Isolated Pancreatic Metastasis of a Malignant Pleural Mesothelioma

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Metastatic malignant mesothelioma of the pleura is uncommon at the time of initial diagnosis. When metastases are present, the major sites always include regional lymph nodes, the contralateral lung, liver, adrenal glands and kidneys. Here, we describe an extremely rare case of isolated pancreatic metastasis of mesothelioma of the pleura in a 40-year-old man who initially presented with epigastric discomfort and hunger pain, which were refractory to medical treatments. The possibility of pancreatic metastatic lesion should be considered in patients with malignant pleural mesothelioma in the presence of refractory epigastric tenderness.

Key Words: abdominal pain, mesothelioma, metastasis, pancreas, pleura
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Mesothelioma is a membrane-based neoplasm that most commonly arises from the pleura but also from the pericardium, peritoneum, tunica vaginalis and ovaries [1]. Generally, malignant pleural mesothelioma predominantly affects males over the age of 50 years and asbestos exposure is the primary cause for the development of malignant mesothelioma. Other potential causes include radiation, viral infection and exposure to a variety of chemicals. The latent period between exposure and the onset of symptoms ranges from 30 to 40 years. Extensive peritoneal infiltration of malignant mesothelial cells is common in patients with extensive abdominal disease at autopsy. However, a search for pancreatic metastasis of the malignant mesothelioma using MEDLINE revealed that peritoneal carcinomatosis with pancreas infiltration is seldom found in case reports. To our knowledge, isolated pancreas metastasis without peritoneal carcinomatosis has not been reported before.

Case Presentation

A 40-year-old male was admitted to hospital with symptoms of intermittent back pain located in the right upper region, with radiation to the anterior chest wall around the intercostals area. He was a heavy smoker, with a smoking history of three packs per day for 20 years. He had worked in an asbestos factory with exposure to asbestos for only 2 months at the age of 17 years. He then quit that job and became a public officer. He denied any other systemic disease or family history. Physical examination revealed clear bilateral breath sounds. Chest X-ray (Figure 1A) revealed a well-defined soft tissue mass over the right posterior mediastinum. Chest computed tomography (CT) (Figure 1B) revealed a $3.7 \times 4.3 \times 6$ cm heterogeneous contrast-enhanced soft tissue mass that was localized in the right paraspinal region of T5, with associated destruction of the T5 vertebral body. Magnetic resonance imaging also showed a lobulated soft

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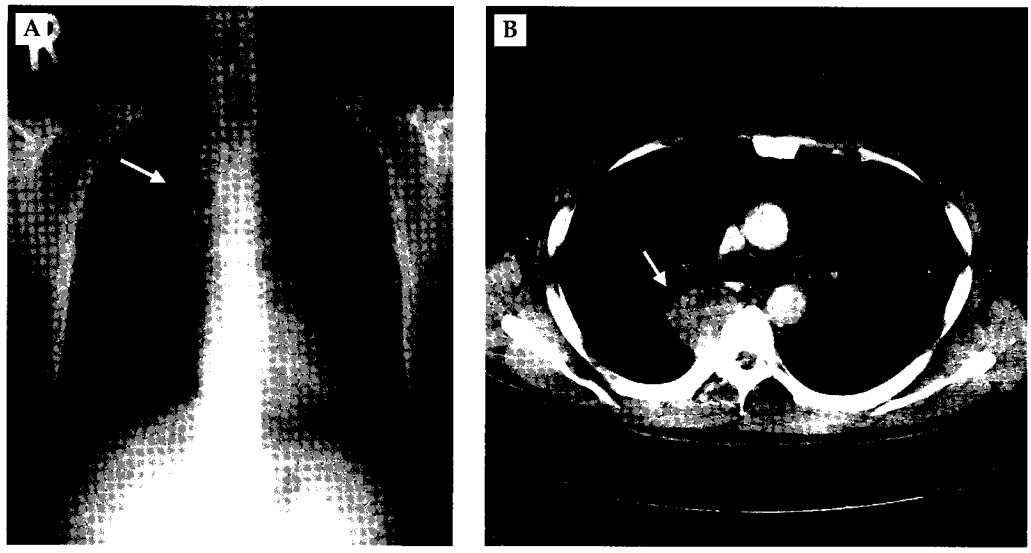


