The diagnostic utility of PAX8 immunostaining of malignant peritoneal mesothelioma presenting as serous ovarian carcinoma: A single-center report of two cases

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Abstract. Malignant peritoneal mesotheliomas (MPMs) are rare and progressive tumors, which may present similarly to primary peritoneal carcinoma or ovarian carcinoma (OC). The current study reports two cases of MPM that initially presented with the features of OC, for which paired box 8 (PAX8) immunostaining was found to be useful for diagnosis. The two patients were women, aged 58 and 56 years, respectively. The primary presenting symptoms and clinical findings included prolonged abdominal pain, abdominal swelling and cough. The two cases were initially diagnosed as OC and were treated with primary debulking surgery. The patient in case 1 had no history of asbestos exposure, while the patient in case 2 did. Final diagnoses were determined based on histological and immunohistochemical results, which included negative PAX8 immunostaining, and which were consistent with MPM. The present cases demonstrated that PAX8 negativity may be a useful diagnostic biomarker for differentiating MPM from OC.

Introduction

Malignant peritoneal mesothelioma (MPM) is a rare disease that typically demonstrates a poor prognosis, with an average survival time of 6-12 months (1). The incidence in the United States is 200-400 novel cases annually (2). Although asbestos exposure is the primary risk factor for the development of MPM, only 30% of reported cases possess a history of asbestos exposure (3).

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The clinical and morphological distinction between MPM and serous ovarian carcinoma (OC) may be difficult due to their overlapping morphological features. This is particularly true when the latter is of low morphological grade and is associated with diffuse invasive peritoneal implants, or when high-grade serous carcinoma has metastasized to the pleura (4). Due to this, a number of studies have attempted to use a variety of immunohistochemical markers to distinguish between the two diseases (5,6). However, few immunostaining markers have proven to be sufficiently specific or sensitive for either type of cancer. Calretinin, Wilms tumor 1 (WT1), D2-40 and mesothelin are expressed in the majority of mesotheliomas (high sensitivity); however, these markers may additionally be expressed in a significant subset of serous OC cases (low specificity) (5). Alternative markers, including Ber-EP4, human epididymis protein 4, cluster of differentiation (CD)15 and B72.3, have been demonstrated to be expressed more frequently in serous OC compared with mesothelioma; however, poor sensitivity or specificity of these markers has limited their use as reliable discriminators (5).

Paired box 8 (PAX8) is a member of the paired box family of transcription factors, and is significant in organogenesis of the Müllerian system (7). In the Müllerian system, PAX8 is expressed in a variety of ovarian tumors, particularly serous carcinoma. Secretory cells of the normal fallopian tube are positive for PAX8 expression, and these cells are thought to be the origin of serous OC in a high proportion of cases (7). Previous studies have suggested that PAX8 immunostaining may be useful for differentiating MPM from serous OC with high specificity and sensitivity (5,6).

A delayed diagnosis of MPM is common due to the long interval between initial asbestos exposure and the onset of symptoms (3). Furthermore, the symptoms, including abdominal pain, ascites and abdominal distention without abdominal pain, are non-specific. Therefore, exact diagnosis of MPM is difficult, and it may appear to present as primary peritoneal carcinoma or OC (3). In the present study, two cases of MPM that were distinguished from OC by immunostaining for PAX8 are discussed.

Case report

Case 1

Patient. A 58-year-old (gravida 2, para 2) woman presented with abdominal distension. The patient had no history of exposure to asbestos, and no significant past medical or family history. The serum cancer antigen 125 (CA125) level was 90 U/ml (normal, <35 U/ml). The sialyl-Tn (STn) antigen level was within normal limits, and the general examination was also normal.

Pelvic magnetic resonance imaging (MRI) revealed small cysts in both ovaries, and lobular nodules at the surface of the ovaries (Fig. 1A). MRI additionally revealed peritonitis carcinomatosa, ascites, disseminated nodules and metastasis to the omentum. Contrast-enhanced computed tomography (CT) revealed a number of small lung nodules, and these findings were considered to represent metastasis to the lung. No lymphadenopathy was observed. Positron emission tomography (PET)-CT demonstrated abnormal fludeoxyglucose (FDG) uptake in the ovarian tumor, disseminated nodules and omentum. These findings suggested a diagnosis of OC.

