

CASE REPORT

Extensive cutaneous metastases of pancreatic adenocarcinoma: a case report and review of the literature

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Key Clinical Message

Herein, we present the case of a patient with pancreatic cancer and nonumbilical cutaneous metastasis. Patients with pancreatic adenocarcinomas can develop extensive cutaneous metastases involving not only abdominal skin but also other unusual sites such as the scrotum.

Keywords

Cutaneous, metastasis, non-umbilical, pancreatic adenocarcinoma.

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is a highly lethal solid tumor entity representing the fourth leading cause of cancer-related mortality in the United States [1]. Etiopathogenesis still remains unknown, although several environmental factors, such as smoking, have been implicated. During PDA development, multiple signaling pathways take part in various stages of pancreatic carcinogenesis from early precursor lesions, histologically defined as pancreatic intraepithelial neoplastic lesions (PanINs 1–3 lesions) to advanced PDA. These histopathological changes are accompanied by infiltrating immune cells, a desmoplastic stromal response, and the accumulation of several mutations, such as KRAS activation, CDKN2A inactivation, and loss of tumor-suppressor genes, including TP53 and DPC4 [2, 3].

Despite significant progress in diagnostic imaging procedures, early diagnosis of PDA remains difficult. Common sites of metastases include the lymph nodes, the peritoneum, the liver, and the lungs. On the other hand, skin infiltration, located mainly in the abdominal wall, is a rare manifestation of PDA; Sister Mary Joseph's nodule is a distinct example. However, nonabdominal skin lesions represent a rare clinical and histological finding. This case report presents the unusual case of a 63-year-old male with PDA who has developed disseminated skin metastatic lesions of lower limbs, gluteal region, scrotum, abdominal, and lumbar area.

Case History and Examination

In December 2014, a 62-year-old male was admitted to our department with acute renal failure (ARF). Upon

thorough clinical examination, the patient was noted to have severe bilateral edema of the lower limbs. Abdominal ultrasound revealed obstructive ARF due to disseminated abdominal lymphadenopathy. Bilateral pigtail catheters were initially inserted, and ARF was resolved. Medical history revealed that the previous month the patient had undergone a cholecystectomy due to recurrent episodes of cholecystitis. As an incidental finding, gallbladder was found to be infiltrated by metastatic low differentiated adenocarcinoma, possibly originating in the upper gastrointestinal (GI) tract. Immunohistochemical testing revealed intense diffuse cytoplasmic positivity for CK7, mild focal positivity for CK20, and positivity for CEA and Ca19.9. At that time, no additional tests were carried out.

At the time of admission, laboratory studies revealed elevated serum creatinine ($\text{Cr} = 3 \text{ mg/dL}$) and abnormal liver enzyme values (elevated $\gamma\text{-GT}$ and ALP). Tumor marker CEA and Ca19.9 values were normal. An abdominal MRI was performed and revealed a mild distention of intrahepatic bile ducts, extensive abdominal lymphadenopathy, as well as a small perihepatic effusion. Chest computed tomography (CT) showed bilateral pleural effusions and mediastinal lymph nodes. As gallbladder pathology suggested an upper GI primary, the patient underwent an upper GI endoscopy, which showed a lesion in the duodenal area. Biopsy was positive for a moderately differentiated adenocarcinoma, CK7 (+), CK20 (+), CK19 (+), MUC1 (+), TTF-1(-), suggesting a hepatobiliary or pancreatic primary. Pathology was similar as the one incidentally detected in the gallbladder. In order to confirm diagnosis of pancreatic cancer, as well as plan treatment, the patient underwent endoscopic ultrasound (EUS). FNA performed on a suspicious lesion located at the head of pancreas was positive for malignancy.

