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Case Report:

Malignant peritoneal mesothelioma presenting with persistent high fever

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Abstract: Malignant peritoneal mesothelioma (MPM) is a rare tumor that develops in the peritoneum. In this paper, we describe an extremely rare case of MPM metastasizing to the appendix in a 48-year-old female who initially presented with a persistent high fever. The woman reported a slight lower abdominal discomfort which had been relieved by urination for four months. She had lost 5 kg of weight. There was no nausea, vomiting, diarrhea, abdominal pain, or abdominal distension. Many broad spectrum antibiotics were given without relief of fever. Computed tomography (CT) scans revealed a thickened omentum majus and diffused multiple omental nodules. An omentectomy, appendectomy, and adnexectomy were carried out. A gross pathologic specimen of omentum tissue revealed a firm gray-white mass. Microscopic and immunohistochemical examinations confirmed the diagnosis of appendiceal and bilateral adnexal metastases of an MPM. These results suggest that MPM should be considered in the differential diagnosis of unexplained persistent high fever. Awareness of such atypical presentations of mesothelioma may help to make a correct diagnosis.

Key words: Malignant peritoneal mesothelioma, High fever, Metastasis
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1 Introduction

Malignant peritoneal mesothelioma (MPM) is a rare tumor that develops in the peritoneum. Most patients present with abdominal distension and/or pain; some present with ascites, tenderness, and palpable masses (Munkholm-Larsen *et al*., 2009). Persistent high fever is exceptional. Owing to the non-specificity of these clinical symptoms, the diagnosis is difficult to make during the early stages of the disease. Here, we describe an extremely rare case of MPM metastasizing to the appendix in a female who initially presented with persistent high fever.

2 Case presentation

A 48-year-old woman presented with persistent high fever. She was a non-smoker and her husband was a farmer. She had been well until four months prior to admission, when she began experiencing chills and fever ranging from 39 to 40 °C. She also reported a slight lower abdominal discomfort which had been relieved by urination. Weight loss of 5 kg and anorexia occurred in the last two months without nausea, vomiting, diarrhea, abdominal pain, or abdominal distension.

Physical examination are shown as follows: temperature 39.5 °C, blood pressure 104/73 mmHg, heart rate 96 beats/min, and respiratory rate 20 breaths/min. Results from chest, heart, and abdominal examinations were unremarkable. Laboratory investigations revealed a white blood cell count

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of 7.7×10^9 L^{-1}, hemoglobin of 7.8 g/dl, and a platelet count of 450×10^9 L^{-1}. The raised C-reactive protein level was 119.5 mg/L and the erythrocyte sedimentation rate was more than 140 mm/h. Blood chemistry was normal. The serum CA-125 level was 63.6 U/ml (ref. 0 to 35 U/ml) and the CA-153 level was 34.3 U/ml (ref. 0 to 25 U/ml). Carcinoembryonic antigen and CA19-9 levels were normal. An assay for the presence of immunoglobulin G (IgG) antibodies to Epstein-Barr virus (EBV) was positive. Assays for immunoglobulin M (IgM) anti-EBV antibody, hepatitis B antigen and antibody, the antinuclear antibody series, and the human immunodeficiency virus (HIV) screening antibody were negative. Results from a purified protein derivative test, four sets of blood cultures, serum and urine protein electrophoresis, and a chest radiograph were all negative. A bone marrow aspiration and biopsy were normal.

Piperacillin/tazobactam, levofloxacin, and metronidazole were given without relief of fever or symptoms. Computed tomography (CT) scans of the abdomen and pelvis were performed, which revealed a thickened omentum majus and diffuse multiple omental nodules (Fig. 1).