A total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and omentectomy were performed. At the conclusion of primary debulking surgery (PDS), the residual tumor size was <1 cm in diameter. The resected specimens were reviewed by a pathologist and the mass was subsequently diagnosed as MPM.

The patient was discharged from hospital on the 14th post-operative day following an uneventful postoperative period. The patient was treated with chemotherapy (75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed) following PDS and remains alive without disease progression, 1 year subsequent to the completion of the first-line chemotherapy.

Pathological findings. Macroscopic examination revealed numerous nodular lesions in the pelvic cavity. Metastatic findings included metastasis to the omentum, measuring ~20 cm (omental cake). The tumor exhibited a number of clusters composed of cuboidal cells with eosinophilic cytoplasm, forming a tubular, papillary and solid arrangement (Fig. 1B). The clusters appeared to include two types of cells (epithelial-like and sarcomatoid-like cells; Fig. 1C and D). In the ovarian specimen, a number of clusters that included epithelial-like cells were observed at the surface of the ovary and infiltrated into the parenchyma of the ovary. There was no evidence of malignant cells in the oviduct or the fimbriae.

Immunohistochemical findings. Epithelial-like cells were positive for calretinin and CAM5.2. Thrombomodulin, D2-40, and CD10 were partially expressed. These cells were negative for WT1, carcinoembryonic antigen (CEA), estrogen receptor (ER), progesterone receptor, Ber-EP4 and PAX8.

Spindle cells were strongly positive for calretinin, CAM5.2 and vimentin. Thrombomodulin and D2-40 were partially expressed. These cells were negative for WT1, CEA, Ber-EP4, desmin, CD10 and PAX8 (Fig. 1E).

Case 2

Patient. A 56-year-old (gravida 1, para 1) woman presented with a cough. The patient had a history of exposure to asbestos, and had no significant past medical or family history. Serum CA125, CA19-9, CEA and STn antigen levels

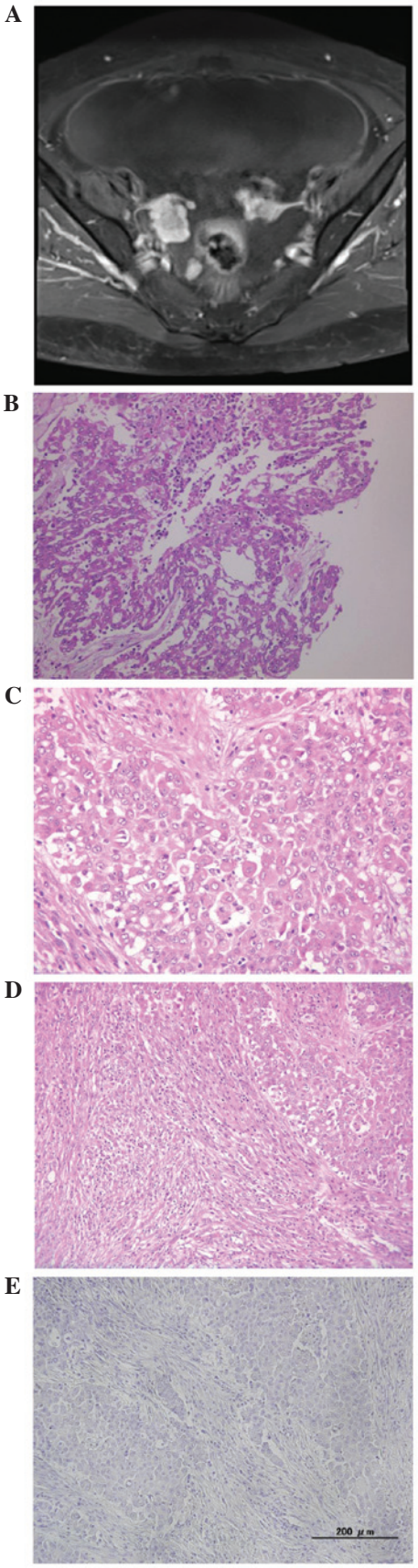

Figure 1. Case 1. (A) Magnetic resonance imaging of the pelvis showing small cysts in the ovaries and lobular nodules at the surface of the ovaries. (B) Cells with eosinophilic cytoplasm formed a tubular, papillary and solid arrangement (H&E; magnification, x100). (C) Epithelial-like cells. (H&E; magnification, x200). (D) Sarcomatoid-like cells (H&E; magnification, x100). (E) Negative paired box 8 immunohistochemical staining in malignant peritoneal mesothelioma (H&E; magnification, x100). H&E, hematoxylin and eosin staining.