Subsequently, a plastic bile duct stent was inserted, as the patient developed symptoms and signs of cholestasis, with concomitant increase of hepatic enzymes and

bilirubin. The patient was discussed at the oncology tumor board where it was decided that chemotherapy should be initiated. He was started on weekly gemcitabine and nab-paclitaxel, as a first-line treatment regimen, according to the local chemotherapy protocol. Chemotherapy was well tolerated, and the patient was clinically improved. Restaging after three cycles based on chest CT and abdominal MRI showed partial response in the mediastinal lymph nodes and stable disease in the abdominal area; the patient consequently received a total of six cycles. Following the completion of six cycles of chemotherapy, the patient presented with clinical deterioration (weight loss, abdominal pain) and was switched to second-line treatment with carboplatin and gemcitabine. Two months later, he presented with scrotum hydrocele and painful edema of the scrotum. Imaging of the scrotum area confirmed edema and showed severe skin thickening, without any focal lesions or enlarged femoral or inguinal lymph nodes. CT of lower abdomen showed severe edema of the subcutaneous tissue of the lower abdomen (Fig. 1). The patient initially received analgesic and antibiotic treatment and was later switched to third-line chemotherapy (FOLFIRINOX regimen). CT imaging after three cycles of chemotherapy showed no disease progression and stable subcutaneous edema of lower abdomen, scrotum and inguinal and femoral regions bilaterally. However, after several months, the patient reported expansion of edema to abdominal and chest wall, as well as lumbar area, gluteal region, and lower limbs (Fig. 2). Urgent admission to hospital was decided, and skin biopsies from skin and subcutaneous tissue of the scrotum, gluteal region, abdominal area, lumbar area, and chest wall were obtained following dermatological consultation. Pathology revealed metastatic foci inside the dermis and multiple clusters of emboli in blood and lymphatic vessels. Immunohistochemistry was positive for CK7, CK20, CD31, MUC2, and focally CEA, suggestive of a pancreatic primary; pathology was similar to the one detected in the gallbladder and duodenum (Fig. 3).

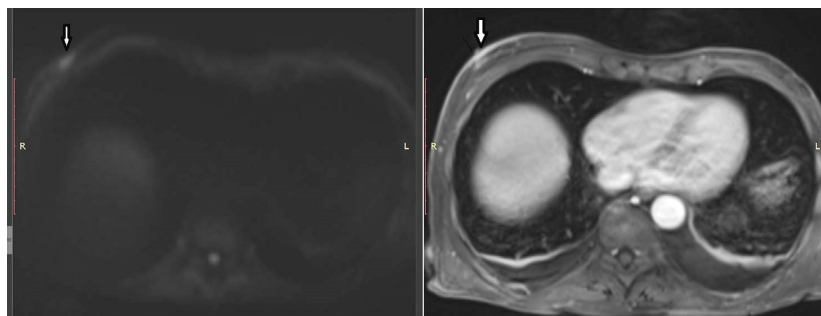


Figure 1. Abdominal MRI. Edema of the subcutaneous tissue of the lower abdomen (white arrow).

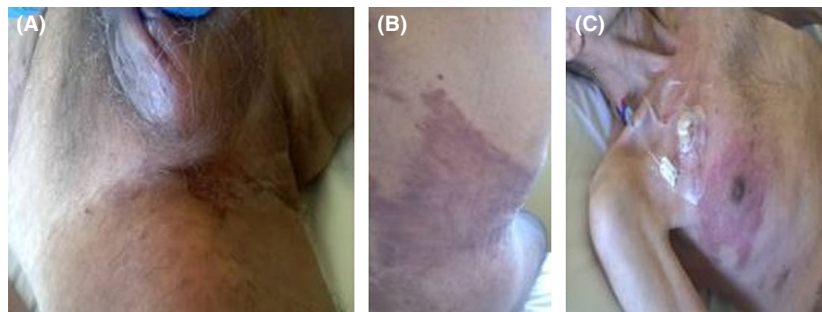


Figure 2. Photographs of our patient showing cutaneous metastasis of pancreatic adenocarcinoma in the (A) scrotum, (B) trunk, and (C) chest wall.

