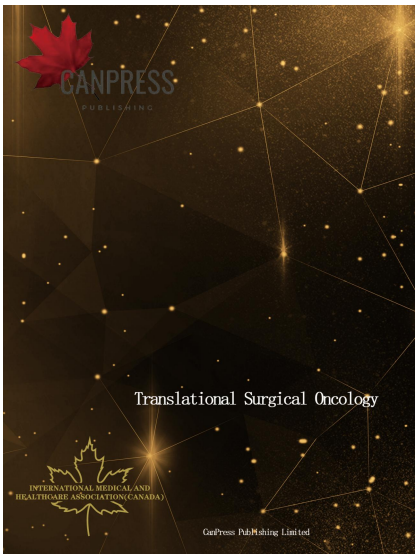
Pancreatic cancer with multiple cutaneous metastases and pancreatitis as first manifestations: a case report



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Abstract

Pancreatic cancer has an insidious onset and a high degree of malignancy, which has the characteristics of difficult early diagnosis, low surgical resection rate, unsatisfactory drug treatment effect and poor prognosis, and most of the patients have already undergone distant metastasis and lost the chance of surgery. A small number of patients start with acute pancreatitis, which is easy to be misdiagnosed by the clinic. In addition, the common sites of distant metastasis of advanced pancreatic cancer are the liver, peritoneum and lungs. Cutaneous metastasis is rare, but in rare cases, it is the only external manifestation of pancreatic cancer. Up to now, about 60 cases of cutaneous metastasis of pancreatic cancer with complete clinical data have been reported in the literature, all of which suggest a poor prognosis. In this case, we present a patient of pancreatic cancer with multiple cutaneous metastases and acute pancreatitis as the first manifestation, and the patient died one month after diagnosis due to the rapid progression of the disease. Clinical awareness and attention to early diagnosis of pancreatic cancer and cutaneous metastases still need to be improved, and positive and timely pathological diagnosis and genetic testing are particularly important to guide treatment and improve the prognosis.

Keywords: Pancreatic cancer, Cutaneous metastases, Early diagnosis, Pathology, Genetic testing

Introduction

Cutaneous metastases from pancreatic cancer are rare, with the incidence of only 0.7% to 9.0% of all cancer patients[1]. In some patients, cutaneous metastasis is detected before the primary lesion, and pancreatic ductal adenocarcinoma (PDAC) is the most common histopathological type of cutaneous metastasis. The common sites of metastasis of pancreatic cancer are the umbilicus (also known as ‘Mary Joseph's nodes’), the skin of the face and neck, the axilla, the anterior thorax, the abdomen, and the back, while cutaneous metastases to the scalp and the genitals are rare[2-4]. Cutaneous metastases can take a variety of forms, including nodules, subcutaneous masses, ulcers, plaques, scarring, and localized thickening of the skin[2,5], and they may be single or multiple, with or without painful symptoms, and are easily confused with lesions such as rashes, hyperpigmentation, granuloma nodosum, and primary tumors of the skin.

Systematic physical examination, laboratory, imaging tests, and pathological biopsies can help identify the origin of the primary tumor. In rare cases, cutaneous metastases are the first manifestation of pancreatic cancer or the first hint of postoperative recurrence1. Surgical excision of cutaneous metastases is only performed in conjunction with radical resection of the primary focus in parallel after other metastatic possibilities have been ruled out, but the efficacy is limited. Meanwhile, a small proportion of patients with pancreatic cancer have acute pancreatitis as the first symptom, and imaging often suggests mass pancreatitis. The symptoms may mask the primary disease, and different treatment decisions will affect the regression of such patients. Here we present a case of pancreatic cancer with multiple cutaneous metastases and acute pancreatitis as the first manifestation. Since the patient was unable to undergo surgical resection and pancreatic puncture, we performed cytological testing of ascites, resection biopsy of metastatic foci, and genetic testing, and diagnosed stage IV pancreatic cancer by combining medical history, laboratory and imaging tests. Unfortunately, the patient's disease progressed rapidly, and despite

multidisciplinary treatment the patient finally died of infection and systemic wasting. Therefore, cutaneous metastasis of pancreatic cancer is rare and suggests a poor prognosis. Early identification of its clinical features and timely pathological diagnosis are essential for choosing appropriate treatment strategies within a short period of time to improve the prognosis.

