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# Pancreatic Metastasis from Small-Cell Neuroendocrine Cervical Cancer - A Case Report and Literature Review

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## Abstract

Secondary tumors of the pancreas are uncommon, comprising approximately 2% to 7.2% of all pancreatic malignancies. Compared to renal cell carcinoma, hematologic malignancies, gastric cancer, and lung cancer, pancreatic involvement from primary cervical cancer is extremely rare. Furthermore, Small-Cell Neuroendocrine Cervical Carcinoma (SCNCC) is a rare subtype of cervical cancer, accounting for less than 5% of all cases. Here, we present a case of SCNCC metastasizing to the pancreas and review the literature pertaining to this uncommon occurrence. In September 2018, a 41-year-old female was diagnosed with stage IVB SCNCC, exhibiting lung metastasis. She underwent concurrent chemoradiation followed by brachytherapy. However, due to the progression of lung metastases, she received Docetaxel/Nedaplatin (DP) as second-line therapy and subsequently additional anlotinib added as third-line treatment. For two years after the initial diagnosis, abdominal imaging examinations revealed no abnormalities. Nevertheless, a follow-up whole-abdominal contrast-enhanced CT scan two years later suggested pancreatic metastasis. Pathological examination, guided by Endoscopic Ultrasound with Fine-Needle Aspiration (EUS-FNA), confirmed the diagnosis of small-cell neuroendocrine carcinoma. Given the morphologically similarity and patient's oncological history, the pancreatic lesions were diagnosed as secondary metastasis from the previously treated SCNCC. She promptly underwent DP chemotherapy, pancreatic irradiation, and followed by further lines of treatment including Etoposide/Cisplatin (EP), Irinotecan/Platinum (IP) and Ceritinib. Although the pancreatic metastases were controlled, metastasis in other organs progressed, leading to her demise in May 2022.

**Keywords: Small-cell neuroendocrine carcinoma; Uterine cervix; Pancreatic metastasis; Case report**

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## Introduction

Small-Cell Neuroendocrine Cervical Carcinoma (SCNCC) is a rare subtype of cervical cancer, accounting for less than 5% of all cases [1]. SCNCC is known for its aggressive nature and poor prognosis. Common metastatic sites include the lung, liver, and bone [2], whereas reports of metastasis to other sites are sporadic. Pancreatic metastasis specifically originating from primary SCNCC is exceedingly rare, with only four recorded instances in the literature to date (Table 1) [3-6]. We present a case of primary SCNCC that exhibited an unusually continuous progression, accompanied by multiple distant metastases, including to the pancreas.

## Case Presentation

A 41-year-old female patient was clinically diagnosed with stage IVB SCNCC (lung metastasis) in September 2018, according to the FIGO 2018 staging system (Figure 1A, 1B). Immunohistochemistry tests indicated a positive status for human papillomavirus on P18. After four cycles of paclitaxel and nedaplatin (TP) chemotherapy combined with pelvic external beam

**Table 1:** Pancreatic metastasis from primary small-cell neuroendocrine cervical carcinoma.

| Age (years) | Stage | Metastasis | | pancreatitis | Diagnostic modality | Interval to pancreatic metastasis | Metastasis of multiple organs | Treatment | Prognosis | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | site | size (mm) | | | | | | | |
| 36 | IB2 | Head and body | NR | Yes | MRI, EUS-FNA, PET/CT | On the 63rd day after initial diagnosis | Yes | EP | NED at 5 months | [3] |
| 48 | IVB | Tail | 70 | No | Abdominal exploration and a needle biopsy | Concurrent | Yes | CyVadic, BCG | NED Over a period months | [4] |
| 38 | IIB | Body | 10 | No | Contrast-enhanced CT, EUS-FNA | 11 months | NR | Chemotherapy | NED at 5 months | [5] |
| 56 | IVB | Head and body | 19.5, 9 | Yes | Ultrasound, EUS-FNA | Concurrent | Yes | EP, paclitaxel, temozolamide and holocranial radiotherapy. | Alive but progress. at 24 months | [6] |
| 41 | IVB | Neck | 18 | Yes | EUS-FNA | 24 months | Yes | DP, pancreas radiotherapy. EP, IP with caritinib, caritinib with anlotinib | Dead at 20 months | Our Case |

NR: Not Reported; NED: No Evidence of Disease; BCG: Bacillus Calmette-Guérin.

radiation therapy of 45 Gy/25 fractions, the number and size of lung metastases decreased significantly and abdominal CT scan indicates normal. Subsequently, she underwent brachytherapy irradiation of 30 Gy/5 fractions. However, five months later (April 2019), a chest CT scan revealed a remarkable increase in bilateral lung metastases. She promptly received two courses of docetaxel with nedaplatin (DP) and achieved a partial response. Nevertheless, due to slight lung metastatic progression, as well as increased lymph nodes in the right inguinal region, anlotinib was added to her treatment plan, along with six additional cycles of DP. After one month (July 2020), a whole-abdominal and pelvic MRI showed decreased lymph nodes in the right inguinal region, chest CT showed stability of lung metastasis.

