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Case Report

First reported case of primary small cell cancer of the pancreas with positive TTF-1 tumor marker ☆,☆☆

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ABSTRACT

Small cell carcinomas are very aggressive malignancies that are most often linked with lung cancer, although they may also develop in the pancreas, colon, rectum, skin, and cervix. SCC of the pancreas accounts for about 1% of these neoplasms. An 88-year-old male with several comorbidities who presented with significant weight loss was diagnosed with metastatic pancreatic neuroendocrine carcinoma after complaining of persistent epistaxis and back pain. This case underscores the significance of using atypical tumor markers, such as thyroid transcription factor 1, to diagnose small-cell pancreatic cancer. It also emphasizes the importance of a multidisciplinary, patient-centered approach to managing these aggressive tumors.

Introduction

Small cell carcinomas (SCCs) are highly aggressive malignancies primarily related to cancers of the lung, which account for 18%-20% of all cases. Unusual locations for SCCs include the pancreas, colon, rectum, skin, and cervix [1]. Small cell carcinoma of the pancreas (SCCP) is very rare, representing only 1% of small cell or neuroendocrine malignant neoplasms in this organ. SCCP is a very aggressive tumor, and hence, it has an

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extremely poor prognosis. Most cases of SCC of the pancreas are metastatic at the time of diagnosis, and therefore, they have very limited treatment options and poor prognosis [2].

SCCP requires advanced imaging, including detailed histopathological examination and evaluation of tumor markers. Tumor markers are important not only for diagnosis but also for staging the cancer, prognosis assessment, and monitoring therapy effectiveness and remission [3].

This case report presents an 88-year-old male diagnosed with an atypical form of SCCP, which was notably marked by the presence of thyroid transcription factor-1 (TTF-1)—a tumor marker predominantly associated with lung and thyroid cancers. The rarity of TTF-1 in pancreatic tumors posed a diagnostic challenge, emphasizing the complexity of using tumor markers in cancer diagnostics. Through careful assessment of imaging and biopsy, a definitive diagnosis of SCCP was confirmed, highlighting the importance of careful interpretation of tumor markers in atypical cases of small cell carcinoma.

Case presentation

An 88-year-old male with a history of hypertension, diabetes mellitus, COPD, beta thalassemia minor, cholecystectomy, and appendectomy came to the emergency department with back pain and unrelieved persistent epistaxis by himself for thirty minutes. He also reported a thirty-pound weight loss over the last year, initiated after he started taking a fat burner pill. Initial emergency department assessment revealed transaminitis with an ALT of 301 U/L (normal range: 7-56 U/L) and an AST of 340 U/L (normal range: 10-40 U/L). The lipase level was significantly elevated at 1,592 U/L (normal range: 0-160 U/L). The prothrombin time (PT) was borderline elevated at 13.5 seconds (normal range: 11-13.5 seconds), and the INR was 1.2 (normal range: 0.8-1.2). Troponin was slightly elevated at 0.05 ng/mL (normal range: 0-0.04 ng/mL), and microcytic anemia. Concerns of acetaminophen overuse were suspected; however, serum levels were within normal limits. An abdominal ultrasound identified multiple liver masses, with the largest in the right hepatic lobe. A computed tomography scan of the abdomen and pelvis (CTAP) revealed a pancreatic mass with biliary obstruction and extensive metastasis involving the liver, bones, spleen, adrenal glands, and peritoneal and retroperitoneal spaces (Figs. 1 and 2).

The electrocardiogram showed a right bundle branch block (RBBB). Chest CT was significant for large mediastinal lymph node conglomerates as well as right hilar adenopathy, most likely metastatic disease from primary pancreatic malignancy. Further imaging to investigate the cause of back pain revealed a T12 vertebral compression fracture and multiple radiolucent lesions indicative of metastasis—a neurosurgery consultation advised against surgical intervention.

An oncology consult led to an image-guided biopsy of the right retroperitoneal mass by IR, confirming a poorly differentiated neuroendocrine carcinoma, small cell type (Fig. 3). The biopsy was positive for tumor markers AB1/AE3, CAM5.2, CK7 (focally), CEA monoclonal (focally), thyroid transcription factor-1 (TTF-1), synaptophysin, chromogranin A, and a high proliferation index with Ki-67 at 95%. CA19-9 levels were within normal limits (10 U/mL, N < 34). Follow-up labs showed increasing bilirubin and alkaline phosphatase levels.