Case presentation

In November 2024, a 39-year-old male patient was referred to the Department of Hepatobiliary and Pancreatic Surgery of the First Hospital of Peking University, who had been diagnosed with acute necrotizing pancreatitis, accompanied by pseudocyst formation, in an outside hospital due to intermittent abdominal pain for more than 3 months. On physical examination, the patient showed positive epigastric tenderness without rebound pain, as well as multiple reddish skin nodules and subcutaneous masses in the upper left armpit, scalp, right lower jaw, anterior abdominal wall, and right lumbar region, which were hard, with poor mobility and no compression pain (Figure 1), and there was no jaundice or other abnormalities, and we learned that his uncle had passed away due to pancreatic cancer. He continued to improve the laboratory tests and imaging examinations.

Laboratory tests showed that liver and kidney function were basically normal, but the following parameters were abnormal: white blood cell count of 16.2*109 (normal range: 3.5-9.5*109), haemoglobin concentration of 93g/L (normal range: 130-175 g/L), neutrophil percentage of 86% (normal range: 40%-75%), albumin 33.7g/L (normal range: 40-55g/L), prealbumin 101.5 mg/L (normal range: 200-400 mg/L), sodium 136.26 mmol/L (normal range: 137-147 mmol/L), and lactate dehydrogenase 302 IU/L (normal range: 100-240 IU/L), which are abnormalities that may be related to the patient's inflammatory stimulus and fasting. Prothrombin time 17.2 s (normal range: 10.1-12.6 s), prothrombin activity 52% (normal range: 85%-128%), International Normalised Ratio 1.52 (normal range: 0.88-1.10), fibrinogen 4.16 g/L (normal range: 2-4 g/L), D-dimer 2.15 mg/L (normal range: < 0.24mg/L), and the coagulation disorders may be related to the patient's infections, anemia and oncological diseases. Unexpectedly, a number of tumor markers were elevated in the patient, including alpha-fetoprotein 22.5 ng/ml (normal range: <10.9 ng/ml), CA19-9 375 U/ml (normal range: <37 U/ml), CA125 121 U/ml (normal range: <35 U/ml), CA72-4 >250 U/ml (normal range: <6.9 U/ml), CA24-2 >300 U/ml (normal range: <20 U/ml), further suggesting the possibility of pancreatic cancer in the patient. At the same time, enhanced computed tomography (CT) of the abdominopelvic region was perfected, suggesting structural destruction of the tail of the pancreatic body, multiple internal foci of mixed low density, and multiple peripancreatic exudates, which was consistent with the manifestation of acute necrotizing pancreatitis, accompanied by the possibility of multiple retroperitoneal swollen lymph nodes, which was alerted to a tumorous lesion, with abdominopelvic effusion, and no hepatic metastases were seen (Figure 2).

Subsequently, we performed cytology of the ascites showing scattered distribution of heterogeneous epithelial cells, and immunohistochemistry showed calretinin (+), CEA (+), CA19-9 (+), and EMA (+), suggesting a tumorous origin of the gastrointestinal tract (Figure 3). Biopsy of excised abdominal wall and lumbar nodes suggested that striated infiltration of tumor cells was visible in the dermal layer of skin tissue, and immunohistochemistry showed CKPan (AE1/AE3) (+++), Vimentin (-), CK7 (++), CK20 (-), CDX-2 (+), CEA (-), AFP (-), p53 (+), S-100(-), HMB45(+/-), CA19-9(+), Ki-67 80% (Figure 3), mismatch repair protein-pMMR: MLH1 nuclear+, MSH2 nuclear+, MSH6 nuclear+, PMS2 nuclear+, PD-L1, CPS:2. Meanwhile, genetic testing showed microsatellite stabilisation (MSS), MET Amplification mutation, TP53 c.375+1G>C mutation. In conclusion, the immunophenotype of pancreatic cancer was met and the diagnosis of stage IV pancreatic cancer was made according to the National Comprehensive Cancer Network (NCCN) diagnostic criteria for pancreatic cancer. Chemotherapy and targeted immunotherapy could not be administered due to the patient's poor general condition. The patient's condition deteriorated rapidly within a short period of time, with rising infection indicators and a progressive decline in haemoglobin, and he eventually died of infection and malignant tumor consumption one month after the diagnosis. The patient and his family signed an informed consent form for the use of his clinical data in this study, in accordance with the principles of ethics and the Declaration of Helsinki.

