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Case Report

Solitary pancreatic metastasis of occult pulmonary small cell carcinoma diagnosed by EUS-FNA cytology: a case report

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Abstract: A 74-year-old man presented with symptoms suggestive of acute pancreatitis, and a mass lesion measuring 25 mm was detected in the pancreatic head. Cytological and histopathological examinations of EUS-FNA specimens taken from the lesion demonstrated small cell (neuroendocrine) carcinoma. Tumor cells were immunoreactive for cytokeratin, synaptophysin, chromogranin A, CD56, and TTF-1, and PET-CT of the chest revealed a small tumor in the upper lobe of the left lung. Pulmonary carcinoma, particularly small cell carcinoma, infrequently presents with a solitary metastatic lesion in the pancreas as an initial manifestation and clinically simulates a primary pancreatic neoplasm. Because primary small cell carcinoma of the pancreas is very uncommon, metastasis from the lung should always be considered when evaluating pancreatic neoplasms showing a "small cell" morphology. Immunohistochemistry for TTF-1 is useful for determining the pulmonary origin of this type of neoplasm, and its application to cytology specimens is recommended.

Keywords: Small cell carcinoma, lung, pancreatic metastasis, EUS-FNA, TTF-1, immunohistochemistry

Introduction

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a widely used procedure to obtain tissue from the pancreas, and cytologic examination of EUS-FNA specimens plays an important role for the early diagnosis of various neoplastic lesions of that organ [1-3]. We report an unusual case of solitary metastasis of pulmonary small cell carcinoma to the pancreas, which appeared as the initial manifestation of the disease and clinically simulated a primary pancreatic neoplasm. Cytologic and histologic examinations of EUS-FNA specimens obtained from the pancreatic lesion strongly suggested a pulmonary origin, and a small lesion was subsequently detected in the lung on a detailed radiological examination.

Clinical history

The patient was a 74-year-old male smoker, who had been treated at a local hospital for diabetes mellitus, hypertension, and hyperlipidemia. He complained of severe epigastric pain of acute onset and was referred to our hospital. Laboratory examination showed a marked elevation of serum amylase (1,213 U/L, normal range: 44~132 U/L) and lipase (4,584 IU/L, normal range: 13~49 IU/L), findings that led to the diagnosis of acute pancreatitis. However, abdominal ultrasound and computed tomography (CT) examination revealed a homogeneously enhancing mass lesion, measuring 25 mm in diameter, in the uncinate process of the pancreatic head (**Figure 1A**, **1B**). The mass was well-circumscribed, and the diagnosis of an endocrine tumor or a malignant lymphoma was favored over an invasive ductal carcinoma. The serum carcino-embryonic antigen was 10.8 ng/mL (normal range: less than 4.1 ng/mL), and carbohydrate antigen 19-9 was 67.9 U/L (normal range: less than 37.0 U/L).

EUS-FNA of the pancreatic mass with duodenal biopsy was performed, and the cytologic and histologic findings strongly suggested metastasis of pulmonary small cell carcinoma. On

