Endoscopic ultrasound-guided fine-needle aspiration for unresectable pancreatic metastasis of esophageal squamous cell carcinoma: A case report and literature review

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Abstract. Metastatic tumors to the pancreas are a rare subtype of pancreatic malignant tumor, particularly those that have spread from the esophagus. The diagnosis and treatment process can be complex when managing patients with tumors that have metastasized to the pancreas. Accurate differentiation between primary pancreatic and metastatic tumors is key in the use of precision therapy for these patients. The present study reports the case of a 53-year-old female patient that presented with symptoms of dysphagia and epigastric pain that had persisted for 3 months. Gastroscopy indicated the presence of a tumor in the lower esophagus, with pathology results demonstrating squamous cell carcinoma. Prior to radical esophageal cancer surgery, computed tomography (CT) scans demonstrated the presence of a tumor in the body of the pancreas. Due to the notable size of the tumor and potential involvement of the large abdominal vessels, esophageal surgery was postponed and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed to confirm the pathological diagnosis. EUS-FNA pathological diagnosis demonstrated that the pancreatic tumor was a result of esophageal tumor metastasis. The patient opted for radiotherapy and chemotherapy for both the esophageal and pancreatic tumors instead of undergoing surgery. The present study reports the clinical and pathological characteristics, and treatment strategies of rare metastatic tumors to the pancreas of esophageal origin.

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Introduction

Metastatic tumors to the pancreas represent a minority of all pancreatic malignancies, typically ranging from 2 to 5% based on reported data (1). Melanoma, renal cell and lung carcinoma are the most common tumors to metastasize to the pancreas, while metastasis of tumors from the esophagus is rare comprising <5% of all pancreatic metastases (2,3). At present, three commonly used methods exist for detecting metastatic tumors to the pancreas: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), surgical intervention and autopsy (4-6). Metastasis to the pancreas is frequently misidentified as a primary tumor, which leads to potentially inappropriate treatment (7). There is a lack of conclusive evidence regarding the effectiveness of surgical resection in prolonging survival of patients with metastatic tumors to the pancreas (8). Accurate identification of the primary site, precise pathological diagnosis and thorough preoperative staging are key factors for achieving optimal patient prognosis; this approach ensures patients receive effective treatment. According to the most recent esophageal cancer diagnosis and treatment guidelines from the National Comprehensive Cancer Network of America (9), patients with metastatic esophageal cancer are, in most cases, not considered candidates for surgical resections. Therefore, misdiagnosing metastatic tumors as dual origin primary tumors for radical resection may lead to unnecessary harm to patients.

EUS-FNA is the primary diagnostic method for obtaining pathological diagnosis of abdominal tumors, particularly pancreatic tumors, due to high accuracy and low rate of complications. EUS-FNA has been shown to have a diagnostic accuracy of >90% in detecting pancreatic tumors (10,11). Therefore, in patients with malignant synchronous or metachronous pancreatic tumors, it is recommended to consider EUS-FNA to determine if the pancreatic tumor is primary or secondary. Cortez *et al* (8) demonstrated that EUS-FNA can assist patients with single pancreatic metastasis by avoiding unnecessary pancreatic tumor resection.

While there are some reported cases (2-6,12,13) of esophageal tumor metastasis to the pancreas, they remain rare occurrences. The present case study aimed to provide

insights for diagnosis and treatment of metastatic tumors to the pancreas.