Discussion

Pancreatic cancer is a malignant tumor that poses a serious threat to human health, ranking 12th in global cancer incidence and 6th in tumor-related mortality, accounting for about 5% of all cancer deaths worldwide[6]. The 5-year survival rate of pancreatic cancer patients is only about 13%, and it will become the second leading cause of cancer-related deaths in 2030[7]. Currently, the youngest case of pancreatic cancer with cutaneous metastasis reported in the literature is 40 years old[2,8], and the present patient was 39 years old, further indicating the increasing trend of the younger generation of pancreatic cancer patients, which has resulted in a gradually increasing socioeconomic burden[9]. It also indicates the lack of means for early diagnosis of pancreatic cancer, as well as the insufficient screening and identification of patients with a family history of pancreatic cancer and non-abdominal first symptoms. Cutaneous metastases from pancreatic cancer are rare, with 679 cases occurring in a study of 7518 autopsied patients, of which pancreatic cancer accounted for only about 2%[5]. PDAC is the most common pathologic type of cutaneous metastasis, and others, such as neuroendocrine neoplasms, mucoepidermoid carcinomas, and pancreatic sarcomas have been reported in small numbers[2,10,11]. Cutaneous metastases can occur in multiple

areas of the body, with nodules to the umbilicus being the most common type of cutaneous metastasis. Metastases to the umbilicus, also known as Mary Joseph's nodes, were first reported in 1928[12]. Others, such as scalp, face and neck, trunk, and perineum, can also occur, and most of them are single-site metastases, and multiple cutaneous metastases are rare, and cutaneous metastases are often associated with widespread dissemination of malignant tumors at the end of the disease and systemic metastases. A median survival of 5 months was reported in the study[8], and another study demonstrated a median survival of 13.7 months for umbilical metastases, which was greater than those with non-umbilical metastases (8.9 months) [13], but both suggest a poor prognosis. In this group of patients, early identification of cutaneous metastases, aggressive pathological and genetic testing, individualized multidisciplinary management and a combination of radiotherapy and chemotherapy may help to improve the patient's prognosis and survival[14]. In this case, the patient had multiple cutaneous metastases with massive carcinomatous ascites formation at the time of consultation. Pathological biopsy and genetic testing were promptly improved during symptomatic treatment, but the patient's condition was too poor to benefit from the screened chemotherapy and targeted drugs. Cutaneous metastasis occurs more often in pancreatic body tail cancer than in pancreatic head/leptomeningeal tumor, which may be related to the fact that pancreatic head/leptomeningeal tumor is closer to the biliary tract and peripheral blood vessels, which causes symptoms earlier and is easily recognized by the clinic; while pancreatic body tail cancer is more ‘quiet’, and most of them are already at advanced stage when they are detected, which is the case of the patient in the present case. Cutaneous metastases can be manifested as nodules, lumps, ulcers, scar hyperplasia, etc. In this case, the patient's anterior abdominal wall and right lumbar metastases were manifested as lumps, while the scalp, the upper part of left armpit and the lower jaw were manifested as nodules similar to rashes, which suggests that metastases in different forms can appear simultaneously, which indicates that it is particularly important for clinicians to recognize this rare phenomenon and conduct systematic and comprehensive physical examination. Various theories of cutaneous metastasis of malignant tumors have been proposed, but their specific mechanisms have not yet been elucidated, including the soil seed theory, direct invasion, lymphatic or blood dissemination, and chemotaxis hypothesis, among which abnormalities of the lymphatic system leading to celiac reflux to the skin is a possible route. It is worth noting that cutaneous metastasis due to surgery/trauma is easy to be overlooked, and abnormalities of the skin tissues around the surgical incision and the drain opening should be paid attention to.

The pathological features of PDAC and the results of genetic testing are also important factors influencing treatment options and prognosis. Microsatellite instability (MSI) is a phenomenon in which the length of microsatellite sequences is altered due to insertion or deletion mutations during DNA replication. MSI results can be classified into microsatellite stable (MSS), microsatellite instability-low (MSI-L) and microsatellite instability-high (MSI-H). Meanwhile, several retrospective studies[15,16] have shown that somatic mutations in the mismatch repair (MMR) gene can also cause mismatch repair deficiency (dMMR)/MSI-H and are associated with a variety of cancers. patients with pancreatic cancer of the dMMR/MSI-H phenotype may be affected from the Immunotherapy with PD-1 inhibitors should also be combined with Combined Positive Score (CPS) and Tumor mutation burden (TMB) to screen for potential benefits of immunotherapy[17]. Targeted therapy is another therapeutic strategy for advanced pancreatic cancer, but the progress is relatively slow and the effect of monotherapy is poor. A large number of phase III clinical trials, including KRAS inhibitors, have made new breakthroughs, and some of the targeted drugs have already been approved for marketing, and in the future, target-immunotherapy combinations will bring a new dawn for pancreatic cancer patients. The pathological and genetic test results of this patient suggested that he was not sensitive to immunotherapy PD-L1 inhibitor drugs, but he showed MET Amplification mutation and TP53 c.375+1G>C mutation, which might be sensitive to some targeted drugs. Surgical resection of skin metastases is mostly pathological biopsy to aid diagnosis, and radical surgery in combination with primary foci is only performed in highly selective patients, and in this case, the patient was too advanced to undergo radical resection.

