Clinical Case Report

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Primary malignant mesothelioma of the diaphragm with liver invasion

A case report and review of literature

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Abstract

Rationale: Malignant mesothelioma is a malignant tumor with poor prognosis, which usually originates in the pleura, peritoneum, and pericardial cavity. Mesotheliomas that originate from the diaphragm are very rare. Here, we report a case of primary malignant mesothelioma of the diaphragm with liver invasion.

Patient concerns: A 66-year-old woman was admitted to our hospital because of a "liver space-occupying lesion," without any special clinical symptoms. Imaging examinations suggested a cystic-solid mixed lesion in the right lobe of the liver.

Diagnosis: The tumor was diagnosed as epithelioid mesothelioma of the diaphragm with liver invasion.

Intervention: The patient underwent abdominal surgery in our hospital to remove the diaphragmatic mass, liver mass, and part of the diaphragm.

Outcomes: The postoperative course was uneventful.

Lessons: Primary diaphragmatic malignant mesothelioma is very rare and may involve liver or lung tissue and be mistaken for liver or lung tumor. Accurate diagnosis depends on careful pathological examination. Immunohistochemical staining is very useful to distinguish this tumor from other liver or diaphragmatic tumors.

Abbreviations: AFP = alpha-fetoprotein, CDX2 = caudal type homebox 2, CK = cytokeratin, CT = computed tomography, GPC-3 = glypican-3, HMB-45 = human melanoma black-45, PAX8 = paired box 8, RFA = radiofrequency ablation, TTF-1 = thyroid transcription factor 1, WT1 = Wilms tumor gene-1.

Keywords: diaphragm, liver, mesothelioma

1. Introduction

Malignant mesothelioma is a malignant tumor originating from the pleura, peritoneum, and pericardial cavity. Malignant mesothelioma is more common in males than in females. Most mesothelioma patients are more than 40 years old, and the clinical symptoms are not specific. The morphology of malignant mesothelioma is varied.[1–3] Diffuse malignant mesotheliomas are primarily classified as epithelioid mesothelioma, sarcomatoid mesothelioma (including desmoplastic mesothelioma), and biphasic mesothelioma. Epithelioid mesothelioma, the most common type, is mainly composed of epithelioid cells. The most frequently observed patterns of epithelioid mesothelioma are tubulopapillary, adenomatoid (microglandular or microcystic), and sheet-like. Sarcomatoid and biphasic mesotheliomas account for <10% and 10% to 15% of all mesotheliomas, respectively. Sarcomatoid mesothelioma often consists of spindle cells arranged in fascicles or a haphazard pattern. Biphasic/mixed mesothelioma is composed of both epithelioid and sarcomatoid types, with each component accounting for at least 10%.[4] The clinical prognosis for malignant mesothelioma is poor. Most patients die within the first 2 years after diagnosis.[5] However, malignant mesotheliomas that originate from the diaphragm or liver are extremely rare. Here, we report a special case where clinical and imaging examination suggested a liver space-occupying lesion, but surgery and pathological examination revealed that the tumor was a primary diaphragmatic mesothelioma with liver invasion.

2. Case presentation

2.1. Ethic approval

The study was approved by the China Medical University Institutional Review Board for human studies. The ethical board approval number is LS[2018]016. Written informed consent was obtained from the patient for use of her clinical records in our study.

2.2. Clinical history

In December 2017, a 66-year-old woman came to our hospital for a "liver space-occupying lesion." Computed tomography (CT) showed a round lesion in the right liver measuring about

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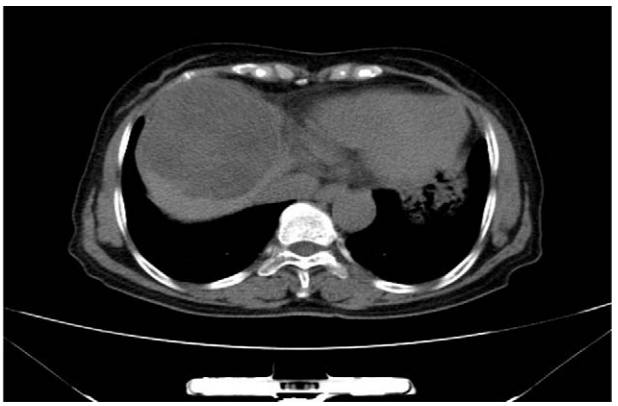

Figure 1. Computed tomography imaging of the tumor. Computed tomography showed a round lesion in the right liver with relatively clear border. The lesion was about 8.2 cm × 8.2 cm × 7.3 cm, and elevated from the liver surface, closely adhering to the right diaphragm.