In September 2020, a follow-up whole-abdominal contrast-enhanced CT scan revealed a hypo-intense nodule, suggestive of possible pancreas metastasis (Figure 1C). Pelvic MRI showed a slight increase and enlargement of lymph nodes in the right inguinal region. Endoscopic Ultrasound (EUS) identified an 18 mm × 12 mm, uneven, hypoechoic, poorly defined nodule in the pancreatic neck, associated with pancreatic duct distortion and slight dilatation posterior to the nodule (Figure 1D). No involvement of the pancreatic head, common bile duct, or vascular invasion was observed. EUS-guided Fine-Needle Aspiration (FNA) using a 22-gauge needle sampled the nodule, and Papanicolaou-stained smears revealed a cluster of uniform-sized atypical epithelial cells (Figure 1E). Histopathological analysis confirmed SCNCC, with no adenocarcinoma or squamous carcinoma components (Figure 1F). Immunohistochemical analysis showed positive staining for SYN, CgA, CK, CK7, TTF-1, and CD56, with a Ki-67 positive rate of 60%, consistent with neuroendocrine tumor metastases. Thus, discontinuing anlotinib, she underwent two cycles of DP therapy and received 30Gy/10 fractions of pancreatic irradiation. Nevertheless, despite the stability of her pancreatic metastases, her lung metastases progressed, necessitating two cycles of etoposide and cisplatin (EP) treatment. Subsequent scans revealed a reduction in the size of her pancreatic metastases, but the lung metastases continued to deteriorate. Therefore, four cycles of irinotecan with platinum (IP) and ceritinib (PD-1 inhibitor) were prescribed. Although her pancreatic metastases remained stable (Figure 1G), there was a further worsening of her lung metastases (Figure 1H), along with the emergence of liver metastasis and multiple post-peritoneal lymph nodes. She received palliative therapy with ceritinib and anlotinib, but continued to worsened and ultimately leading to her demise in May 2022.

## Discussion

Secondary tumors of the pancreas are rare [7-9], accounting for approximately 2% to 7.2% of all pancreatic malignancies diagnosed through EUS- or CT-guided FNA [10,11]. Typically, they arise from primary tumors in organs such as the kidney, lung, breast, colon, ovary, and rectum [10]. Renal cell carcinoma is the most common source of solitary pancreatic metastases [7], followed by hematologic malignancies [12], gastric [9] and lung cancer [13], with one-third of lung cancers being small cell carcinoma [11]. Conversely, pancreatic involvement from SCNCC is extremely rare [14]. The interval between the establishment of the primary SCNCC diagnosis and the development of pancreatic metastasis ranged from simultaneous occurrence with the primary SCNCC [4,6] to 2 years, as in our case (Table 1).

In most cases, secondary involvement of the pancreas is overlooked in clinical settings, as patients with pancreatic metastasis often exhibit multiple, potentially life-threatening metastatic lesions in other organs, while symptoms associated with pancreatic lesions are not prominent [8]. Occasionally, however, obstructive pancreatitis may arise as a manifestation due to pancreatic metastasis (Table 1) [3,6]. Notably, pancreatic metastasis can sometimes occur as an isolated event in the early stages of the disease, with no signs of synchronous metastases to other organs [7,11,15]. Furthermore, the primary tumor is frequently very small and may have been undetected at the time of identification of the pancreatic tumor. In such instances, the pancreatic tumor may be erroneously diagnosed as a primary neoplasm [9,12].

A diagnosis of pancreatic metastasis is typically made using imaging modalities, including ultrasonography, EUS, CT, MRI/MRCP, and PET (Table 1) [3,5,6,14]. The recent increase in the use of simultaneous Endoscopic Ultrasound-guided Fine Needle Aspiration (EUS-FNA) has enabled pathological diagnosis prior to selecting appropriate therapeutic strategies (Table 1) [3,5,6,14,15]. EUS-FNA is equally effective as CT-guided biopsies in achieving specimen adequacy and definitive diagnoses, while avoiding unnecessary open surgical biopsies or resection of the tumor [11]. In particular, cytologic examination of the pancreatic tumor through EUS-FNA facilitates an early and accurate diagnosis of solitary pancreatic metastasis in some