Figure 1. *(A) Chest X-ray revealed a well-defined soft tissue mass in the right posterior mediastinum (arrow). (B) Chest computed tomography revealed a 3.7 × 4.3 × 6 cm heterogeneous contrast-enhanced soft tissue mass in the right paraspinal region of T5 (arrow).*

tissue mass with isometric T1 signal intensity and intermediate/high T2 signal intensity in the posterior mediastinum at the T4–6 level, and it had invaded into the right aspect of the T4–6 vertebral bodies with a central low signal intensity component with contrast enhancement (data not shown).

The posterior mediastinal tumor was excised and the right lower lobe wedge was removed via thoracotomy on August 2, 2002. The pathologic report revealed biphasic malignant mesothelioma that contained both an epithelioid pattern with tubulopapillary proliferation of epithelioid cells and a sarcomatoid pattern with interlacing fascicles comprised of spindle cells. The tumor cells were immunoreactive for vimentin and cytokeratin (Figure 2). Between August and December, 2002, the patient underwent four courses of adjuvant concurrent chemoradiation therapy (CCRT) with a regimen comprising dacarbazine, cyclophosphamide, epirubicin and vincristine. After completion of the four courses of CCRT, he did not return to the clinic for further follow-up between 2003 and 2005 and he denied experiencing any symptoms during this period.

On October 27, 2006, the patient reported clinical manifestations of hunger pain and abdominal distention, and a physical examination showed tenderness over the epigastric area. Initially, a proton pump inhibitor was prescribed empirically based on the preliminary diagnosis of peptic ulcer disease. However, after 2 weeks of treatment, the epigastric discomfort persisted and a palpable mass lesion was found. Therefore, abdominal CT was performed and revealed a mass (1.66 × 9.6 × 13.3 cm) located over the pancreatic head and body, with external compression on the superior mesentery artery and the confluence of splenic vein and superior mesentery vein, without any evidence of peritoneal carcinomatosis or lymph node metastasis (Figure 3). Because the serum CA 19-9 level was elevated to 4,099 U/mL, a pancreatic malignancy was highly suspected and the patient underwent a subtotal pancreatectomy on November 14, 2006. Microscopically, the pancreatic tumor shared similar morphological features with the original tumor. Furthermore, the tumor cells were immunohistochemically positive for cytokeratin, vimentin, calretinin and cytokeratin 5/6 (CK 5/6) (Figure 4). According to the overall features, metastatic malignant mesothelioma was confirmed. After surgery, the patient continued regular follow-up at the outpatient clinic.

Discussion

Asbestos is widely recognized as a significant risk factor for the development of mesothelioma. Case-control studies have estimated that almost 90% of males with mesothelioma had prior exposure to asbestos, whereas only 20% of females had prior history of exposure [2]. In contrast, cigarette smoking is not considered to be a risk factor for the development