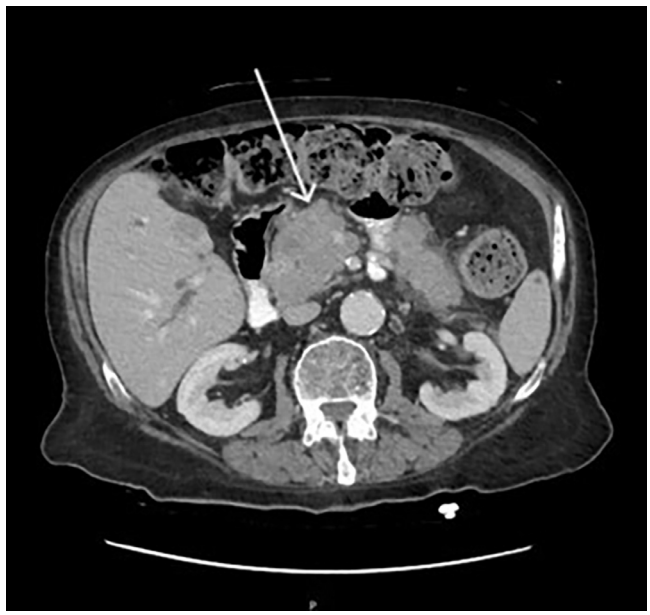

Fig. 1 – CTAP reveals a 5.4 × 5.4 cm pancreatic head mass, likely cancer, encasing <180° of the superior mesenteric artery and surrounding the superior mesenteric vein.

The oncology team suggested chemotherapy and a palliative hepatic stent, but the patient declined both and changed his status to DNR/DNI. Despite referrals for home hospice and visiting nurse services, he did not qualify. He could walk independently with a walker and was stable at discharge, with instructions emphasizing medication management, lifestyle changes, and follow-ups. However, within 24 hours of discharge, he returned to the ED with increased back pain after a fall. He remained stable and was discharged to a subacute rehabilitation facility for further management and support, with a focus on medication optimization and patient education.

Discussion

Small cell carcinoma of the pancreas (SCCP) is an exceedingly rare and highly aggressive tumor, accounting for approximately 1% of all primary pancreatic neoplasms [2]. The biological origins of SCCP are not well understood. Still, it is hypothesized that these cancers may originate from totipotent stem cells within the pancreatic ductal system, capable of differentiating into various endocrine cells. This hypothesis stems from a 1972 report by Patchefsky et al., which described a pancreatic "oat" cell tumor with elevated levels of urinary 5-hydroxyindoleacetic acid, suggesting an islet cell origin [4].

Advanced SCCP, often with diffuse metastases at diagnosis, is the usual presentation. Our 88-year-old patient complained of severe back pain and weight loss, and abdominal imaging showed diffuse metastatic disease involving multiple organs—very characteristic of this malignancy. This

