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CUTANEOUS METASTASIS OF PANCREATIC CARCINOMA AS AN INITIAL SYMPTOM IN THE LOWER EXTREMITY WITH OBSTRUCTIVE LYMPHEDEMA TREATED BY PHYSIOTHERAPY AND LYMPHATICOVENOUS SHUNT: A CASE REPORT, REVIEW, AND PATHOPHYSIOLOGICAL IMPLICATIONS

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ABSTRACT

Cutaneous metastasis from pancreatic cancer is relatively rare as an initial symptom, and it is generally localized on the periumbilical area that is known as Sister Mary Joseph's nodule. We report a rare case of a 49-year-old female who developed cutaneous metastasis of pancreatic cancer as an initial symptom. The patient was referred to our department for treatment of lymphedema due to surgical treatment of cervical cancer and underwent combined physiotherapy and, 2 months later, a lymph venous anastomosis (LVA) for treatment of the lymphedema. Two months after the operation, she developed erythema on her right leg which spread from the leg to the groin in series. This pattern corresponded to the direction of lymph drainage, which may have been enhanced by the conservative physiotherapy and LVA treatments. These facts suggest a possible relationship between cutaneous metastasis of carcinoma and treatment for lymphedema. Alternatively, the lymphedematous limb may be a privileged site for cancer growth, and metastatic seeding could have taken place from pre-existing hematogenous spread at the time of operation.

Keywords: cutaneous metastasis, lymphedema, lymphatic-venous anastomosis, cancer

Cutaneous metastasis of visceral malignancy is relatively rare, especially in pancreatic cancer as an initial symptom (1). We report a rare case of a female who developed cutaneous metastasis of pancreatic cancer as an initial symptom in the lower extremity where combined physiotherapy and lymph venous anastomosis (LVA) had been applied for treatment of lymphedema due to surgical treatment of cervical cancer.

CASE PRESENTATION

Clinical History

A 49-year-old female was referred to our clinic for treatment of bilateral lymphedema (right > left) of 18-month duration with a 2-month history of physiotherapy treatment. She had been diagnosed with cervical cancer 3 years before presentation and underwent radical hysterectomy and regional lymph node dissection. Postoperative chemotherapy was canceled during the first course due to side effects, and she did not return to the hospital.