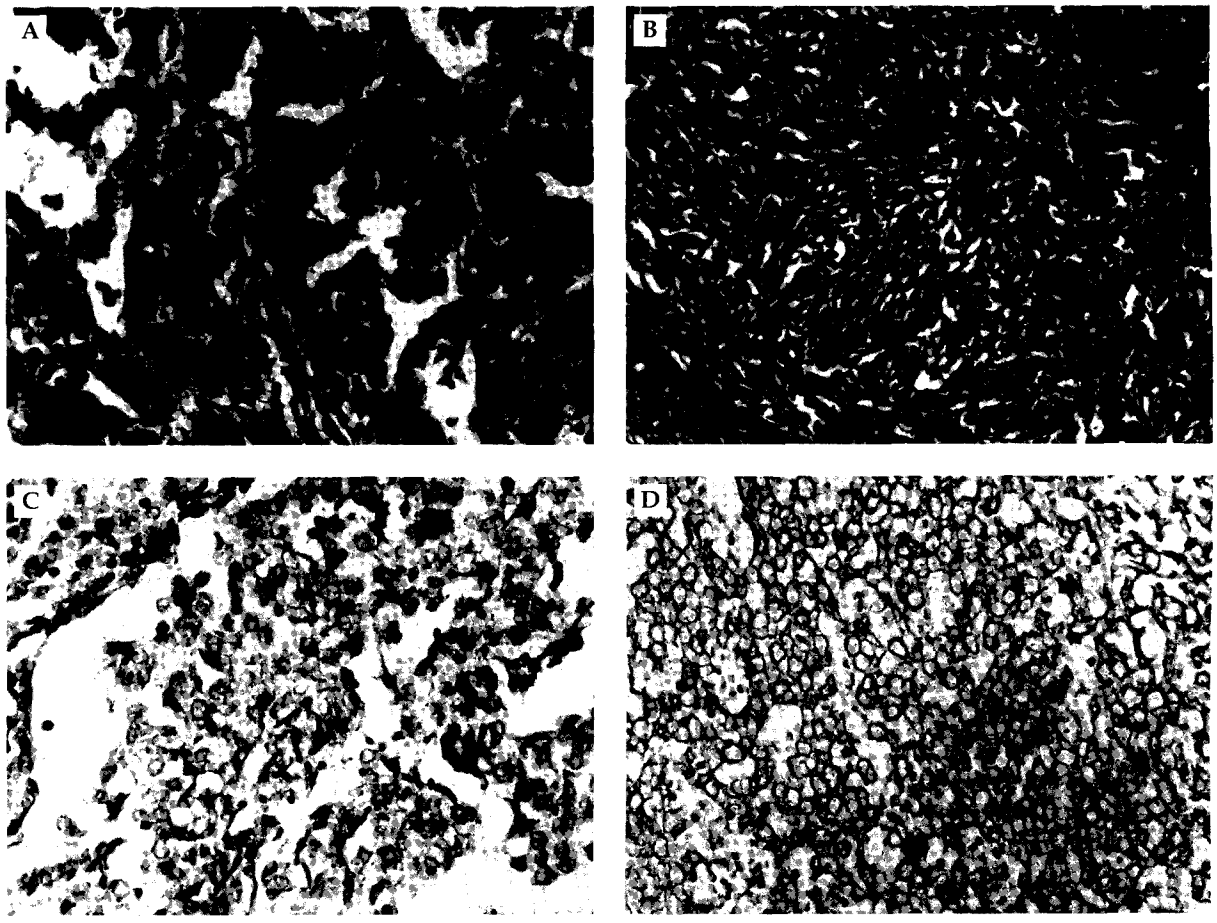


Figure 2. *Microscopic views of the tumor show: (A) an epithelioid pattern with tubulopapillary structures lined by pleomorphic epithelioid cells; (B) a sarcomatoid pattern composed of interlacing fascicles of spindle cells (hematoxylin & eosin; original magnification, 200×). Immunohistochemistry revealed the tumor was positive for: (C) vimentin; (D) cytokeratin (original magnification, 400×).*