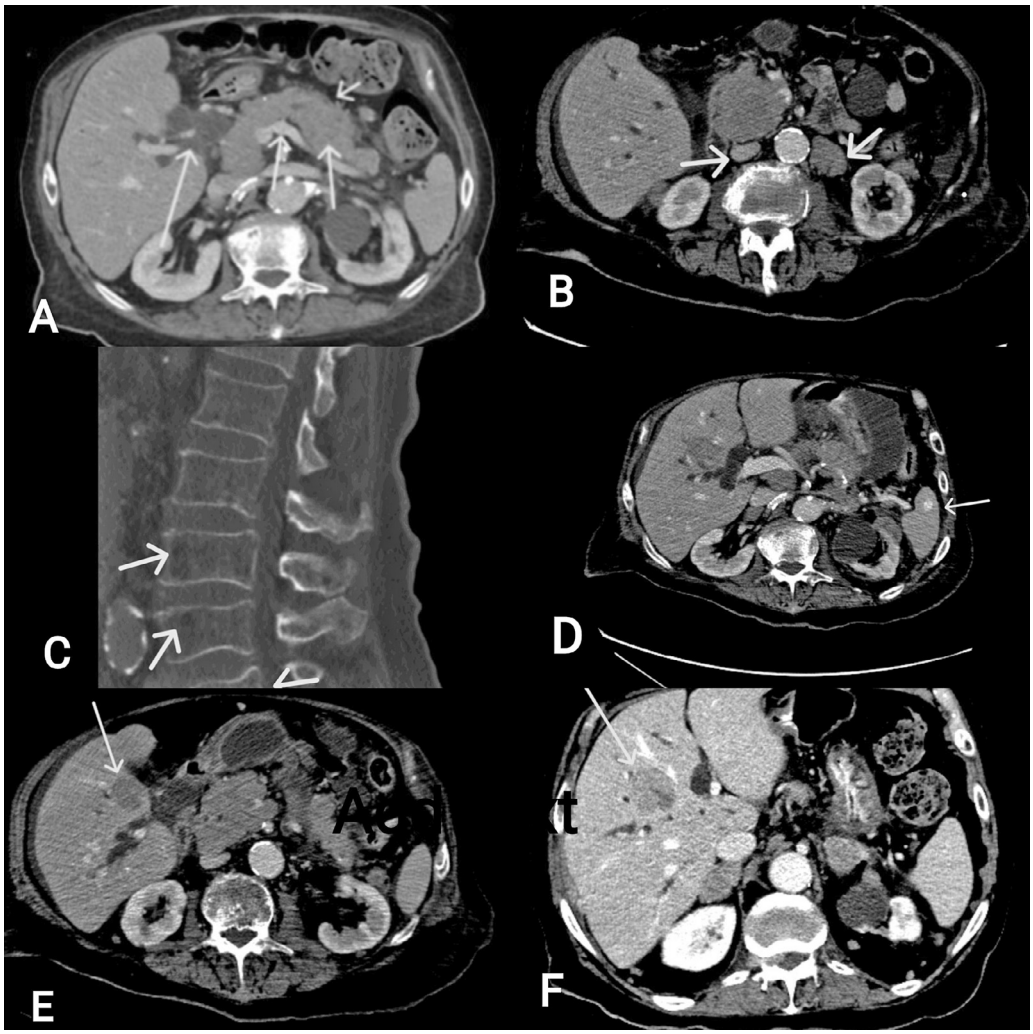

Fig. 2 – Inflammatory changes with main pancreatic duct dilatation up to 6 mm are seen (A), along with extensive metastasis to the adrenal glands (B), bones (C), spleen (D), and liver (E, F).

diffuse metastasis is characteristic of SCCP and often involves peripancreatic lymph nodes, the liver, and other distant sites. Again, in contrast to the pulmonary type, SCCP is not usually associated with paraneoplastic syndromes, as in our case [5,6].

The diagnosis of SCCP is confirmed by histologic analysis of a tumor biopsy and focusing on neuroendocrine differentiation markers such as chromogranin and synaptophysin, which were both present in our patient. Other positive neuroendocrine markers included CAM5.2 and CK7. However, in light of these results, the absence of CA19-9 and other histological features determined that the mass was not of the typical pancreatic ductal origin but of SCCP arising from the islet cells.

A unique feature of our case is the expression of thyroid transcription factor-1 in the tumor biopsy, a marker largely restricted to lung and thyroid cancers [7]. This is all the more interesting, with no primary pulmonary or thyroid mass in our patient. Expression of TTF-1 has also been reported in extrapulmonary organs, including the bladder, prostate, and cervix; however, it is not normally expressed in the pancreas. Incidentally, another report has circulated regarding the expression of TTF-1 in a primary tumor of the common bile duct, suggesting its more widespread expression in various malignancies [8].

It is no surprise that poorly differentiated small cell carcinomas would assume atypical tumor markers. As mentioned above, these carcinomas are considered to emanate from totipotent stem cells capable of differentiating into many FW cell types. This could explain the unexpected expression of TTF-1 in some gastrointestinal small-cell cancers [9,10]. The appearance of TTF-1 in SCCP underlines the complexity of such cases and puts particular emphasis on comprehensive evaluations. Thus, the detection of TTF-1 should institute a thorough investigation rather than invasive measures next in the sequence. This ensures that the site of the primary tumor is more accurately determined, reflecting the need for holistic assessment in the management of complex cancer presentations.