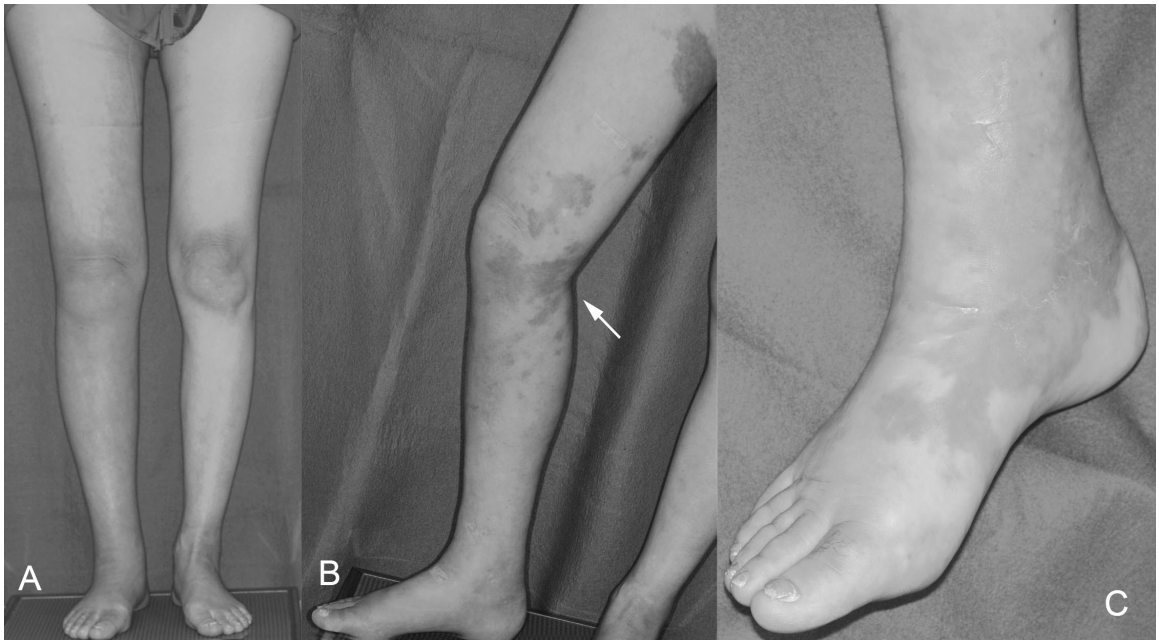

Fig. 1. Initial patient presentation demonstrating a right leg, which was 3 cm bigger than the left at the level of 10cm below the caudal margin of the patella in circumference (A) with minimal erythema. Two months after operation (B), the erythema which first appeared on the lower leg, had spread to the upper leg and a lymph-venous anastomosis was performed in the lower leg (arrow). Four months after operation (C), tenderness and erythema became worse.

Physical examination revealed that her right leg was 3 cm larger than the left at the level of 10cm below the caudal margin of the patella in circumference (*Fig. 1A*). She was diagnosed with chronic lymphedema, and a LVA at the foot and lower leg was performed on the right side.

Two months after operation, she developed erythema accompanied by tenderness at the site of the LVA. Erythema occurred initially in her right lower leg, with the upper leg and ankle following (*Fig. 1B*).

Three months after the operation, because back-flow from the lymphatic vessel to the vein was thought to be causally related to the erythema, we applied a ligature at the anastomosis site of her lower leg. The erythema of the region was improved temporarily but diffused to the right groin, left upper leg, and right foot in series.

Four months after the operation, tenderness and erythema became worse and she was admitted for further examination and treatment (*Fig. 1C*). Laboratory blood values were: white blood cells 4700µl, red blood cells 355(10^4/µl, hemoglobin 10.8g/dl, hematocrit 31.2%, platelets 23.810^4/µl, total protein 6.1g/dl, albumin 2.6g/dl, total bilirubin 0.4mg/dl, asparate aminotransferase 16IU/l, alanine aminotransferase 8IU/l, alkaline phosphatase 224IU/l, lactase dehydrogenase 123IU/l, γglutamyltransferase 3IU/l, blood urea nitrogen 21mg/dl, creatinine 0.81mg/dl, uric acid 4.6mg/dl, sodium 142mEq/l, kalium 4.3mEq/l, chloride 107mEq/l, calcium 9.0mg/dl, blood sugar 125mg/dl, and C-reactive protein 0.21mg/dl. Imaging findings by abdominal computed tomography scanning revealed a bile stone and hepatic cysts.

After admission, her symptoms did not improve with edema in both legs worsening, and the erythema developed into an ulcer. One month after admission, she displayed jaundice. Laboratory findings revealed

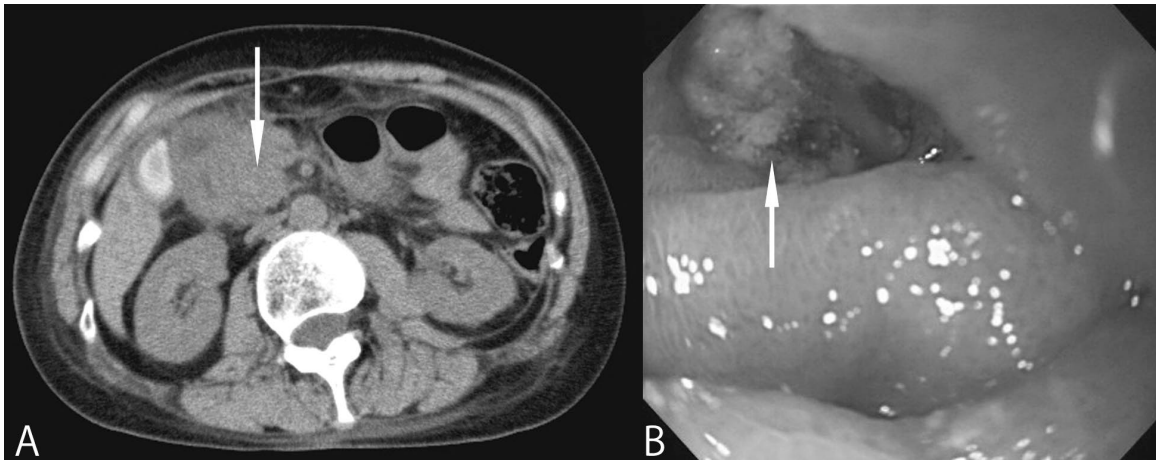

Fig. 2. Abdominal CT (A) showed a mass in the head of the pancreas (arrow). On endoscopy of the papilla of Vater, a tumor was seen (B, arrow).