8.2 cm × 8.2 cm × 7.3 cm with a relatively clear border. The lesion was elevated from the surface of the liver and closely adhered to the right diaphragm (Fig. 1). Enhanced CT showed nodular enhancement in the tumor mass. Ultrasonography showed a cystic solid echogenic lesion above the right lobe of the liver. The shape of the mass was irregular, and the internal echo was slightly reticulated. Positron emission tomography-CT showed an increase of fluorodeoxyglucose uptake in the liver adjacent to the diaphragm. The patient was generally in good condition and had no remarkable clinical symptoms. She denied any history of asbestos exposure. Based on the imaging examination, the tumor was considered a liver tumor, and laparotomy was performed to remove the tumor. During the surgery, it was found that the tumor grew from the right side of the diaphragm and bulged downward into the liver. The tumor was grayish white, and about 8 cm × 8 cm × 7 cm in size. The right liver was partially invaded. The intact tumor, including 1 cm margins in the diaphragm, and part of the liver infiltrated by the tumor were surgically removed. The patient recovered well after surgery and was not treated with radiotherapy or chemotherapy. After 11 months of follow-up, the patient was in good condition and had no evidence of recurrence.

2.3. Immunohistochemical staining

The resected specimens were fixed with 10% neutral-buffered formalin and embedded in paraffin blocks. Tissue blocks were cut into 4-μm slides. Histological evaluation was performed on hematoxylin and eosin stained sections. The tumor tissue sections were processed for immunohistochemical staining for cytokeratin (CK)-pan, CK5/6, CK7, CK18, CK19, CD31, CD34, caudal type homebox 2 (CDX2), human melanoma black-45 (HMB-45), hepatocyte, paired box 8 (PAX8), glypican-3 (GPC-3), vimentin, D2-40, thyroid transcription factor 1 (TTF-1), Wilms tumor 1 (WT1), calretinin, and Ki-67. All of these antibodies were purchased from Maixin, Fuzhou, China. After incubation with primary antibody, antibody detection was accomplished using the streptavidin–peroxidase method.

2.4. Morphological and immunohistochemical findings

Grossly, the tumor was located in the right side of the diaphragm and bulged downward into the liver. The size of the tumor mass was about 8 cm × 8 cm × 7 cm. The cut section was cystic and contained clear liquid. The texture was soft, and the color was gray-white. No obvious bleeding or necrosis was found in the tumor.

Microscopically, the tumor tissue was mainly composed of epithelioid cells, which formed microcysts, cords, or small nests (Fig. 2). The tumor cells were large and round or oval shape with abundant, clear cytoplasm. The nuclei were blunt, ovoid, and eccentric without nucleoli. The eccentric nuclei and clear cytoplasm made the tumor cells appear similar to the signet ring cells, but the mitotic figures were few. Tumor cells were interspersed with a large amount of fibrous stroma with hyaline change.

Immunostaining showed almost all the tumor cells were strongly positive for CK-pan, CK5/6, CK7, CK18, CK19, WT1, calretinin, D2-40, and vimentin. PAX8, TTF-1, GPC-3, HMB-45, hepatocyte, CDX2, CD34, and CD31 tested negative in the tumor cells. The percentage of cells that stained positively for Ki-67 was about 5% to 10% (Fig. 3).

3. Discussion

According to the patient's clinical information, histological features, and immunohistochemical staining, the tumor was diagnosed as epithelioid mesothelioma (microcystic type) of the diaphragm with liver involvement. Primary diaphragmatic malignant mesothelioma is extremely rare. To date, only 7 cases have been reported in the literature. A summary of these cases is listed in Table 1.[6–11] The cases consisted of 4 females and 3 males (4:3). The patients' ages ranged from 48 to 66 years and the average age was 57 years. Only 1 patient had a history of asbestos

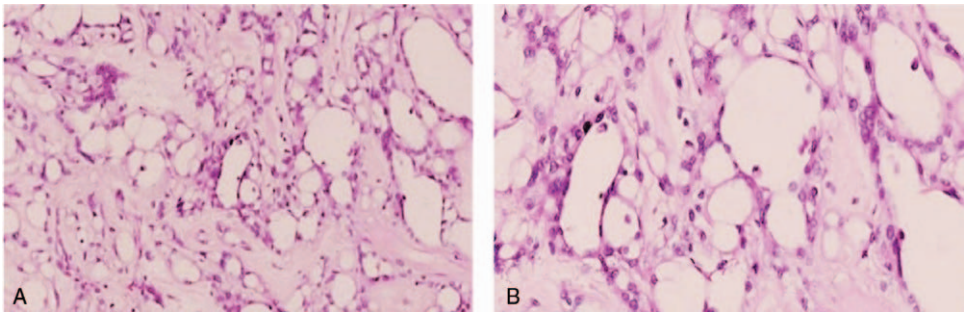

Figure 2. Morphological change of the tumor. (A) Epithelioid tumor cells formed microcysts, cords, or small nests. The stroma exhibited fibrosis and hyaline change (H&E staining, ×200). (B) The tumor cells were large and round or oval shape with abundant, clear cytoplasm. The nuclei were blunt, ovoid, and eccentric without nucleoli. The mitotic figures were very few (H&E staining, ×400).