However, this paper is limited by the single case study and the rapidly progressing disease course of the patient, and information on the molecular mechanism of cutaneous metastasis and response to drug therapy cannot be fully explored, which has some limitations in reflecting the general clinical features or prognostic patterns of cutaneous metastasis of pancreatic cancer; at the same time, pathological biopsy of the primary pancreatic lesion was not performed, which may result in the differences in the molecular characteristics between the primary lesion and metastatic lesion being masked.

In conclusion, pancreatic cancer with cutaneous metastasis is very rare and associated with poor prognosis. Clinicians should pay more attention to this phenomenon, and systematic physical examination, timely laboratory and imaging tests, and genetic testing are helpful for diagnosis. In the future, more emphasis should be placed on early diagnosis, integration of molecular pathology, application of novel testing techniques and sharing of multidisciplinary collaboration experiences, in order to provide clinicians with a more guiding diagnostic and treatment framework for cutaneous metastasis of pancreatic cancer.

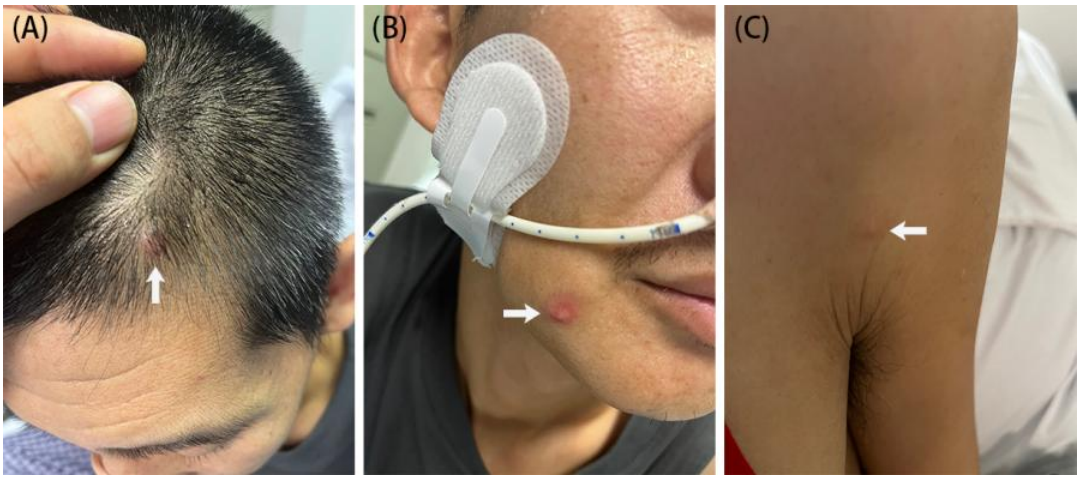

Figure 1. Cutaneous metastatic nodule presentation. Scalp (A), mandible (B), and upper left axilla (C), resembling a rash with hard texture, no tenderness or pressure, and poor mobili.