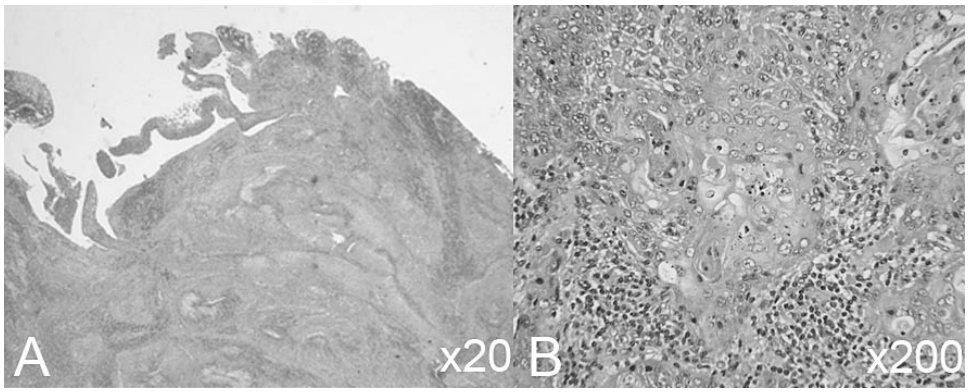

Fig. 3. (A,B) Hematoxylin and eosin stain of the original cervical cancer was diagnosed as squamous cell carcinoma with focal keratinization.

aspartate aminotransferase 225IU/l, alanine aminotransferase 584IU/l, total bilirubin 5.3mg/dl, direct bilirubin 3.6 mg/dl in the serum. Serum tumor marker levels reached carcinoembryonic antigen 12.2ng/ml and carbohydrate antigen (CA) 19-9 1204U/ml. Abdominal computed tomography scanning showed a mass in the head of the pancreas and invasion into the common bile duct (*Fig. 2A*). Examination of the papilla of Vater with an endoscope showed obstruction of the common bile duct by tumor. Biopsy was performed at that site with a diagnosis of a poorly differentiated adenocarcinoma (*Fig. 2B*). Fluorodeoxy glucose positron emission tomography imaging showed regional glucose uptake in the head of the pancreas, left axilla and mediastinal. She was diagnosed with adenocarcinoma of the head of the pancreas and stage IVb.

Six months after the operation, she died from the adenocarcinoma. According to the results of autopsy, the erythema was caused by cutaneous metastasis of carcinoma.