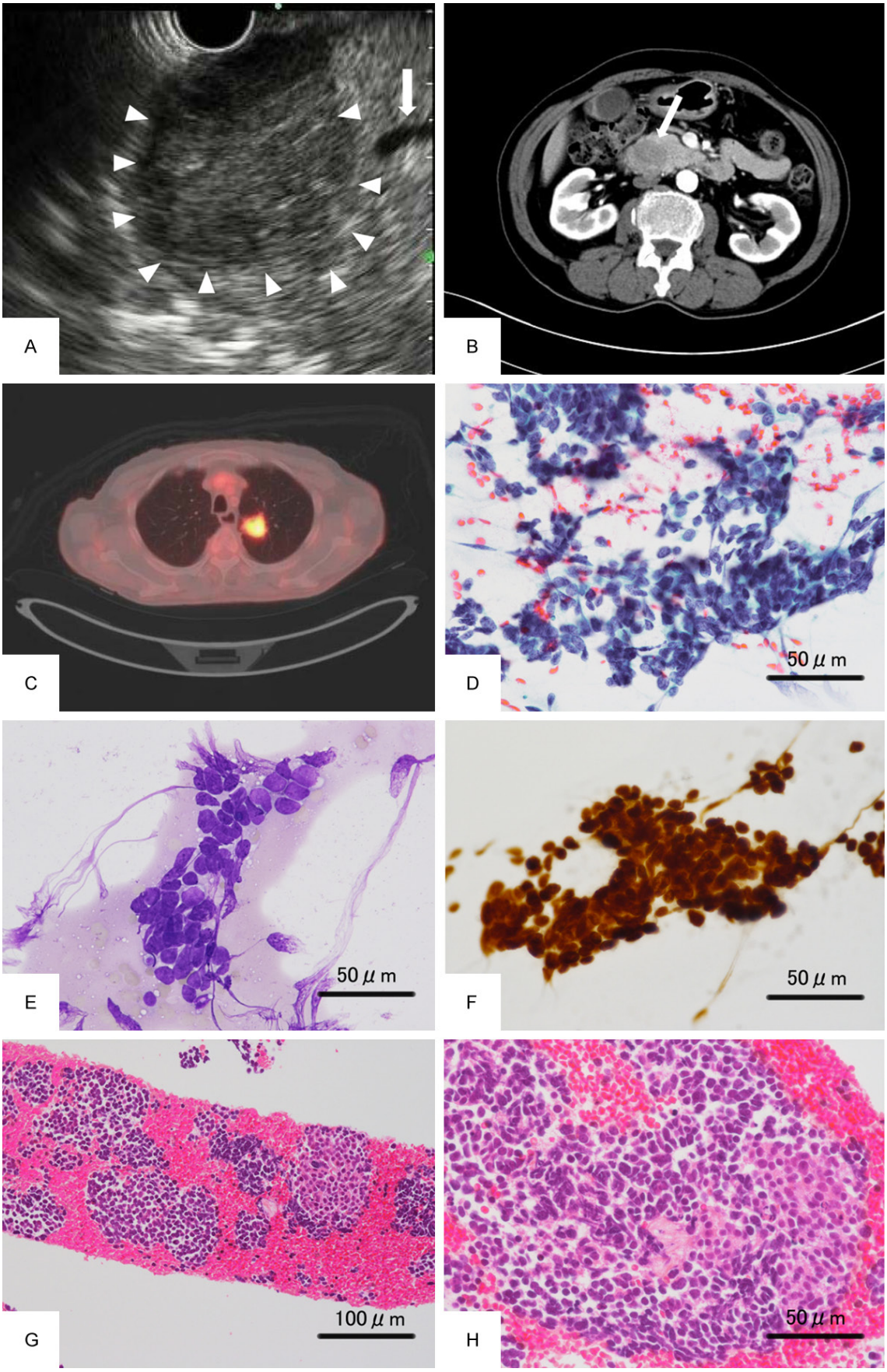
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Figure 1. A. Abdominal ultrasonography on admission. A well-demarcated mass lesion (surrounded by arrowheads) was seen in the pancreatic head. The main pancreatic duct was slightly dilated (arrow). B. Abdominal CT with contrast enhancement. The mass lesion in the pancreatic head was homogeneously enhanced (arrow). C. PET-CT of the chest. A tumor was demonstrated in the upper lobe of the left lung. D. Smear preparation of the EUS-FNA specimen. Many small or medium-sized cells with hyperchromatic nuclei and scant cytoplasm formed irregular clusters (Papanicolaou stain, ×400, scale bar 50 μm). E. Smear preparation of the EUS-FNA specimen. Some cells formed thin trabeculae with irregular contours (CytoQuick stain, ×400, scale bar 50 μm). F. Immunostain for TTF-1. The nuclei of tumor cells showed intense immunoreactivity for TTF-1 (×400, scale bar 50 μm). G. Histopathology of the EUS-FNA specimen. The tumor consisted of a dense proliferation of small cells with hyperchromatic, elliptical or angulated nuclei and scant cytoplasm (H&E stain, ×200, scale bar 100 μm). H. Histopathology of the EUS-FNA specimen. Slightly larger cells with more abundant, pale cytoplasm were admixed (right side of the figure) (H&E stain, ×400, scale bar 50 μm).

review of the chest radiograph taken on admission, a small, vaguely nodular shadow was found in the left upper lobe, and positron emission tomography (PET)-CT confirmed a pulmonary tumor, measuring 2 cm in diameter (**Figure 1C**). One week later, hoarseness due to palsy of the left recurrent nerve suddenly developed, which was considered to have been caused by metastasis to the mediastinal lymph nodes. Distant metastases to bone or organs other than the pancreas have not been demonstrated. The patient has been treated with a chemotherapeutic regimen for small cell carcinoma of the lung (cT1cN2M1b, stage IVA), and both the pulmonary and pancreatic tumors have begun to reduce in size. The case is recent, thus the follow-up period remained short.

Cytologic findings

The specimens obtained by EUS-FNA were examined with Papanicolaou and CytoQuick (Muto Pure Chemicals, Tokyo, Japan) stains. The smear preparations contained many atypical cells of small or medium size that formed loosely cohesive, small clusters of irregular shapes or were present as single cells on a clear background (**Figure 1D**). The atypical cells had elliptical or angulated nuclei with abundant, evenly distributed chromatin and indistinct nucleoli. Many streaks of chromatin were also observed. The scant cytoplasm was palely stained and had an indistinct margin. The cells occasionally showed “paired-cell binding”, “nuclear molding”, and a thin trabecular arrangement (**Figure 1E**). For immunohistochemical study, a part of smeared material was detached from the original slide glass and transcribed on a new glass. Atypical cells showed intense nuclear expression of thyroid transcription factor-1 (TTF-1) (clone SP141, Roche Diagnostics, prediluted) (**Figure 1F**).