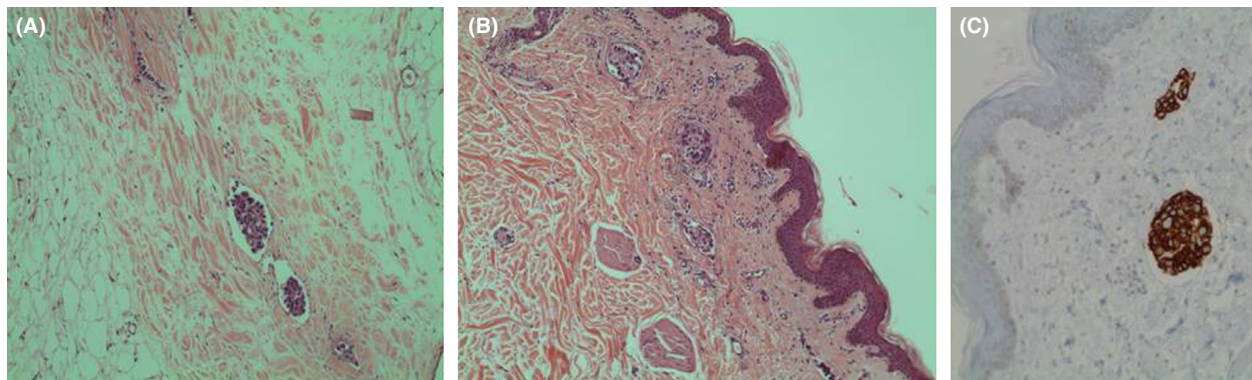


Figure 3. Pathology of cutaneous metastasis. (A) Clusters of neoplastic emboli in blood vessels into subcutaneous tissue, (B) Metastatic foci in the dermis, (C) positive immunohistochemistry staining for CK7 (CK7 +) in metastatic foci and blood vessel emboli.

Discussion

In this report, we present the unusual case of a patient with PDA, who developed extensive cutaneous metastases during the course of the disease. Due to lack of capsule, pancreatic tumors spread easily at an early stage through lymphoid vessels to the retroperitoneal tissues around the pancreas; therefore, they initially metastasize to the regional lymph nodes, peritoneum, and liver through blood circulation.

Skin lesions are reported in <10% of patients with malignant disease, most commonly in lung, breast, and colon cancer. However, they are rather uncommon in PDA; in addition, the majority of cases reported in the literature include periumbilical lesions. The exact mechanism of skin metastasis is unknown, although several theories have been proposed. It is believed that circulating cancer cells seek for a familiar microenvironment in distant tissues, which will allow them to install themselves and subsequently form a metastatic lesion. It is suggested that the occurrence of skin lesions in PDA could be partly explained by Paget's theory (soil and seed) [4].

Most recently, according to the theory of the “premetastatic niche”, the primary tumor has the capacity to cause systematic changes in distant regions by producing signals. It has been postulated that bone marrow cells have an important role in this process; more specifically, they respond to chemokines secreted by the primary tumor, become mobile, install themselves in peripheral organs such as the skin, and prepare the premetastatic niche [5, 6].

During the metastatic process, the cancer cell adopts additional properties that work as equipment for its metastatic journey, such as the acquirement of chemokine receptors and the increased production of proteolytic enzymes, growth, and angiogenetic factors. Recently, the signaling pathway between SDF-1(CXCL-12) and the CXCR4 receptors is being studied for its possible role in the metastatic process in PDA [7, 8]. Dissemination of cancer cells through lymph and blood circulation might play an important role in the development of skin metastases. The role of VEGF-D/C-/VEGFR-3 and CCL19/CCL21 signaling pathways in lymph node metastasis in PDA is currently being investigated, and results are

Table 1. Review of case reports of nonumbilical cutaneous metastasis from pancreatic cancer.