A specimen of the cervical carcinoma obtained from the prior hospital admission

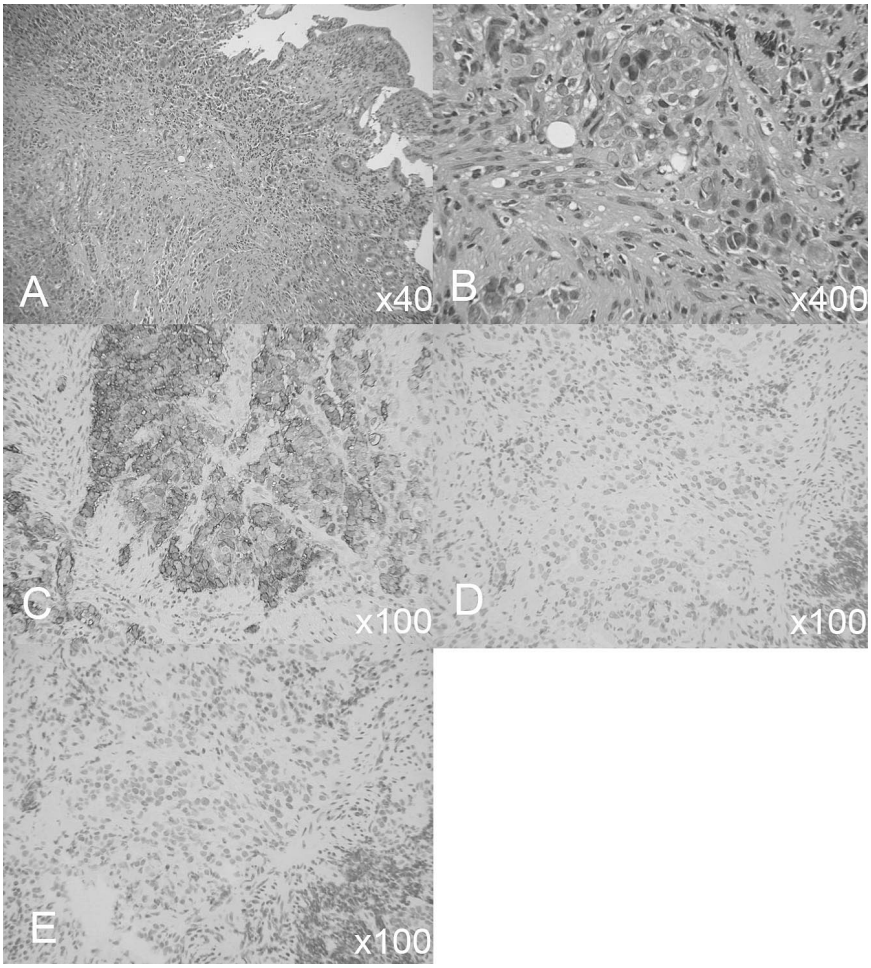

Fig. 4. (A,B) Hematoxylin and eosin stain of the tumor of the papilla of Vater revealed a poorly differentiated adenocarcinoma without duct formation. The tumor cells showed membrane staining for CA 19-9 (C) and was negative for estrogen (D) and progesterone receptor (E).

was examined to determine the origin of the skin metastasis. Microscopic examination revealed multilayered tumor cells with keratinization characteristic of squamous cell carcinoma (*Fig. 3A,B*), which was not seen in the pancreatic cancer or skin metastasis.

The tumor of the papilla of Vater revealed adenocarcinoma without duct formation. CA 19-9 was positive, but estrogen and progesterone receptors were negative. It was diagnosed as a priority differentiated adenocarcinoma (*Figs. 4A-E*). The specimen of skin from the lower leg revealed a poorly differentiated carcinoma without duct formation, but CA19-9 was focally positive (*Figs. 5A-C*) with tumor cells invading the lymphatic channel (*Fig. 5D*). In light of the positive immunohistochemical staining for CA19-9 in the tumor of the papilla of Vater and the skin, the cutaneous metastasis of pancreatic carcinoma was documented.