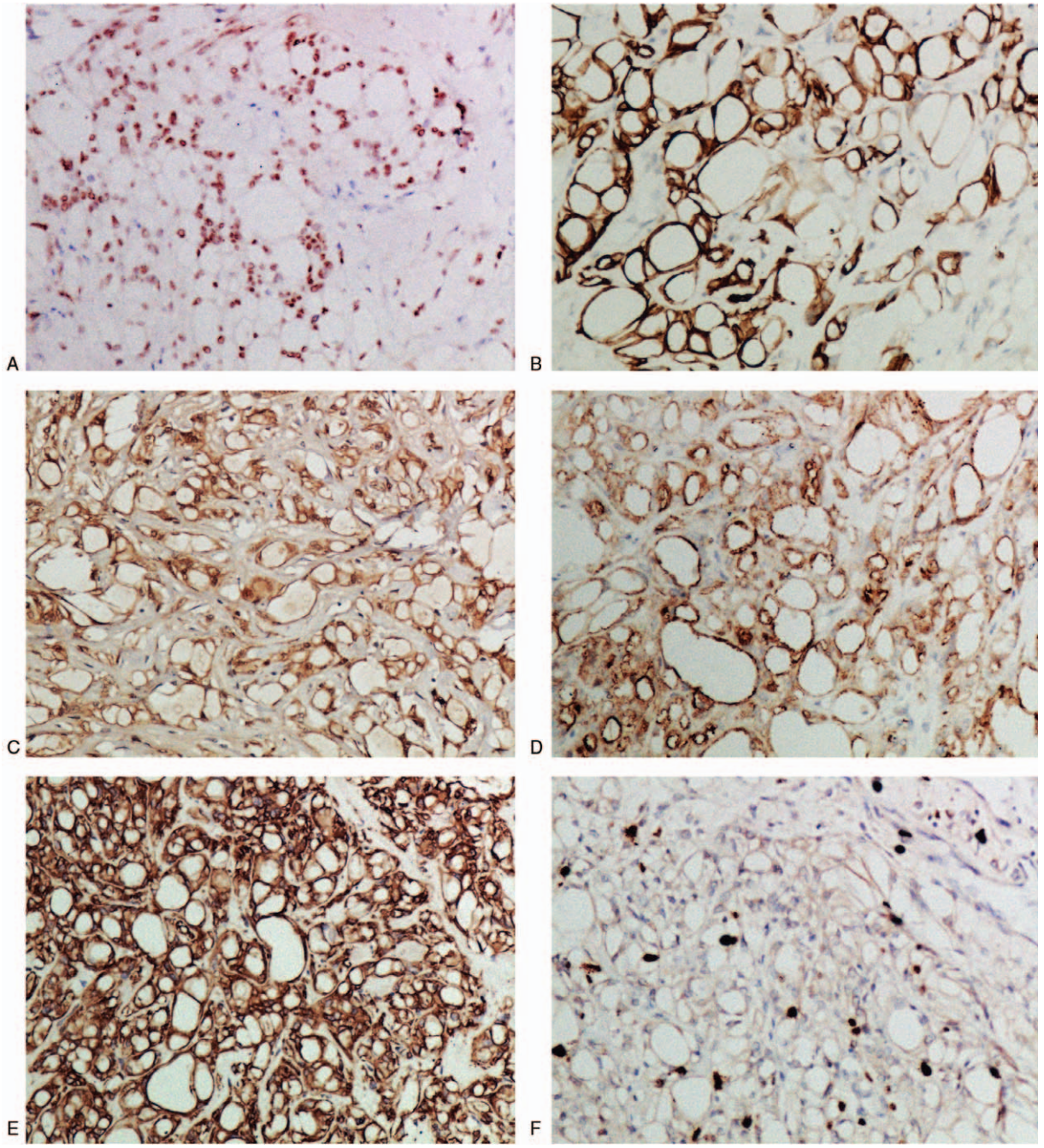

Figure 3. Immunohistochemical staining of the tumor. The tumor cells were strongly positive for Wilms tumor 1 (A), cytokeratin 5/6 (B), calretinin (C), D2–40 (D), and vimentin (E) staining. (F) Ki-67 proliferative index was about 5% to 10%. (S–P method, ×200).