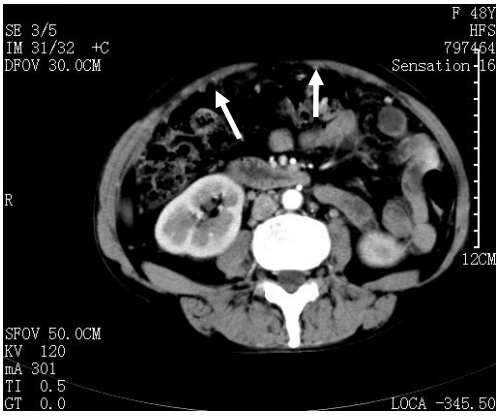

Fig. 1 Computed tomography (CT) scans of the abdomen and pelvis

The result revealed the obviously thickened omentum majus with diffused multiple omental nodules (arrows)

Laparoscopy was performed. Multiple nodules within the omentum majus and small intestinal wall and a small amount of ascites were found. A thickened omental cake adhered to the wall. There were numerous adhesions between the uterus, urinary bladder, and rectum; part of the intestinal canal adhered to the right side of the pelvic cavity and the abdominal wall. An omentectomy, appendectomy, and adnexectomy were carried out. A gross pathologic specimen of omentum tissue revealed a firm gray-white mass. Microscopic (Fig. 2) and immunohistochemical (Fig. 3) examinations confirmed the diagnosis of appendix and bilateral adnexal metastases of an MPM. Chemotherapy was refused. She was discharged on Day 15 after surgery.

3 Discussion

Peritoneal mesothelioma was first described by Miller and Wynn (1908). It is a rare tumor that arises from mesothelial cells lining the peritoneal cavity. In the oncology literature before 2000, patients with MPM were reported to have a poor prognosis, with a median survival of less than one year (Markman and Kelsen, 1992; Eltabbakh *et al.*, 1999). Recent studies have reported a median survival of 60–90 months (Feldman *et al*., 2003; Sugarbaker *et al*., 2003). This improvement is attributed to progress in treatment. Yan *et al*. (2006) found a sex difference in the prognosis. Women had longer survival with an estimated five-year survival rate of 63%, compared with 42% for men. Current studies have found a strong association between peritoneal mesothelioma and asbestos exposure (Welch *et al*., 2005). The disease affects more men than women, possibly because of the higher male occupational exposure to asbestos. However, like our case, other cases of this abnormality are not related to asbestos exposure. Other etiologies or cofactors have been linked to malignant mesothelioma development, e.g., Simian virus 40 (SV40), genetic predisposition, and exposure to certain other mineral fibers such as erionite (Yang *et al*., 2008). The latent period between asbestos exposure and disease onset averages about 20–30 years (Chua *et al*., 2009).

The most frequently reported symptoms are abdominal pain (40%) and abdominal distension (40%). Conventional symptoms, such as weight loss and fever (20%), incidental findings (10%) (Munkholm-Larsen *et al*., 2009), night sweats, and hypercoagulability occur less frequently (Le *et al*., 2003). Presentations with fever of unknown origin (Sethna and Sugarbaker, 2005), intestinal obstruction

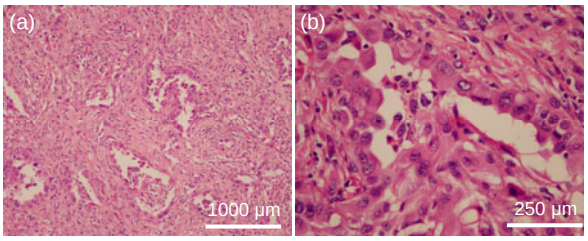

Fig. 2 Microscopic views showing epithelioid tumor cells with papillary or adenoidal structures, some spindle-shaped with interlacing fascicles and notable atypical nuclei
Stained with hematoxylin and eosin