DISCUSSION

Cutaneous metastasis of visceral malignancy is relatively rare, particularly for

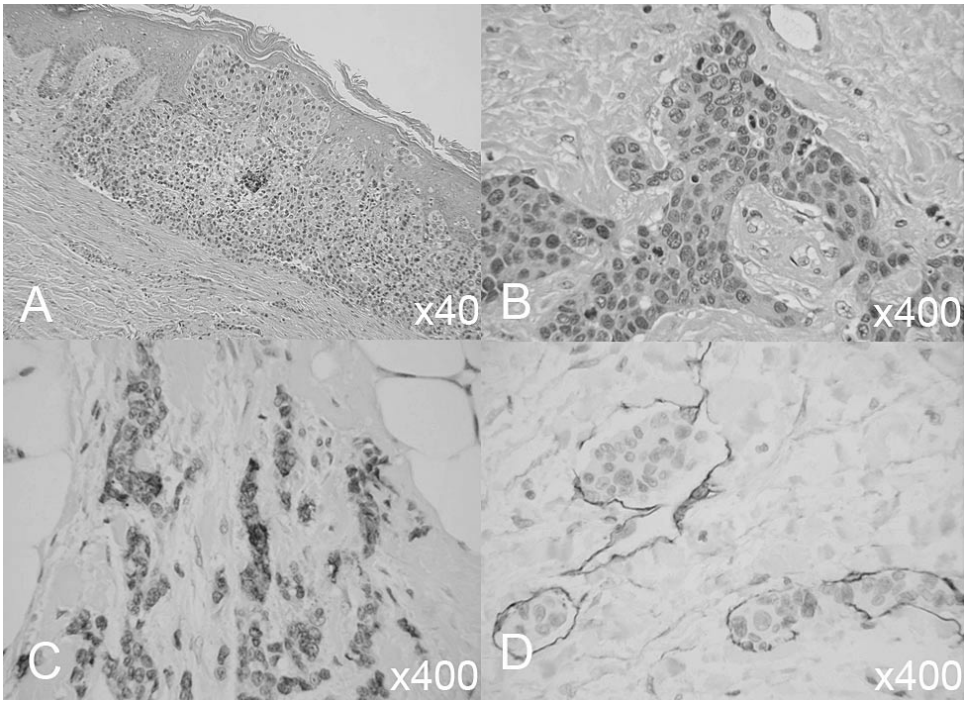

Fig. 5. (A,B) Hematoxylin and eosin stain of the skin from the lower leg revealed a poorly differentiated carcinoma without duct formation. The tumor cells demonstrated focal membrane staining for CA 19-9 (C), and tumor cells were seen invading the D2-40 positive lymphatic vessels (D).

pancreatic cancer (1). From the anatomical locations, cutaneous metastasis of visceral malignancy is most often found in the thoraco-abdominal region. Cutaneous metastasis from pancreatic cancer is generally located in a periumbilical area, which is known as Sister Mary Joseph's nodule (2,3). Horino et al (4) reported 49 cases of metastatic pancreatic carcinoma to the skin. In 46 cases, the skin metastatic lesions were the first signs of the pancreatic cancer with umbilical lesions as the most common metastatic location on the skin (45.5%). The location sites of primary pancreatic carcinoma were the head (32.3%), body (12.9%), tail (32.3%) and body-tail (19.4%) (4). Hisham reviewed 17 cases of non-umbilical cutaneous metastasis of pancreatic carcinoma and found that the site of the skin metastasis was mostly in the head (5).

In our case, although the site of skin metastasis was the lower leg, the primary tumor was found at the head of pancreas. Considering that the skin was focally stained positive with CA19-9, the cutaneous metastasis of pancreatic carcinoma was demonstrated. Brownstein et al reported that clinical presentation of the skin metastasis classified into three types: nodular (85.7%), inflammatory (12.2%) and sclerodermoid (2.1%) (6). Because there was erythema and tenderness, this case can be classified as inflammatory metastatic growth. Inflammation is thought to arise from obstruction of the lymphatic collectors by tumor cells. Our pathological findings revealed tumor cells present in lymphatic vessels and supports this theory.

After reviewing the published data, the authors could not find any reports concerning the relationship between treatment of peripheral lymphedema and cutaneous metastasis of carcinoma. In this case, erythema, which was the first sign of the pancreatic carcinoma,

occurred four months after the beginning of combined physiotherapy and two months after LVA. The erythema occurred at the same site as the anastomosis and spread from right leg to right groin in series which coincides with the direction of lymph drainage under treatment by basic conservative physiotherapy. Because cutaneous metastasis of pancreatic carcinoma occurred in a short period after starting treatment of lymphe-dema, there might be a cause-and-effect relationship between cutaneous metastasis and treatment of lymphedema. Alternatively, lymphedema represents an immunocompromised site vulnerable to "opportunistic" neoplasms (7). Also, the site of the LVA operation would have experienced localized leakage from both lymphatic and blood vessels providing access to the site for metastatic cells which could have been circulating in either or both vasculatures. Because LVA is a shunt operation from the lymph duct to the vein, there is a possibility that metastasis through the lymph system could travel directly to the blood vascular system. Since most secondary lymphedemas develop after resection of cancer, a cautionary note is offered to consider the changes of lymph flow from conservative therapy and the timing of performing LVA.

CONCLUSION

Pancreatic carcinoma rarely develops cutaneous metastases, which are generally situated at the umbilical area. We report a rare case of metastasis in the lymphedematous leg where combined physiotherapy and LVA had been performed, and where the lesions spread in the direction of treatment to enhance lymph flow. This clinical presentation indicates a possible relationship between metastasis and treatment of lymphedema or alternatively, a situation where the lymphedematous limb was vulnerable to an "opportunistic" neoplasm, which seeded and grew in this vulnerable terrain.

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