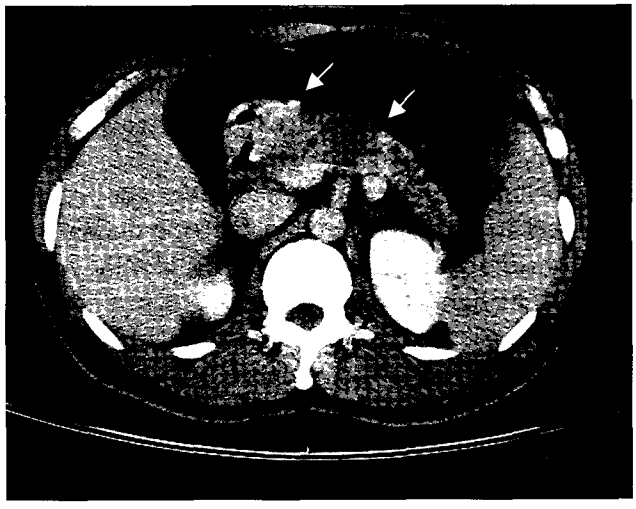


Figure 3. *Computed tomography of the abdomen revealed a mass over the pancreatic head and body (arrows) with external compression on the superior mesentery artery, the confluence of the splenic vein and the superior mesentery vein, without evidence of peritoneal carcinomatosis or lymph node metastasis.*

of mesothelioma [3]. According to a cohort study, there appears to be a dose-response relationship between asbestos exposure and mesothelioma, and a positive correlation between the time between exposure and disease onset with the risk of developing mesothelioma [4]. However, our patient reported only 2 months of exposure to asbestos without any other risk factors and the mesothelioma was diagnosed only 23 years after the exposure to asbestos. Based on reviews of the relationship between exposure to asbestos and mesothelioma, possible co-factors in the pathogenesis of asbestos-related mesothelioma include genetic predisposition, diets poor in fruit and vegetables, viruses, immune impairment and recurrent serosal inflammation [5].

Falconieri et al reviewed 171 cases of malignant mesothelioma at autopsy and discovered that 54% of patients had distant metastases [6]. The most commonly involved organs were the liver (56%), adrenals

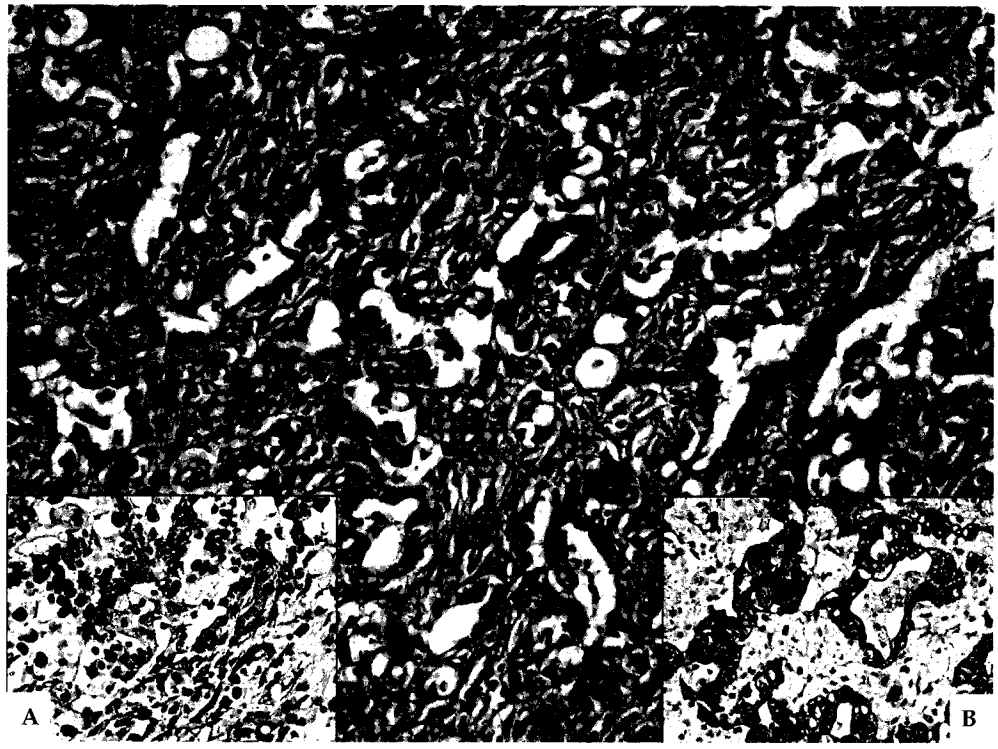


Figure 4. *The pancreatic tumor had tubulopapillary structures in epithelioid cells, which were similar to the original mesothelioma (hematoxylin & eosin; original magnification, 200×). The inserted figures show immunoreactivity for: (A) vimentin; and (B) cytokeratin (original magnification, 400×).*