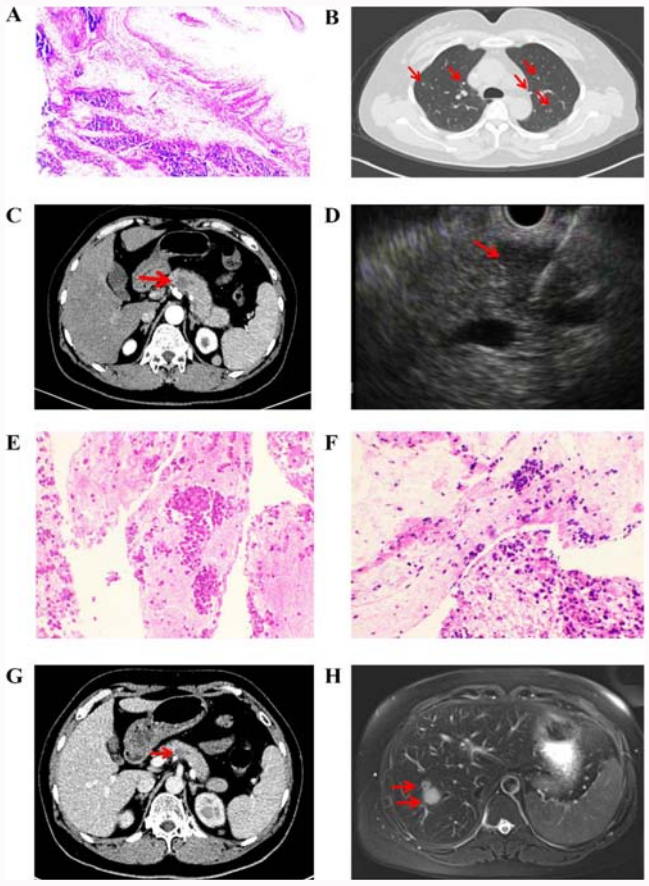


**Figure 1:** A. Representative tumor section revealed the small-cell NEC component in the uterine cervix specimen.
B. Chest CT showed multiple metastatic masses in bilateral lungs (arrowed).
C. Enhanced abdominal CT in arterial phase demonstrated a faintly attenuating 18-mm mass in pancreatic neck (arrowed).
D. EUS showed a 18 mm × 12 mm, irregular, hypoechoic nodule in pancreatic neck (arrowed), associated with pancreatic duct distortion and posterior dilation.
E, F. EUS-FNA smear and histopathology exhibited small round cells with hyperchromatic nuclei, scant cytoplasm, evident atypicality.
G. Abdominal CT showed reduction in size of the hypo-intensity nodule in pancreatic neck.
H. Chest CT indicated an increase in multiple lung lesions.

cases, even when the primary tumor remains clinically silent [11].

However, distinguishing primary pancreatic cancer from pancreatic metastases arising from cancers in other parts of the body can be challenging, particularly when original tissue is rare or lacks specific markers. Based on several observations, we diagnosed the pancreatic tumor as metastatic disease. Firstly, the tumor had not been detected on previous abdominal imaging examinations, even two months prior, and the rapid clinical progression was incompatible with primary pancreatic Neuroendocrine Carcinoma (NEC). Secondly, the patient had a prior history of cancer and exhibited lung metastasis at the time of initial diagnosis. Additionally, pathological and immunohistological examinations performed *via* EUS-FNA revealed small-cell NEC morphologically resembling those found in the primary cervical carcinoma diagnosed two years ago. Therefore, we conclusively diagnosed the pancreatic tumor as a heterochronic pancreatic metastasis stemming from SCNCC. Given the minimal increase and enlargement of lymph nodes in the right inguinal region, hematogenous spread was considered more likely than lymphatic spread.

Once diagnosed with metastatic carcinoma, immediate resumption of systemic chemotherapy is crucial [16]. Recommended regimens for pancreatic metastasis arising from SCNCC include cisplatin/etoposide (Table 1) [3,6] and carboplatin/etoposide, as well as paclitaxel (Table 1) [3], bevacizumab, and atezolizumab [17]. In patients with jaundice, endoscopic biliary drainage is typically the preferred therapeutic approach [16]. Given the high radiosensitivity of small-cell NEC, palliative radiation therapy for symptomatic metastatic lesions is often effective, and concomitant chemoradiotherapy may also be considered for palliative purposes [16]. Despite administering these treatments in our case, the patient's disease continued to progress and passed away eighteen months later.

## Conclusion

We have presented a rare instance of a patient with primary SCNCC who developed pancreatic metastasis. In patients presenting with a pancreatic mass, the possibility of metastatic tumors should be taken into account, especially if they have a prior history of malignancy. EUS-FNA is the most recommend modality for diagnosis. Typically, the prognosis for these patients is unfavorable. Currently, there is no established adequate treatment strategy for cancer that metastasizes to uncommon locations.

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