Case report

A 53-year-old female patient presented to Guangyuan Central Hospital (Sichuan, China) in March 2024 with dysphagia and epigastric pain that had lasted for 3 months, with no other accompanying symptoms. The patient underwent upper gastrointestinal endoscopy and pathological biopsy and was diagnosed with squamous cell carcinoma of the lower esophagus (Fig. 1A and B). The patient did not exhibit any other symptoms such as malnutrition, anemia or jaundice. The levels of carbohydrate antigen 19-9 and 125 in the blood test were 10.06 U/ml (normal range <37.00 U/ml) and 10.33 U/ml (normal range <35.00 U/ml), respectively. From a computed tomography (CT) scan (256-row GE Revolution CT, Revolution APEX; GE Healthcare; slice thickness was 1 mm) prior to surgery on March 2024, the thoracic surgeon identified a pancreatic tumor (Fig. 2A-C). Due to the potential of the tumor to infiltrate the celiac trunk vessels and multiple retroperitoneal lymph nodes, the multidisciplinary treatment (MDT) team opted to verify the pathological diagnosis of the tumor before proceeding with extensive multi-organ surgery. Subsequently, the patient underwent EUS scanning in April 2024, demonstrating a tumor measuring ~34.4x30.2 mm in the body of the pancreas. The echogenicity characteristics indicated that, in comparison with normal pancreatic tissue, there was a lower echo intensity with uniform punctate medium-high echoes present, which were slightly higher compared with that of the echoes observed in primary pancreatic cancer. The tumor exhibited clear demarcation from surrounding pancreatic tissue and invaded compression on the splenic and common hepatic artery. A few enlarged lymph nodes were observed in the retroperitoneum. Based on the EUS scan results, the initial determination of the tumor stage was uT4N1Mx. (According to the 8th American Joint Committee on Cancer TNM Staging of Pancreatic Cancer) (14). In April 2024, EUS-FNA was conducted on the tumor in the body of the pancreas, which resulted in retrieval of a notable number of cells and tissue (Fig. 2D-F). The pathologist initially did not consider the present case to be a metastatic tumor to the pancreas. However, components indicative of keratinization and intercellular bridges that were less consistent with common pancreatic adenocarcinoma were identified in cytological [hematoxylin and eosin (H&E) and Papanicolaou stained]and histological (H &E stained)sections. Due to the patient history of esophageal squamous cell carcinoma, immunohistochemistry was conducted to assist in diagnosis. P40 and P63 were positive, with a Ki67 proliferation index of 70% (data not shown), which confirmed metastasis of esophageal squamous cell carcinoma to the pancreas (Fig. 3A-F). Tissue was immersed in 10% neutral formalin at room temperature for >20 h, after which it was embedded in paraffin blocks. The paraffin blocks were sectioned to a thickness of 4 μm and baked at 60˚C for 30-60 min. Paraffin sections were immersed in fresh xylene and descending ethanol solutions, respectively. The tissue was then rinsed with tap water and PBS and heated to 100˚C. Following treatment with 3% H_2O_2 for 10 mins at room temperature, 10% normal goat serum (Scientific Phygene) was added at 37˚C for 30 min to block nonspecific binding. Primary