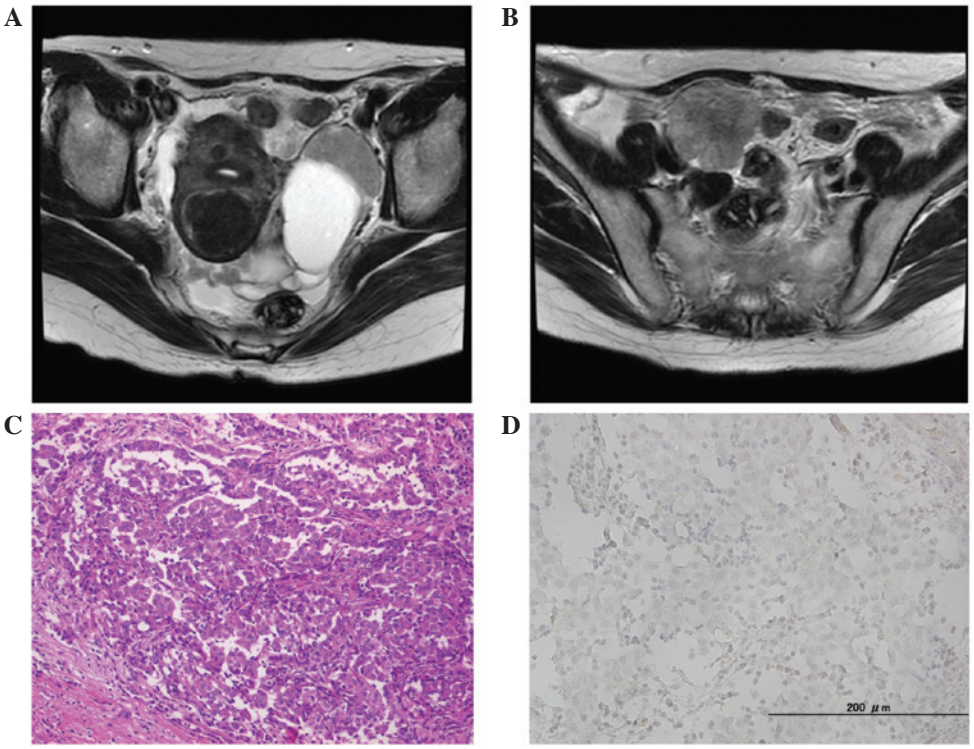

Figure 2. Case 2. (A) MRI T2-weighted imaging of the pelvis showing a mass with two cysts, measuring 99 x 42 mm, in the left adnexal region. (B) MRI T2-weighted imaging of the pelvis showing a solid mass, measuring 46x38 mm, in the right adnexal region. (C) Cells with eosinophilic cells formed a papillary and solid arrangement (hematoxylin and eosin staining; magnification, x50). (D) Negative paired box 8 immunohistochemical staining in malignant peritoneal mesothelioma (magnification, x200). MRI, magnetic resonance imaging.

were within normal limits, and the general examination was additionally normal.

Pelvic MRI revealed a mass with two cysts, measuring 99x42 mm, in the left adnexal region (Fig. 2A), and a solid mass, measuring 46x38 mm in the right adnexal region (Fig. 2B). It additionally revealed peritonitis carcinomatosa, ascites, disseminated nodules and metastasis to the omentum. No lymphadenopathy was observed. Contrast-enhanced CT suggested the possibility of thickened pleura, but there was no indication of metastasis to the lung. PET-CT revealed abnormal FDG uptake in the adnexal tumor, but no abnormal uptake in the pleura and lung. These results suggested a diagnosis of primary OC.

TAH, BSO and omentectomy were performed as the PDS. At the conclusion of surgery, residual tumors were <1 cm in diameter. The resected specimens were reviewed by a pathologist and the mass was subsequently diagnosed as MPM.

The patient was discharged from hospital on day 14 subsequent to surgery, following an uneventful postoperative period. The patient was treated with chemotherapy (75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed) following surgery, which was well-tolerated. The patient remains alive without disease progression 3 years subsequent to completion of first-line chemotherapy.

