given the large volume of ascites, we performed the cytological examination of exfoliated cells by examining the ascitic fluid to distinguish benign from malignant mesothelial lesions. The cytological diagnosis included HE staining and IHC staining. A large number of proliferating heterogeneous cells were seen in HE-stained sections of ascites and exfoliated cell blocks, which were suspected to be malignant tumor cells. However, a morphological overlap

existed between the atypical reactive mesothelial hyperplasia and malignant mesothelioma. Hence, further immunochemical staining was performed to clarify the diagnosis and origin of the tumor. The IHC technique improved the reliability of pure cytology diagnosis.

Since most of the markers are not 100% specific for different types of tumors, the International Mesothelioma Interest Group recommends that the detection of tumor markers should include at least two mesothelioma markers in addition to pan-cytokeratin. Calretinin (CR), cytokeratin 5/6, WT-1, and podoplanin are the best positive mesothelioma markers in identifying tumor cell origin, whereas claudin 4, MOC31, BER-EP4, CEA, B72.3, BG8, TTF-1, and Napsin A are the best markers of epithelial origin. However, variations in antibody staining are seen between laboratories; therefore, the guidelines do not recommend a specific group of antibodies[9].

In contrast, the inconsistency in the response of the mesothelial spectrum markers calretinin and WT-1 on exfoliated cell blocks selected by our laboratory does not categorize the mesothelial origin, although the sensitivity of WT-1 for mesothelioma ranges from 70% to 100%. An analysis of a single-center study found that among 218 cases of peritoneal mesothelioma, all patients were immunoreactive positive for calretinin, 94% of whom exhibited WT1 expression. In the remaining 13 WT-1-negative cases, the laboratory used four negative malignant epithelial tumor markers, including B72.3 ($n = 13$), CEA ($n = 11$), Ber-EP4 ($n = 12$), and CD15 ($n = 12$), to support the diagnosis of mesothelioma[10]. Establishing mesothelial lineage is the first step in diagnosing malignant mesothelioma (MM), and it is particularly important to select markers with high sensitivity and specificity. Recent studies have shown that HEG1 shows higher sensitivity and specificity than calmodulin, D2-40, and WT-1, which may serve as an effective diagnostic tool for MM[11].

PAX-8 is a transcription factor involved in the development of the thyroid, kidney, and Müllerian duct systems and is also expressed in the thyroid, renal cell, ovarian, cervical, endometrial, thymic epithelial, and ocular epithelial cancers. Although its immunoreactivity in peritoneal mesothelioma ranges from 0% to 9%, PAX-8 remains a key IHC marker to discriminate between carcinoma and mesothelioma, especially in a group of negative antibodies[10,12]. CK20 is an important component of the intestinal epithelium and is expressed exclusively on the gastrointestinal epithelium, urinary epithelium, Merkel cells of the epidermis, and malignant tumors originating from these sites. Studies have shown a lack of CK20 reactivity in MM; only one case report of diffuse and strongly positive mesothelioma for CK20 is available[13]. Therefore, the IHC results in this case showing cancer markers of CK20 (-), Pax-8 (-), CEA (-), and TTF-1 (-) largely support the diagnosis of mesothelioma.

In some cases, morphologically distinguishing benign from malignant mesothelial hyperplasia is difficult, especially when evaluating effusion cell specimens. The five mesothelioma markers desmin, GLUT-1, EMA, p53, and IMP-3 are no longer recommended for the routine differentiation of benign from malignant mesothelial lesions[14]. p16 pure hapten deletion was found to be 100% specific for MM by FISH. However, it has never been reported in benign mesothelial hyperplasia. Therefore, the detection of p16 (CDKN2A) deletion by FISH, in this case, supported the diagnosis of MM. Similarly, BaP1, MTAP, 5-hmC, and EZH2 have high specificity for MM. A new routine diagnostic marker will be developed in the future after combining these markers or changing their detection methods to improve sensitivity[15]. Some studies have also confirmed the value of circulating and tissue microRNAs in the early diagnosis of MM. However, large-scale and standardized studies are needed to verify and evaluate the clinical relevance of circulating and tissue microRNAs[16].

In terms of differential diagnosis, peritoneal carcinoma can have an ovarian, fallopian tube, gastric, pancreatic, colonic, renal, pulmonary, and, more rarely, breast origin. In this case report, the negative CK20, CDX2, TTF1, CEA, PAX8, and Des are important to exclude gastrointestinal, pulmonary, ovarian, and renal tumor metastases.