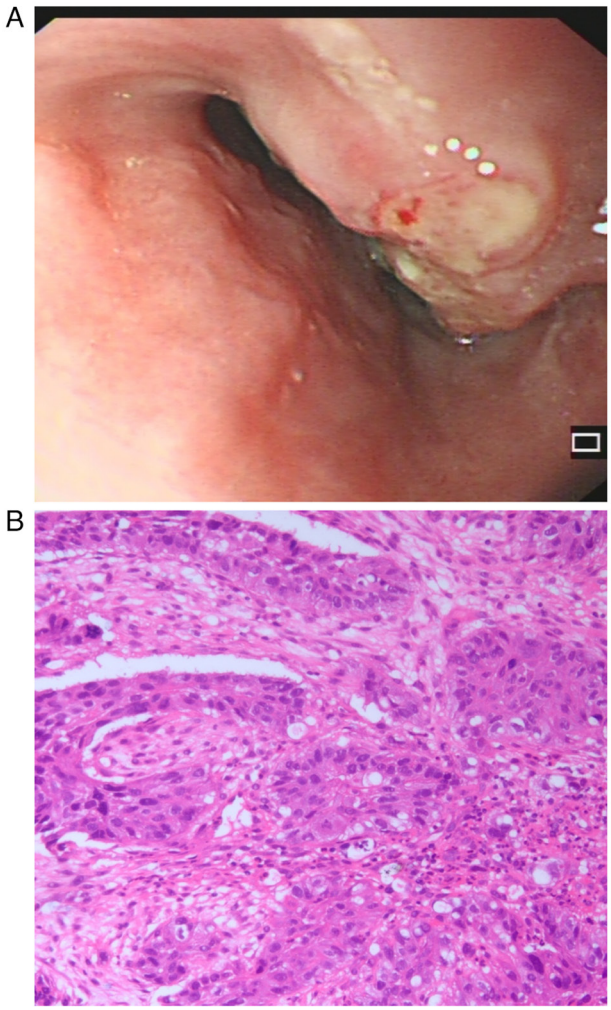

Figure 1. Upper gastrointestinal endoscopy revealed distal esophageal cancer, and pathological biopsy confirmed the diagnosis of squamous cell carcinoma. (A) Gastroscopy identified a notable elevated neoplasm in the distal esophagus. (B) Representative image of histological examination of the biopsy tissue stained with hematoxylin and eosin, which confirmed the diagnosis of squamous cell carcinoma (magnification x100).

antibodies against Ki-67 (cat. no. SP6, 1:200, MXB biotechnologies), p63(MX013, 1:200, MXB biotechnologies), and p40 (MX048, 1:200, MXB biotechnologies) were added and incubated at 37˚C for 2 h. The samples were then washed 3 times with PBS (2 mins). Subsequently, added horseradish peroxidase (HRP)-labeled goat anti-rabbit IgG as the secondary antibody (Everything Biotechnology Co, Hefei, China, BL003A) for P40 and Ki67, and HRP-labeled goat anti-mouse IgG as the secondary antibody (Everything Biotechnology Co, Hefei, China, BL001A; all 1:200 and incubated at 37˚C for 30 mins. The samples were washed again 3 times with PBS with each wash lasting 2 mins. A volume of 10 μl freshly prepared DAB solution was added to the samples at room temperature for 5-8 min, samples were rinsed with tap water and counterstained with hematoxylin for 30-60 sec at room temperature, followed by rinsing with tap water to restore the blue color. The samples were dehydrated by using ethanol gradients. Sections were treated with xylene 3 times for 2 mins each to achieve transparency. Finally, the sections were sealed with neutral gum and observed under a light microscope (Olympus, Tokyo,

Table I. Cases of pancreatic metastasis in esophageal cancer.

No. of cases	Age, years	Sex	Symptoms	Site of primary esophageal tumor	Site of the primary tumor metastasis to the pancreas	Method of diagnosis	Treatment	Survival time, months	(Refs.)
2	NA	NA	NA	NA	NA	EUS-FNA	NA	NA	(2)
1	54	Male	Chest discomfort	Lower	Tail	Surgery	Surgery and chemotherapy	9	(4)
4	NA	NA	NA	NA	NA	Autopsy	NA	NA	(5)
1	70	Female	NA	NA	Tail	Surgery	Surgery	24	(6)
1	68	Male	NA	Lower	Body	Surgery	Surgery and chemotherapy	9	(3)
1	67	Male	Abdomen pain	Upper, middle and lower	Tail and body	EUS-FNA	Adjuvant therapy	1	(12)
1	64	NA	Weight loss	NA	Head	EUS-FNA	Radiotherapy	10	(13)