Author	Age	Sex	Metastatic site	Pancreatic tumor site	Time of diagnosis	Year
Edelstein [31]	60	M	Face, neck	NS	NS	1950
Sakai <i>et al.</i> [32]	47	M	Herpes zoster-like	Head	NS	1969
Sironi <i>et al.</i> [29]	72	M	Right thigh	Head	NS	1991
Lookingbill <i>et al.</i> [28]	NS	NS	Abdomen	NS	NS	1993
Taniguchi <i>et al.</i> [30]	63	F	Left axilla, chest	NS	NS	1994
Ohashi <i>et al.</i> [27]	79	M	Neck, chest, abdomen	NS	NS	1995
Ohashi <i>et al.</i> [27]	65	M	Back	NS	NS	1995
Fukui <i>et al.</i> [25]	49	M	Face, chest	NS	NS	1995
Puri <i>et al.</i> [24]	45	M	Scalp, face, neck, back	NS	NS	1995
Miyahara <i>et al.</i> [26]	60	M	Face, neck	Tail, body	NS	1996
Miyahara <i>et al.</i> [26]	43	M	Scalp	Uncus	NS	1996
Miyahara <i>et al.</i> [26]	65	M	Mentum	Uncus	NS	1996
Nakano <i>et al.</i> [33]	80	M	Occipital scalp	Tail	NS	1996
Nakano <i>et al.</i> [33]	80	M	Arm, chin, chest, thighs	Tail	NS	1996
Horino <i>et al.</i> [13]	65	F	Chest wall	Head	After surgery	1999
Florez <i>et al.</i> [12]	48	M	Buttock	Head	Pretreatment	2000
Gawrieh <i>et al.</i> [23]	45	F	Temporal scalp	NS	Pretreatment	2002
Takeuchi <i>et al.</i> [34]	77	M	Left axilla	Tail	Pretreatment	2003
Otegbayo <i>et al.</i> [21]	59	M	Face, chest, abdomen, back	NS	Pre- treatment	2005
Ambro <i>et al.</i> [22]	63	M	Scalp	Ductal	NS	2006
Jun <i>et al.</i> [20]	68	M	Right forearm, chest	Body, tail	Pretreatment	2006
Takemura <i>et al.</i> [19]	85	M	Left temple	NS	Pretreatment	2007
Hafez A [14]	55	F	Neck	Head	Pretreatment	2008
Van Akkooi <i>et al.</i> [18]	59	M	Scalp	NS	Pretreatment	2010
Saif <i>et al.</i> [4]	46	F	Chest, abdomen, right supraclavicular area	NS	Postsurgery and chemotherapy	2011
Bdeiri K [17]	70	F	Scalp	Tail	Pretreatment	2013
Kaoutzianis <i>et al.</i> [16]	43	M	Scalp	NS	After surgery	2013
Zhou <i>et al.</i> [14]	76	F	Scalp, chest, abdomen	Tail	Pretreatment	2014

promising. Research focused on these pathways may also provide further evidence regarding the mechanism of skin infiltration [9].

Lookingbill *et al.* have concluded that the development of skin metastases in PDA may result from either direct infiltration through adjoining tissue, or local/distant metastasis [10]. However, the molecular mechanisms that are responsible for selection of skin as a proper location to develop distant metastases are still under investigation. Interestingly, supporting evidence suggests that cancer cells have a propensity to metastasize to specific organs. Micro-RNAs have been found to play an important role in organ-specific gene modulation. The relationship between miR-21 and metastasis in PDA is a characteristic example [11].

In this report, we present an unusual case of a patient with PDA, who developed non-periumbilical skin metastases. Our case is unique in that cutaneous metastases were extensive in several parts of the lower trunk and developed gradually during the course of the disease. No more than 26 cases of non-periumbilical skin metastasis in PDA have been described worldwide since 1959

[4, 12–34] (Table 1). In addition, this report is the only one presenting a case of scrotum metastasis.

According to published case reports, the presence of non-periumbilical metastases is usually the first clinical demonstration of the disease, leading to the clinical suspicion of PDA. In that case, the development of skin metastases is associated with disseminated metastatic disease and short survival. In the case of our patient, skin metastatic lesions developed later in the course of the disease, while the patient was already on second-line chemotherapy.

In conclusion, herein, we describe the unusual case of a patient with PDA and extensive cutaneous metastasis. We consider this case report an excellent food for thought regarding the mechanisms surrounding organ-specific homing and colonization of cancer cells during the metastatic process.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authorship

IK: participated in the writing of the paper. PE: also participated in the writing of the manuscript. KD, NO, MB and CR: participated in data collection. NK: had the original concept and participated in manuscript preparation. All authors read and approved the final manuscript.

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