Histologic findings

The EUS-FNA specimens showed the typical appearance of small cell (neuroendocrine) carcinoma. The tumor mostly consisted of a dense proliferation of small cells with elliptical or angulated nuclei and scant cytoplasm (**Figure 1G**), but slightly larger cells with more abundant, pale cytoplasm were intermingled (**Figure 1H**). The formation of rosettes or tubules was not observed. Mitotic figures and apoptotic cells were scattered. The cytoplasm was immunoreactive for cytokeratin (partly) (clone AE1/AE3, Dako, 1:400), synaptophysin (clone 27G12, Leica, 1:200), chromogranin A (clone 5H7, Leica, 1:400), and CD56 (clone 1B6, Leica, 1:100), and the nuclei were immunoreactive for TTF-1. The duodenal biopsy specimen showed invasion by small cell carcinoma.

Discussion

Secondary (metastatic) neoplasms involving the pancreas are not uncommon based on studies of autopsied material [4-6], but they are overlooked in clinical settings in most cases because patients with pancreatic metastasis usually have multiple, often life-threatening, metastatic lesions in other organs while clinical symptoms due to pancreatic lesions are not prominent [5]. However, pancreatic metastasis occasionally occurs as an isolated event at the early stage of the disease without evidence of synchronous metastases to other organs [4, 7, 8], and, more importantly, the primary tumor is often very small and has escaped notice at the time when the pancreatic tumor is detected. In these situations, the pancreatic tumor can be mistaken for a primary neoplasm [1, 6].

Common origins of metastatic pancreatic neoplasms include the lung, kidney, breast, skin (especially melanoma), stomach, and large

intestine [1, 3, 5, 6, 8, 9]. Although solitary and often delayed metastasis of renal cell carcinoma to the pancreas is well-known [2-4], lung cancers metastasizing to the pancreas have been documented less frequently [6, 8-10]. It should be noted that the metastasis of lung cancer frequently forms a single nodular lesion simulating a primary neoplasm of the pancreas [5, 10]. Among lung cancers, small cell carcinoma more frequently develops pancreatic metastasis than adenocarcinoma or squamous cell carcinoma [10, 11], and a few cases have been reported of metastasis of lung cancer in patients presenting with features of acute pancreatitis, as seen in our case [11-14].

The occurrence of small cell (neuroendocrine) carcinoma is very rare in the pancreas [15, 16]. The majority of pancreatic neuroendocrine carcinoma cases involve large cell neuroendocrine carcinoma [17, 18], and small cell carcinoma accounts for only approximately 1% of all pancreatic malignancies [15, 16]. In the present case, the cytologic findings were typical of small cell carcinoma, and the nuclear immunoreactivity for TTF-1 of tumor cells strongly supported a pulmonary origin [19]. Benning et al. reported 19 patients with metastatic pancreatic neoplasms diagnosed by EUS-FNA [1]. The series included four pulmonary small cell carcinoma patients, and in one of them the pancreatic mass was the initial manifestation of the disease [1]. Among more recent studies, Raymond et al. showed that metastases to the pancreas occupied 7.2% of pancreatic malignancies diagnosed by EUS- or CT-guided FNA [8]. In 18.8% of these cases, the pancreatic lesions were the first manifestation of malignancy. The most common primary site was the lung, followed by the kidney and gastrointestinal tract, and one third of the lung cancers were small cell carcinoma [8].

The cytologic differential diagnosis of small cell carcinoma of the pancreas includes benign neuroendocrine neoplasms [3, 20], acinar cell carcinoma [3, 21], malignant lymphoma, and primitive neuroectodermal tumor (PNET) [22]. Each of the first three has a characteristic cytologic appearance that can be used to readily identify the entity. On the other hand, the differential diagnosis of small cell carcinoma from primary pancreatic PNET is almost impossible based on the morphologic findings alone [22]. The occurrence of primary PNET in the pancreas is extremely rare, and mostly limited to pediatric and adolescent populations [22]. The definite diagnosis depends on a cytogenetic study, which demonstrates a typical chromosomal translocation [22]. A rare case of pancreatic metastasis of small cell carcinoma of the urinary bladder has also been reported [9].

Cytologic examination of the pancreatic tumor by EUS-FNA facilitates an early and accurate diagnosis of solitary pancreatic metastasis in some cases, even when the primary tumor is clinically still silent [8]. It contributes to avoiding unnecessary open surgical biopsy or resection of the tumor and enables the early start of adequate chemo- or radiotherapy. The present case emphasizes the importance of considering the possibility of metastasis of lung cancer in cases of solitary pancreatic tumor, particularly in patients showing a “small cell” morphology [3, 10]. The immunoreactivity of tumor cells for TTF-1 is, although not entirely specific, a finding that strongly suggests a pulmonary origin [19], and the immunostaining of cytologic preparations is recommended.

Disclosure of conflict of interest

None.

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