NA, not available; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

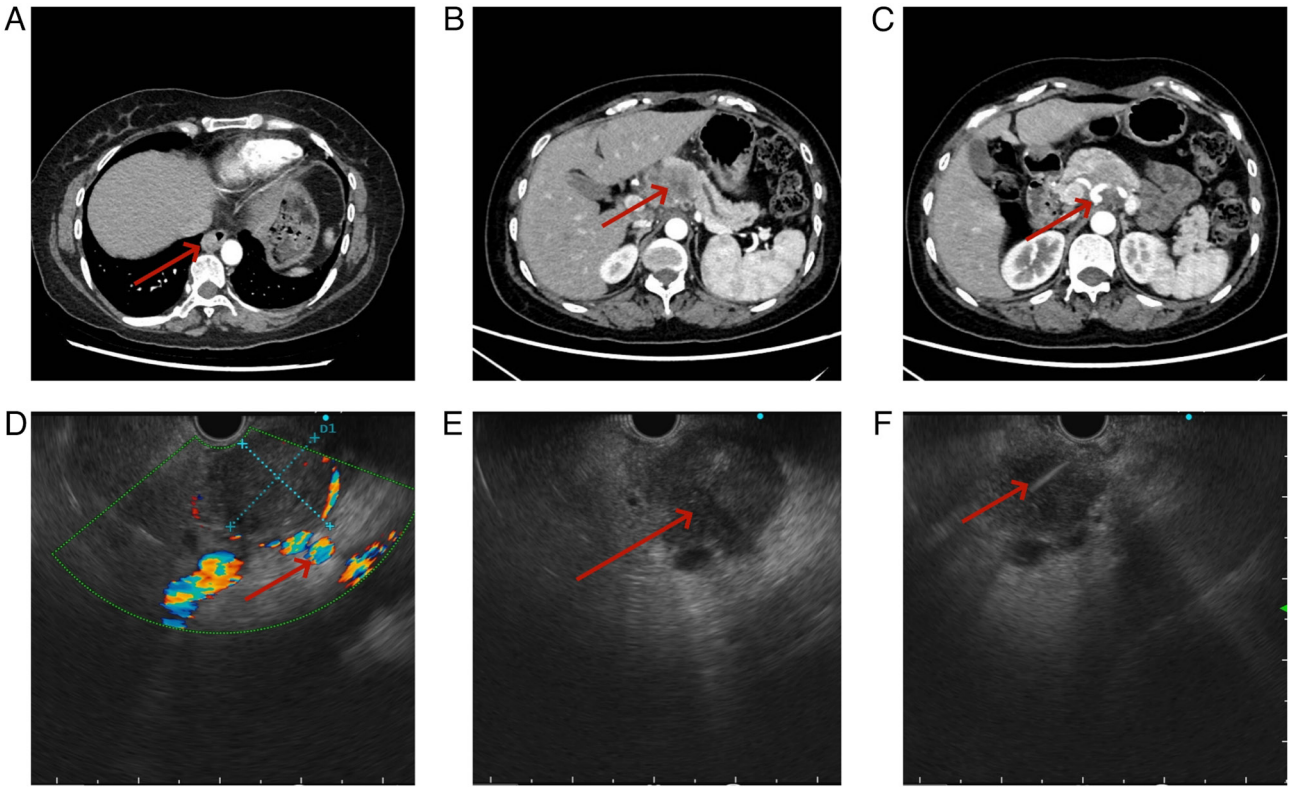

Figure 2. Esophageal and pancreatic tumors on CT scans, as well as the characteristics of pancreatic tumors observed through EUS. (A) CT demonstrated a tumor in the distal esophagus (arrow), (B) CT demonstrated a tumor in the body of the pancreas (red arrow). (C) CT demonstrated the pancreatic tumor that invaded the splenic artery and common hepatic artery (red arrow). (D) EUS demonstrated a pancreatic tumor invading the splenic artery and the common hepatic artery (The red arrow indicates these arteries). (E) EUS demonstrated that the echo intensity of the tumor was low, and that the boundary between the tumor and surrounding pancreatic tissue was clear (red arrow). (F) EUS-FNA was performed to obtain pathological tissue of the pancreatic tumor. Arrow indicates the successful insertion of the 22G needle into the tumor, guided by endoscopic ultrasound). EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

Japan). The Papanicolaou staining was conducted as follows: Slides were immersed in 95% ethanol solution for a minimum of 15 mins at room temperature. Following washing with clean water 2 to 3 times, they were stained with hematoxylin dye. Once the coloration was clearly visible, the slides were rinsed with water. Subsequently, the slides were immersed in a lithium