exposure. It has been pointed out that the history of asbestos exposure is closely related to the occurrence of pleural mesotheliomas, but mesotheliomas in peritoneum, liver, diaphragm, and other organs have no obvious relationship with asbestos exposure history.[12–14] All 7 patients presented with liver or diaphragm tumors during the initial examination, and underwent surgical resection. The median size of the tumors was 12 cm (range 4–20 cm). The cut surface was grayish white, tough, and nodular. Five cases were epithelioid type (71.4%), 1 was biphasic (14.3%), and 1 was sarcomatoid type (14.3%). Only 2 patients experienced tumor recurrence. One patient was found tumor recurrence 23 months after surgery, and cured by radiofrequency ablation and reoperation.[11] Another patient gave up treatment for economic reasons, and died of liver and pericardial tumor recurrence after half a year.[7]

It was reported that primary hepatic malignant mesothelioma occurs in the Glisson's capsule, hepatic falciform ligament, or fibrous connective tissue, and extends to the liver parenchyma. Moreover, the tumor may further metastasize or directly invade adjacent tissues, such as the diaphragm, peritoneum, and pancreas, after the liver has developed lesions.[9–14] The tumor often displays as a space-occupying lesion of the abdomen or thoracic cavity, tightly adhering to diaphragm, and often involving liver or lung. Due to the similarities observed during

Table 1

Summary of primary diaphragmatic mesotheliomas.

Reference	Year	Sex	Age	Asbestos exposure	Diameter (cm)	Belly ache and fever	Location	Surgery	Histologic subtype	Outcomes
[6]	2003	Male	50	No	20	No	Left thoracic cavity and left diaphragm	Yes	Sarcomatoid	Disease-free
[9]	2009	Female	66	Yes	4	Not available	Right lobe of Liver	Yes	Biphasic	Disease-free during 6 months follow-up
[11]	2008	Female	53	No	Not available	No	The dome of the liver and the neighboring diaphragm	Yes	Epithelioid	Recurrence 23 months after the initial surgery, cured after RFA and reoperation
[7]	2012	Male	64	No	17.5	Yes	Left lobe of liver and left diaphragm	Yes	Epithelioid	Died of liver and pericardial tumor recurrence 6 months after surgery
[10]	2015	Male	56	No	Not available	Yes	Right lobe of liver and right diaphragm	Yes	Epithelioid	Not available
[8]	2018	Female	48	No	Not available	Yes	Right lobe of liver and right diaphragm	Yes	Epithelioid	Not available
Present case	2017	Male	66	No	11	No	Right lobe of liver and right diaphragm	Yes	Epithelioid	Disease-free during 11 months follow-up

RFA = radiofrequency ablation.

imaging examinations, these tumors are often mistaken for liver or lung tumors. An accurate diagnosis depends on gross and microscopic pathological examination.

Immunohistochemical staining is very useful for the diagnosis of malignant mesothelioma. The WHO has recommended CK5/6, calretinin, and WT1 as the most useful mesothelial markers. Simultaneously, the International Mesothelioma Interest Group suggests that any combination of markers should contain at least 2 mesothelioma markers and 2 other cancer-related markers. Calretinin, CK5/6, WT1, and D2–40 are considered to be the best indicators for differentiating mesothelioma.[3,15] In this case, the tumor cells were epithelioid, and positive for calretinin, WT1, CK5/6, and D2–40 staining, which confirmed the diagnosis of malignant mesothelioma.

Primary diaphragmatic mesothelioma invading into the liver needs to be differentiated from other tumors of the liver or diaphragm. First, primary liver tumors involving the diaphragm should be excluded (i.e., hepatocellular carcinoma, cholangiocarcinoma, angioleiomyolipoma, angiosarcoma), as well as other cancers that metastasize to the liver. Hepatocellular carcinomas or gastrointestinal cancers often show elevated blood tumor markers, such as alpha-fetoprotein (AFP) for hepatocellular carcinomas, and carcinoembryonic antigen or carbohydrate antigen 19–9 for gastrointestinal cancers. Immunohistochemically, hepatocellular carcinoma is positive for AFP, GPC-3, and hepatocyte; angioleiomyolipoma is positive for HMB-45 and melan A; and angiosarcoma is positive for CD31 and CD34. These liver tumors are often negative for WT1, calretinin, and D2–40 staining, which distinguishes them from mesothelioma. Second, other primary diaphragmatic tumors also need to be considered. Most of the primary diaphragmatic lesions are benign, in which a cyst (such as mesenchymal cyst and bronchial cyst) is the most common lesion, followed by lipoma, neurofibroma, and other benign tumors derived from mesenchymal tissue. The most common primary malignant diaphragmatic lesion is rhabdomyosarcoma.[16,17] This lesion is also negative for WT1, calretinin, and D2–40 staining, and can be easily excluded.

In summary, we report a rare malignant mesothelioma that originated from the diaphragm. Primary diaphragmatic malignant mesothelioma may involve the liver or lung tissue, and may be mistaken for a liver or lung tumor. An accurate diagnosis depends on careful pathological examination. Immunohistochemical staining is very useful to distinguish this tumor from other liver or diaphragmic tumors.

Author contributions

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