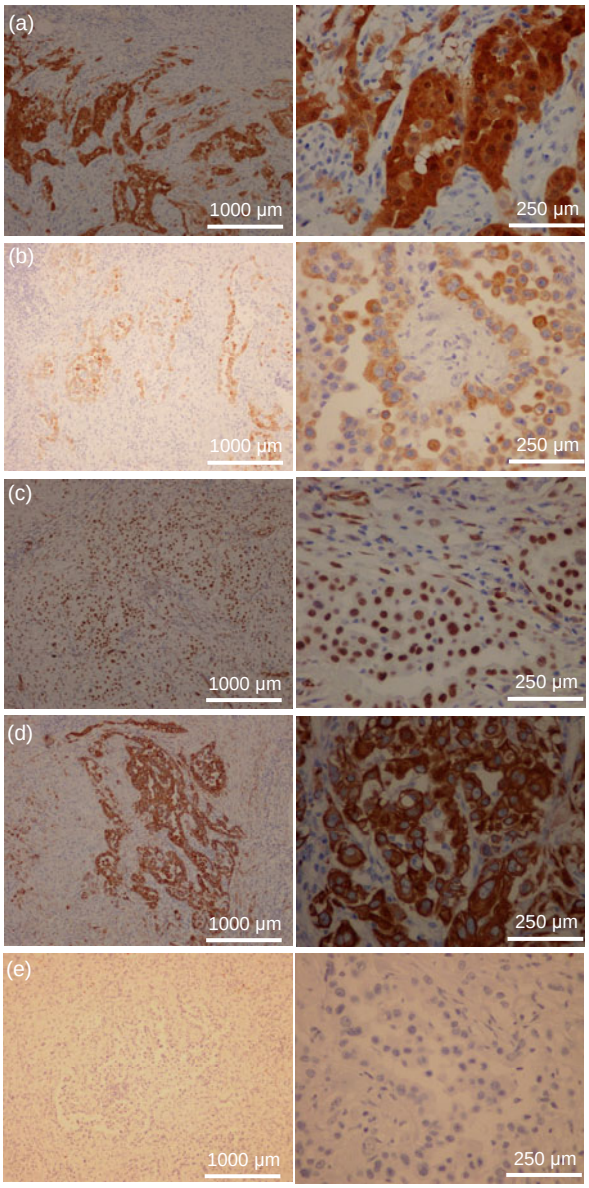

Fig. 3 Immunohistochemical preparation showing tumor cells positive for calretinin (a), CK5/6 (b), WT-1 (c), and pankeratin (d), and negative for CD15 (e)

(Kerrigan *et al*., 2003), or surgical emergency (Kerrigan *et al*., 2003; de Pangher Manzini, 2005) have been reported. To our knowledge, our case is the first report of MPM presenting with persistent high fever over such a long time. The reported cases of MPM presented with fever and other related symptoms. The complaint of slight discomfort in the lower abdomen, which is the critical clue to the diagnosis, was easily overlooked. Therefore, the detailed history is extremely important for identifying the key symptoms and making a correct diagnosis.

The definitive diagnosis of peritoneal mesothelioma depends on histologic and immunohistochemical examinations. Laparoscopic biopsy of the peritoneum with immunohistochemistry helps to increase diagnostic accuracy. MPM is characterized by positive staining for the following immunohistochemical markers: epithelial membrane antigen (EMA), calretinin, Wilms' tumor-1 protein (WT-1), cytokeratin 5/6, antimesothelial cell antibody-1, HBME-1, mesothelin, and thrombomodulin (Marchevsky, 2008; Yang *et al*., 2008). Recently, serum markers CA-125 and CA-153 have been found useful in the diagnosis and monitoring of peritoneal mesothelioma (Yang *et al*., 2008). Prospective serum markers for diagnosis and follow-up are soluble mesothelin-related protein (SMRP) and osteopontin. SMRP levels are elevated in more than 71% of mesotheliomas (Yang *et al*., 2008). In our case, immunohistochemistry found calretinin, cytokeratin 5/6 (CK5/6), WT-1, and pankeratin positive, and CD15 negative. Serum markers CA-125 and CA-153 were also elevated, but not specific for MPM.

The reported metastatic sites of MPM include the liver, lung, heart, brain, thyroid, adrenals, kidneys, pancreas, bone, soft tissue, skin, and lymph nodes (Pappa *et al*., 2006). Our case is the first report of MPM with appendiceal involvement.

The case presented is remarkable in two respects: first, presenting with persistent high fever, and second, the appendiceal metastasis of MPM.

4 Conclusions

MPM should be considered in the differential diagnosis of unexplained persistent high fever. A detailed history is vital for making the diagnosis.

Clinicians must pay more attention to the symptoms no matter how minor. Finally, CA-125 and CA-153 are helpful in making the diagnosis of MPM.

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