SCCP management is challenging because it is an extremely rare and extremely aggressive disease. As these tumors are often metastatic at presentation, there is a limited

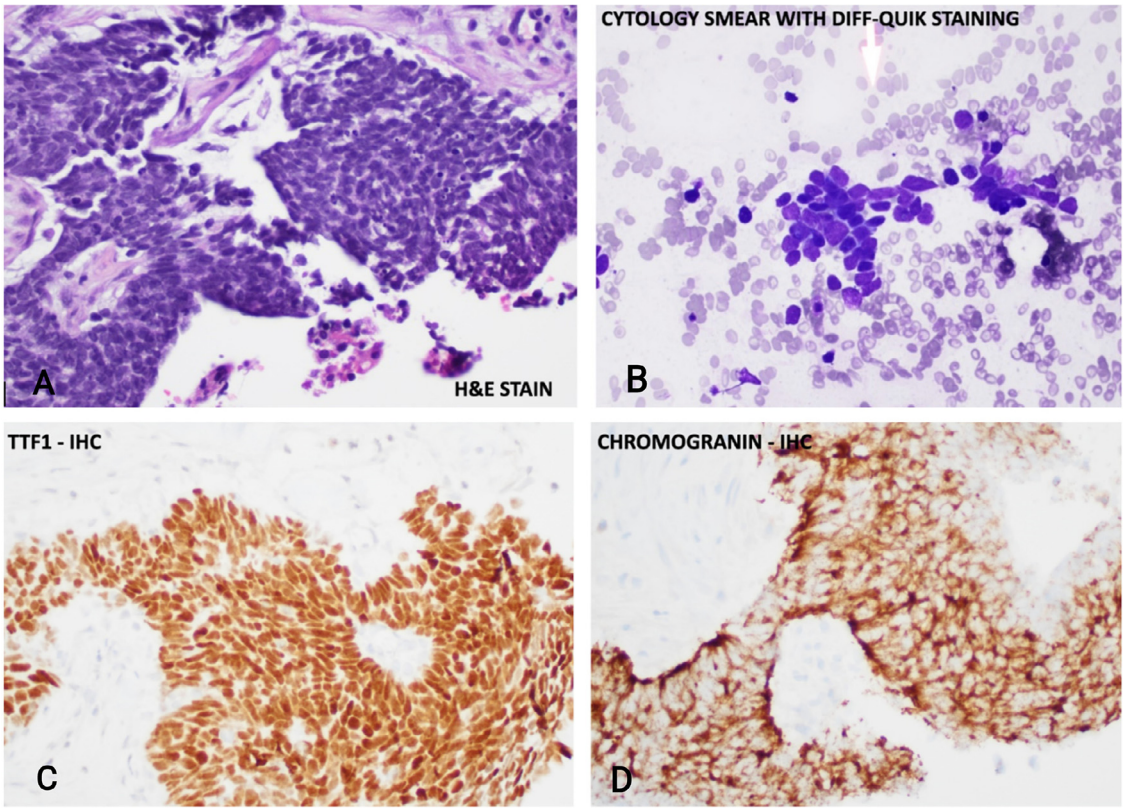

Fig. 3 – (A) A cell block of pancreatic mass FNA displays sheets of neoplastic cells with hyperchromatic nuclei with scant cytoplasm and nuclear molding. (B) Diff-Quik smear shows cellular with loosely cohesive sheets of monotonous cells. (C) TTF-1 immunohistochemistry shows diffuse and strong nuclear staining in the neoplastic cells. (D) Chromogranin immunohistochemistry shows diffuse and strong membranous staining in the neoplastic cells.

scope for treatment choices. Historically, chemotherapies like those for small cell lung cancer—including cisplatin and etoposide—have been used, with some cases responding to regimens used to treat malignant lymphoma [11,12]. More recent experiences with such immunotherapeutic agents as ipilimumab and nivolumab are promising in some cases of pancreatic SCC [13,14]. However, even with these efforts, the prognosis is still very grim, with an overall median survival of 4 months for SCCP patients who present with metastatic diseases [15].

Conclusion

Small cell carcinoma of the pancreas is an extremely rare and very aggressive malignancy that causes diagnostic difficulties and requires therapeutic efforts. This present case, therefore, supports the inclusion of atypical tumor markers, such as thyroid transcription factor 1, in the panel and the need for a proper diagnostic workup. The diagnosis also brings a ray of hope in management in this otherwise grim prognosis by being made at an early stage and accurately. It underlined the adoption of a multidisciplinary approach to management with a patient-centered focus when treatment options are limited.

Patient consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

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