Pathological findings. Macroscopic examination revealed numerous nodular lesions in the abdominal cavity, including the ovary, omentum and ileum. The tumor exhibited a number of clusters composed of eosinophilic cells, forming a papillary and solid arrangement (Fig. 2C). Identical findings were observed in the ovary and ileum specimens.

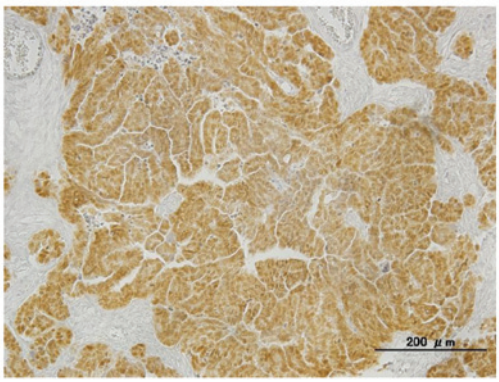

Figure 3. Strong positive paired box 8 immunohistochemical staining in a high-grade serous carcinoma (magnification, x100).

Immunohistochemical findings. Tumor cells were strongly positive for calretinin, cytokeratin (CK)7, CK20, D2-40 and CK5/6. CEA was partially expressed. The cells were negative for WT1, ER, Ber-EP4 and PAX8 expression (Fig. 2D).

Discussion

MPM is a rare malignancy of the peritoneum that typically remains confined to the abdominal cavity until the advanced stages of tumor progression. According to the World Health Organization classification, histological subtypes of MPM include epithelioid, sarcomatoid and biphasic (mixed epithelioid and sarcomatoid) (8). Treatment methods for MPM include cytoreductive surgery and hyperthermic

intraperitoneal chemotherapy; these therapies have resulted in an improvement in the survival of affected patients, with median survival times ranging from 29.5 to 94 months (9). All patients provided written informed consent to be included in the present study.

Patients with MPM do not present with distinctive symptoms, and the non-specific symptoms commonly observed make diagnosis and early treatment difficult. MPM is frequently misdiagnosed as OC. The clinical and morphological distinction between these malignancies may be difficult due a number of overlapping morphological features, including papillary structures, that exist between the two (4).

Imaging is a significant tool for diagnosis. However, pathological examination of biopsy or resection material is essential to confirm the diagnosis. In the present cases, it was not possible to differentiate MPM from OC by imaging alone.

Immunohistochemistry has a significant role in the distinction between MPM and serous OC. A panel of immunohistochemical antibodies is used to exclude malignant mesotheliomas; this panel includes WT1, calretinin, CK5/6 and BerEP4. An additional panel is typically performed to exclude adenocarcinoma of unknown origin and includes CK7/CK20, thyroid transcription factor 1, caudal type homeobox 2, gross cystic disease fluid protein 15 and WT1 (6). Although the aforementioned immunomarkers are useful, they have a number of limitations. Therefore, it is necessary to identify a marker with high sensitivity and specificity that may be added to the traditional immunohistochemistry panel of antibodies. PAX8 is a member of the PAX family of transcription factors, and previous studies have demonstrated that high levels of PAX8 expression are specific to serous adenocarcinoma, while all mesotheliomas are PAX8-negative (5-7). Our group has observed PAX8 nuclear positivity (Fig. 3) in 65/67 cases of serous adenocarcinoma (97%) (unpublished data).

In the present two cases, a diagnosis of MPM was confirmed through immunohistochemical evaluation, which revealed that both were negative for PAX8. The present immunohistological analyses were consistent with the aforementioned results regarding PAX8-negativity in mesotheliomas.

In conclusion, the present cases indicated that PAX8 immunostaining is a useful tool for differentiating MPM from serous OC, and it is important to consider rare clinical conditions, including peritoneal mesotheliomas, in patients exhibiting common and non-specific symptoms, including abdominal pain, ascites and abdominal distension without abdominal pain. Although MPM is a rare disease, the possibility of MPM should be considered in patients presenting with the aforementioned symptoms. In addition, a history of asbestos exposure is not essential for the disease to occur, and radiological assessment and traditional immunostaining evaluation may lead to misdiagnosis as it may be difficult to differentiate MPM from serous OC. Thus, a thorough comprehensive approach that includes PAX8 immunostaining is important for achieving a precise diagnosis and for the correct treatment of patients exhibiting MPM.

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