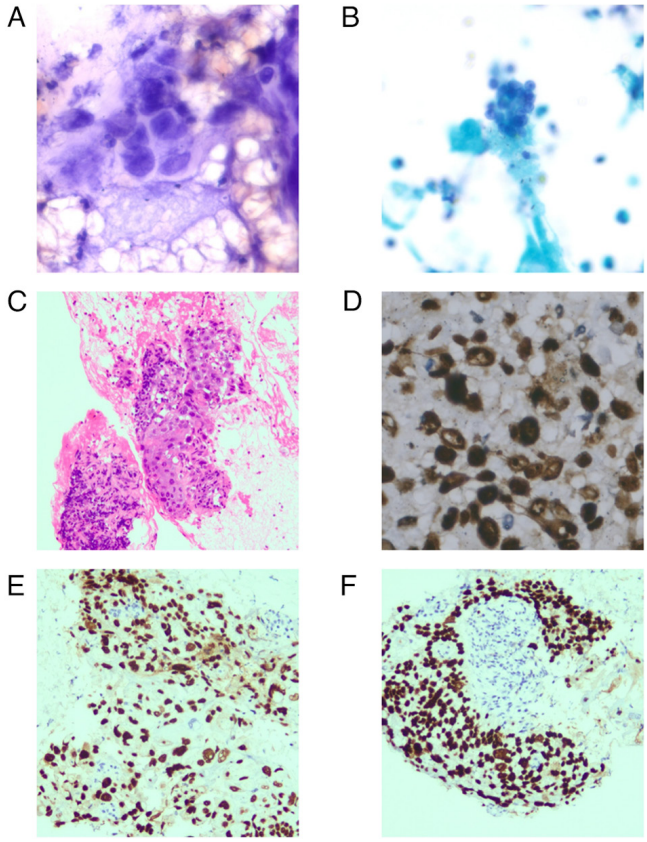

Figure 3. Microscopic cytological and histological features of pancreatic tumor biopsy tissue obtained through endoscopic ultrasound guidance. (A) Cytological analysis of pancreatic tumor obtained through EUS-FNA demonstrated a substantial number of cells with pronounced atypia (magnification x400). (B) Cytological analysis of pancreatic tumor obtained through EUS-FNA demonstrated a substantial number of cells with pronounced atypia with papanicolaou stained(magnification x200). (C) Representative pancreatic tumor pathological tissue stained with hematoxylin and eosin showed potential squamous cell carcinoma features(magnification x100). (D) Ki-67 were highly expressed in pancreatic tumor tissue(magnification x400). (E) Immunohistochemical indicators P40 associated with squamous cell carcinoma, were highly expressed in pancreatic tumor tissue(magnification x100). (F) Immunohistochemical indicators P63 associated with squamous cell carcinoma, were highly expressed in pancreatic tumor tissue(magnification, x100). EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

carbonate solution for 1 to 2 mins. After reverting to blue, the slides were rinsed with water and then transferred to a 95% ethanol solution for dehydration, allowing them to sit for 1 min to eliminate any excess water and immersed in orange G6 stain for 3 mins. Following this, they were immersed in 80, 95, and 95% ethanol solutions for 10 sec each. The samples were placed in EA36 solution followed by thorough rinsing with water. Finally, the samples were dehydrated using 95% ethanol 3 times and sealed with gum.

Following discussions with the MDT team, the patient elected to forgo surgery and instead underwent a combination of radiotherapy and chemotherapy concurrently. The patient received cisplatin-based chemotherapy regimen in conjunction with fluorouracil, (Cisplatin, 80 mg/m^2, iv, d1 and Capecitabine, 1,000 mg/m^2 oral, twice daily, d1-14) alongside concurrent radiotherapy for esophageal and pancreatic tumors (60 Gy in 30 fractions). In May 2025, the patient finished the initial cycle of treatment. Ongoing monitoring will be conducted to evaluate the efficacy and long-term outcomes of this treatment approach.