(31%) and kidneys (30%). Metastases to the pancreas, thyroid gland, stomach, bones and cerebrum were also noted in small numbers (3–6%). In our patient, malignant mesothelioma was found at the age of 40 and the isolated pancreas tumor shown on abdominal CT developed 3 years after pleurodectomy and four courses of CCRT. Because of the greater enhancement of the normal pancreas, primary or metastatic malignant tumors appear as lower density lesions [7]. These are often associated with obstruction of the pancreatic duct. Therefore, we could not differentiate whether the mass was a primary lesion or metastatic by imaging studies.

Because of the increased expression of CA 19-9 to 4,099 U/mL and findings of abdominal CT studies, primary pancreas cancer of adenocarcinoma was initially proposed. CA 19-9 is a tumor-associated antigen, which is elevated in pancreatic cancers, cancers of the upper gastrointestinal tract, ovarian cancer, hepatocellular cancer, colorectal cancer, inflammatory conditions of the hepatobiliary system and in thyroid diseases. Walz et al have emphasized that metaplastic changes in mesothelial cells were responsible for the production and secretion of CA 19-9 in the lining and fluid content of splenic cysts [8]. Holtzman et al presented a case of benign multicystic mesothelioma of the peritoneum, which was uniquely characterized by an elevated serum CA 19-9 level and a tissue biopsy with positive immunostaining for CA 19-9 [9]. Therefore, two possible reasons for the elevated CA 19-9 level in our patient include pancreatic duct obstruction by the tumor and abnormal secretion of CA 19-9 from mesothelial cells.

The pathological differentiation between metastatic mesothelioma in the pancreas and pancreatic primary adenocarcinoma is challenging. Electron microscopy was considered a useful diagnostic tool for the recognition of malignant mesotheliomas. However, in this case, we consider the immunohistochemistry (IHC) panel to be as valuable, convenient and rapid as electron microscopy for the establishment of a definitive diagnosis of malignant mesothelioma [10]. In addition to markers that support a diagnosis of adenocarcinoma, including CA 19-9 and carcinoembryonic antigen, there are now a number of commercially available antibodies that are reliable markers for mesothelial differentiation including calretinin, cytokeratin 5/6 and Wilms' tumor-1 antigen. There is no single marker

that has sufficiently high sensitivity and specificity for malignant mesothelioma. In our patient, the primary lesion was diagnosed as a malignant pleural mixed mesothelioma based on histological and IHC marker findings. The findings from the IHC markers are consistent with the diagnosis of metastatic mesothelioma of the pancreas.

In conclusion, local control of pleural mesothelioma improves the survival rate. Thus, an increasing number of patients presenting with spread of the disease to unusual sites is much more likely. The possibility of pancreatic metastatic lesions should be considered in patients with malignant pleural mesothelioma in the presence of epigastric discomfort.

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惡性肋膜間皮瘤併發單獨性的胰臟轉移 — 病例報告

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轉移的惡性肋膜間皮瘤在一開始診斷時並不常見。當轉移發生時，主要轉移的部位大多在局部的淋巴結、對側肺臟、肝臟、腎上腺和腎臟。我們在此描述一位四十歲男性剛開始以上腹部不適及飢餓造成疼痛來表現，且對藥物治療反應不佳，後被診斷為惡性肋膜間皮瘤併發單獨性胰臟轉移的罕見病例。當難治的上腹部疼痛發生在惡性肋膜間皮瘤的病人時，胰臟轉移的可能性仍然是必須列入考慮的。

關鍵詞：腹痛，惡性間皮瘤，轉移，胰臟，肋膜

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