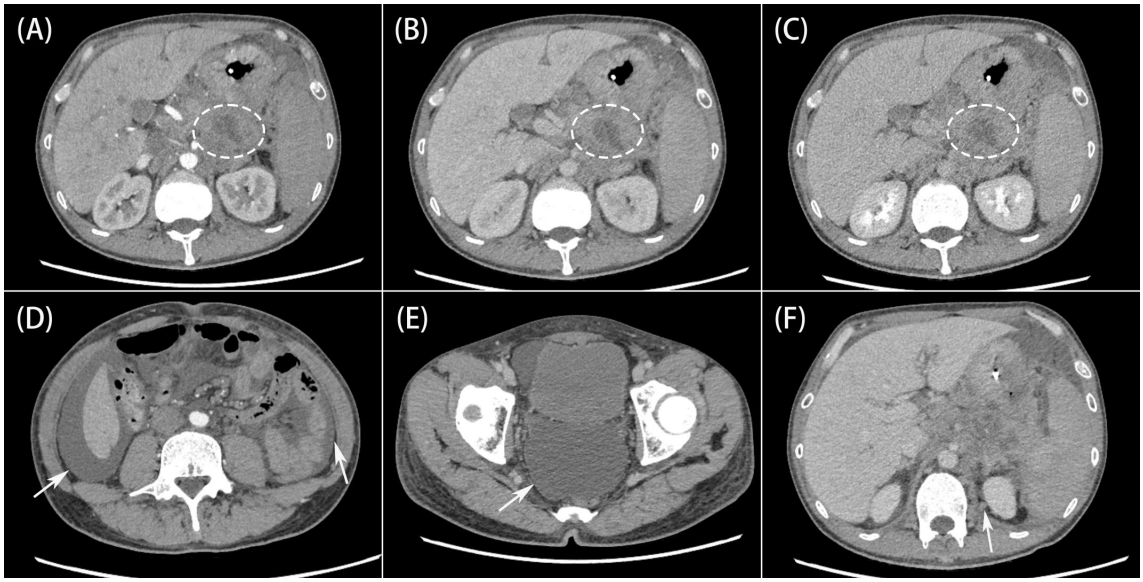

Figure 2. Imaging presentation of the tumor. Enhanced CT suggests structural destruction of the tail of the pancreatic body, multiple foci of mixed hypodensity, and multiple peripancreatic exudates, (A, B, C). It is poorly demarcated from the stomach, duodenum and colonic splenic flexure. Abdominopelvic fluid accumulation is massive (D, E). Multiple soft tissue densities in the retroperitoneum, visible as enlarged lymph nodes in the left retroperitoneum indicated by the arrow (F).

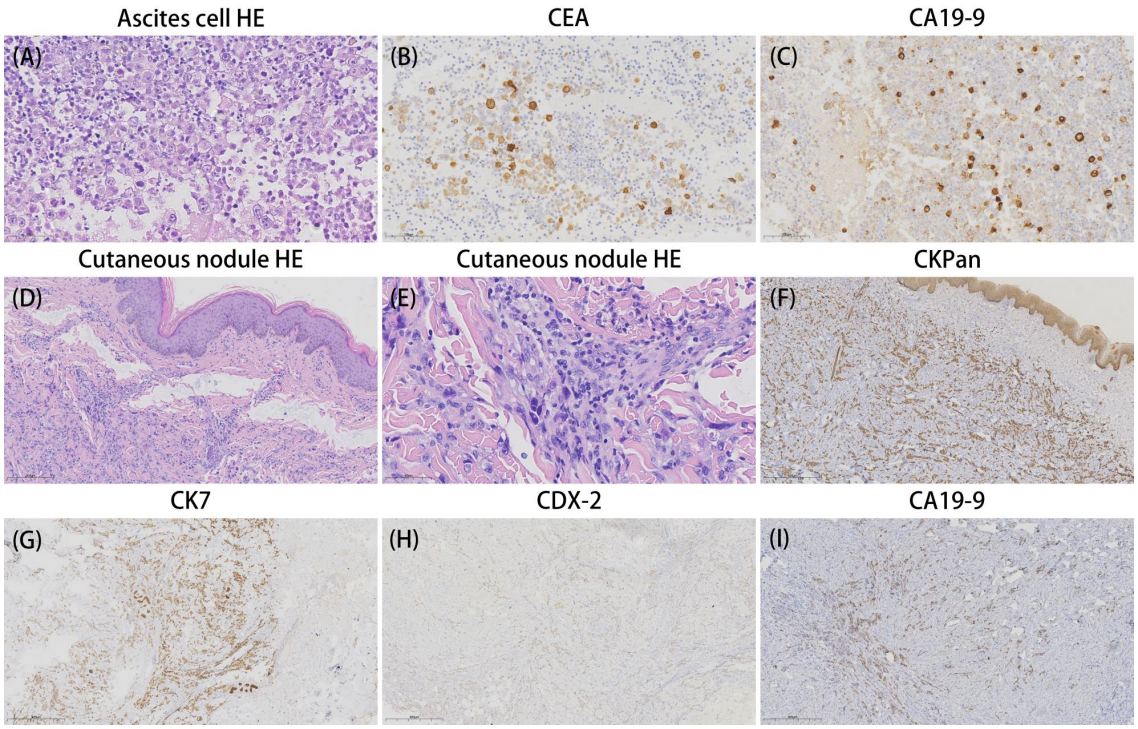

Figure 3. Pathological findings of the tumore. Ascites cytosmear showed heterogeneous epithelial cells with distinct nuclei (H&E; A, ×40), and immunohistochemistry showed CEA (+) and CA19-9 (+) (B&C, ×20). Striated infiltration of tumor cells was observed in the dermis of the cutaneous metastatic nodule, with visible nucleoli and readily visible nuclear schizophrenic images (H&E; D, ×10; E, ×40), and immunohistochemistry showed CKPan (AE1/AE3) (++++), CK7 (++), CDX-2 (+), and CA19-9 (+) (F, G, H&I, ×4).

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Competing interests

The authors declare that they have no competing interests.

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