Discussion

While most pancreatic tumors are primarily of pancreatic origin, metastatic tumors may occasionally arise. Esophageal cancer represents a rare source of metastatic tumors to the pancreas. As esophageal cancer is the ninth most common malignant tumor and the seventh leading cause of cancer-related mortality from GLOBOCAN 2018 (15), reports of pancreatic metastasis originating from esophageal cancer may increase in the future, as detection methods and awareness improve. The predominant histological type of esophageal cancer is squamous cell carcinoma. The incidence of esophageal cancer is highest in Asia, particularly in China, with a higher prevalence in males compared with females (13.6 per 100,000 vs. 4.3 in women (16,17). Lymph node metastasis is considered to be a key factor impacting the survival of patients with esophageal cancer. Typical areas of lymph node metastasis in esophageal cancer vary depending on location of the tumor. For lower esophageal cancer, the incidence of lymph node metastasis in the perigastric region is higher compared with the lower and upper mediastinum regions (18). Middle and lower esophageal cancers are more likely to metastasize to celiac lymph nodes, which can lead to involvement of the pancreas through metastasis to the paraaorta, celiac artery, perigastric region, posterior surface of the pancreatic head, and station 16a1 or16a2 of the common hepatic artery (19). Depending on involvement of multiple lymph nodes, pancreatic metastasis of esophageal tumors may occur (20,21). Esophageal squamous cell carcinoma with pancreatic metastasis is a rare occurrence, representing <5% of all pancreatic tumors (2). The available literature on this topic consists of sporadic case reports with limited information, resulting in a lack of unified treatment guidelines. The present studies analyzed existing 11 cases of pancreatic metastasis of esophageal cancer to inform future treatment strategies (Table I) (1-4,13,15,16). The age of patients with pancreatic metastasis of esophageal cancer was >50 years old. Patients often presented with non-specific symptoms that resemble those of solitary esophageal or pancreatic cancer, including abdominal pain, jaundice, and dysphagia. Tumors in the lower esophagus exhibited a higher incidence of metastasis to the pancreas, particularly to the body and tail of the organ, compared with upper esophageal cancer. As there is currently no standardized diagnosis and treatment plan, this may have resulted in the generally short survival time (< two years) (22).

The prognosis for distant metastatic esophageal cancer is generally poor compared with that of localized esophageal cancer (23). There is debate on whether simultaneous surgical resection of metastases and primary lesions can enhance patient prognosis (24,25). Nonetheless, unnecessary surgical interventions may result in increased surgical trauma and financial burden for patients. The results of the present study and previous clinical experience indicate the importance of obtaining a precise pathological diagnosis as it serves as a key foundation for determining treatment strategy. It is advisable for patients with pancreatic or malignant tumors in other locations to utilize pathological diagnosis

to differentiate between primary and metastatic pancreatic tumors. Therefore, EUS-FNA could be recommended as the primary method for obtaining pathological tissue from pancreatic solid tumors (26). EUS-FNA should be considered in suspected cases of metastatic tumors to the pancreas. In the present case, distinct ultrasound characteristics of pancreatic metastasis of esophageal squamous cell carcinoma were identified. Metastatic tumors to the pancreas exhibit higher echogenicity, uniformity and well-defined boundaries in contrast to primary tumors: Previous studies have seldom summarized the endoscopic ultrasound morphological image characteristics of metastatic tumors to the pancreas for diagnosis (22,27). However, there is limited research on ultrasonic features of pancreatic metastasis of esophageal squamous cell carcinoma, and the occurrence of this type of tumor is rare. Further studies with larger sample size are needed to draw further conclusions.

In conclusion, metastatic tumors to the pancreas are rare and typically present as a pancreatic mass accompanied by extra-pancreatic malignant tumors. It is important to consider the potential for metastasis, rather than solely focusing on dual-source tumors. EUS-FNA may serve as an effective pathological complement for this patient population. The present study demonstrates the feasibility of obtaining pancreatic tissue via EUS-FNA to confirm metastatic pancreatic cancer, thereby facilitating the development of treatment strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JT and WZ collected data and wrote the manuscript. JT and ZW confirm the authenticity of all the raw data. JT, XX and WZ performed imaging and histopathological analysis. PZ was involved in drafting the manuscript, revising it critically for important intellectual content, patient data analysis and gave final approval of the version to be published. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of any potentially identifiable images or data contained in the present study.

Competing interests

The authors declare that they have no competing interests.

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