MPM is considered to be a chemotherapy-resistant malignant tumor. CRS combined with HIPEC is a commonly used treatment regimen for MPM. Some studies have found that this regimen can improve the survival rate of patients with MPM. However, the CT results of the patient revealed no signs of tumor in the peritoneum, which might be due to the small tumor size. Therefore, bidirectional chemotherapy was used instead.

Bidirectional chemotherapy is a promising, well-tolerated treatment that can simultaneously kill cancer cells from both sides (peritoneal cavity and peripheral blood vessels) *via* simultaneous intraperitoneal perfusion and intravenous administration. It can also improve resection rates in patients with diffuse MPM, which was initially considered unresectable or borderline resectable[17]. The best treatment is cisplatin in combination with pemetrexed, while the combination of cisplatin and gemcitabine is the second choice[18]. HIPEC is a potential therapeutic strategy for patients with refractory malignant ascites who cannot undergo curative CRS. Randle *et al*[19] found complete resolution of malignant ascites in 93% of patients after HIPEC. In the present case, the patient also had a significant resolution of ascites after receiving a course of HIPEC.

At present, immune checkpoint inhibitor therapy is the focus of anti-tumor therapy. The future challenge will be to assess a four-drug combination with bevacizumab, anti-PD-1/PDL1 antibody, pemetrexed, and platinum, which has recently been proven efficient in patients with non-small cell lung cancer, given that a biological rationale supports the synergy between anti-VEGF therapy and immunotherapeutics. Local regional adjuvant therapy (early postoperative intraperitoneal chemotherapy and/or normothermic intraperitoneal chemotherapy) associated with systemic chemotherapy may also be

beneficial in adequate clinical conditions[20]. A multi-center, double-blind, randomized phase 3 trial of nivolumab (an antibody against PD-1) was conducted in patients with MM who had previously relapsed after first-line platinum chemotherapy. The results showed that the median progression-free survival and median overall survival was 3.0 and 10.2 mo, respectively, in the nivolumab group and 1.8 and 6.9 mo, respectively, in the placebo group[21]. In a double-blind, phase 3 randomized study of nivolumab *vs.* placebo in patients with unresectable MM, the survival (median, 9.2 *vs.* 6.6 mo) and PFS (time to event) were longer (median, 3.0 *vs.* 1.8 mo) after nivolumab treatment[22]. In the two open-label, single-arm, phase 2 studies, among patients with measurable and unresectable MM and/or disease progression after the first-line platinum regimen, 3%-7% of patients achieved partial remission, and 31%-38% of patients were under control after receiving trametamab[23]. However, in the subsequent double-blind, placebo-controlled, phase 2B trials, the median overall survival of the intention-to-treat population did not differ between the treatment and comfort groups[24]. Although some data suggested that immunotherapy had a certain effect on MPM, this case report did not support the aforementioned treatment strategy, and hence more clinical studies are needed for confirmation in the future.

Patients with MPM have a poor prognosis with a median survival of 3-6 mo if not treated, 11-17 mo with chemotherapy alone, and 55-61 mo with CRS combined with HIPEC, with a 5-year survival rate of 52% [25,26]. Our patient did not undergo surgery and died after two courses of bidirectional chemotherapy (with the addition of intraperitoneal thermoperfusion chemotherapy and immunotherapy in the second course), just 2 mo after the first visit[27]. The patient's sudden disease progression after receiving chemotherapy might be related to insensitivity to chemotherapy or the high disease progression after treatment with immune checkpoint inhibitors[28], in addition to the p16/CDKN2A deletion and negative WT-1 expression that was related to a poorer prognosis[29].

CONCLUSION

In this study, we reported the case of a female patient with peritoneal mesothelioma, which is a rare and difficult-to-diagnose malignancy. The patient presented with massive ascites, no history of asbestos exposure, and no obvious signs of tumor on CT, and was finally diagnosed based on the histology and immunohistochemistry of cells shed from the ascites. Unfortunately, the patient died due to disease progression after two courses of anti-neoplastic therapy. Clinicians should consider the possibility of MPM in case of massive unexplained ascites. In addition, patients with MPM have a poor prognosis, and CRS combined with HIPEC for patients who can tolerate surgery or have resectable lesions may improve the prognosis.

FOOTNOTES

Author contributions: Huang X and Hong Y are the co-first authors who contributed equally, organized the case content, and wrote the manuscript; Xie SY and Huang HM wrote the manuscript and organized the images; Liao HL wrote and reviewed the manuscript and organized the table; Long WJ and Liu JH were responsible for the supervision and review of the manuscript.

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