

# SKIN METASTASES AS THE PRESENTING SIGN OF PANCREATIC DUCTAL ADENOCARCINOMA IN A RENAL TRANSPLANT PATIENT

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Metastases of the skin from visceral carcinoma are uncommon. The frequency varies from 0.7% to 9.0%.<sup>1</sup> Such wide variation may represent in part the diligence with which cutaneous metastases are sought. In skin metastases, the most frequent primary tumors in men are carcinoma of the lung, carcinoma of the large intestine, melanoma, and squamous cell carcinoma of the oral cavity.<sup>2,3</sup> In women, they are carcinoma of the breast, carcinoma of the large intestine, melanoma, and carcinoma of the ovary.<sup>2,3</sup> Metastatic carcinoma of the pancreas involving the skin is rare. Brownstein and Helwig<sup>2</sup> recorded 15 cases in 724 patients with metastatic tumors. In studying 50 patients with cutaneous metastases, Tharakaram<sup>4</sup> could not record any case of pancreatic origin. Furthermore, skin metastases as the presenting sign of a pancreatic carcinoma are even more uncommon. Miyahara et al.<sup>5</sup> reviewed the literature and found only 20 cases in which the cutaneous metastases were present prior to the diagnosis of pancreatic carcinoma.

Solid organ transplantation with immunosuppression is associated with an increased incidence of tumors occurring in the recipient. However, pancreatic carcinoma has a very low incidence in transplanted patients.<sup>6</sup> We report a transplanted patient who presented with multiple metastatic lesions in the skin, developing quickly, as the first sign of pancreatic carcinoma. As far as we know, this event has not been reported in a transplant recipient.

## Case Report

A 51-year-old extremely obese woman presented in September 1995 with a three-month history of multiple nodules in the skin of the neck, thorax, abdomen and both legs. The nodules appeared 15 days after an episode of acute laryngitis and had gradually enlarged. One nodule located in the left popliteal region made it difficult for the

patient to stand up. Her past medical history revealed a renal transplantation for end-stage kidney disease in September 1992. Post-transplant treatment included cyclosporin A, prednisolone, and azathioprine. The patient had no rejection episodes in the interval.

Physical examination disclosed multiple nodules on the neck, thorax, abdomen, back and both legs. These nodules were bluish, 1-4 cm in diameter, firm in consistency, and tender to palpation. A punch biopsy was performed on an abdominal nodule. Pathological examination showed anaplastic carcinoma, with abundant clear cells, dermo-hypodermal in location. The source of the tumor was not conclusive. Routine blood tests revealed normochromic anemia, with a hemoglobin of 9.8 g/dL and hematocrit of 29.6%. Serum hCG and AFP levels were normal. Serum LDH and uric acid were 721 U/L and 8.9 mg/dL, respectively. X-ray and CT scan of the chest showed a 3-cm round mass in the left lung close to the hilum, consistent with pulmonary metastasis. Abdominopelvic CT scan showed no abnormalities. A gammagraphic study revealed pathologic uptake in both left femoral condyles. Immunosuppression regime was continued. Several days later, the patient developed diplopia, right exophthalmos, and confusion. CT scan of the head revealed a hyperdense right orbital and sphenoidal mass. The patient's condition continued to deteriorate and she died in October 1995. An autopsy was performed.

## Pathology Findings

Sections of the skin biopsy showed an anaplastic carcinoma involving the deep dermis and hypodermis (Figure 1A). The tumor was composed of solid polygonal large cell sheets, cords and nests. The cells displayed atypia, mild pleomorphism, high mitotic activity, and extensive clear cell change (Figure 1B). The nuclei were vesicular, with prominent basophilic nucleoli, and hyperchromatic. Zonal necrosis dominated portions of the medium power fields in the center of the tumor. Ductal or acinar differentiation was not present. The Alcian blue-PAS staining for mucin was positive in scarce cells. Some of them showed neutral mucin and others acidic mucin. Immunohistochemical study revealed diffuse cytoplasmic reactivity for epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA).

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Accepted for publication 31 March 2000. Received 11 October 1999. patient to stand up. Her past medical history revealed a renal transplantation for end-stage kidney disease in September 1992. Post-transplant treatment included

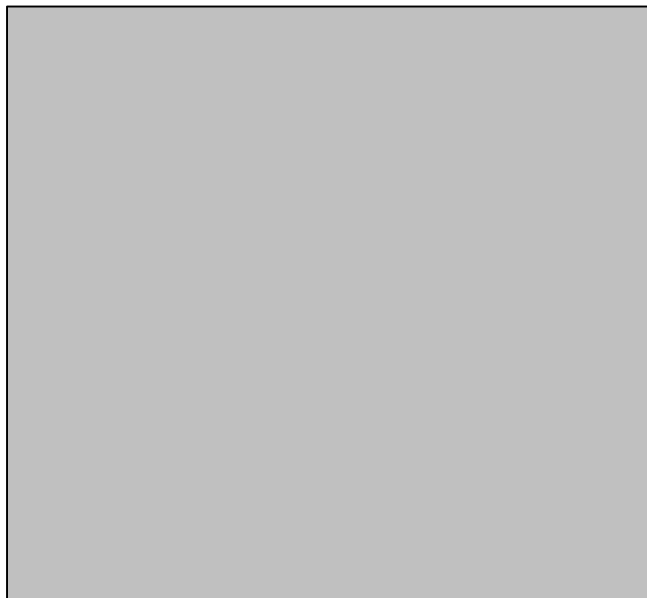


FIGURE 1A. Histologic features of the biopsy of an abdominal nodule, low magnification shows a solid tumor in the reticular dermis (H&E stain, 10x).

At autopsy, the pancreas showed an ill-demarcated, solid, firm, yellow-to-white tumor in the tail, 3 cm in diameter. Histologically, this tumor consisted of a mixture of irregular glands and sheets and nests of large cells. These displayed marked atypia, with single cells showing mucin-filled intracytoplasmic vacuoles (Figure 2). Some neoplastic cells contained large bizarre nuclei. Clear cells were scarce. The mitotic activity was high. Scattered foci of necrosis were present. At the advancing edge of the neoplasm, the peripancreatic adipose tissue, perineural sheaths, lymphatic channels and venous vessels were invaded. Metastases of this poorly differentiated ductal adenocarcinoma were present in the liver, mesentery, spleen, left adrenal, pericardium, mediastinal lymph nodes, left lung, right sphenoid wing and orbit, right frontal cortex of brain and skin. Left femoral bone was not explored. Multiple, 1-4 cm, cutaneous, firm nodules in the neck, thorax, abdomen, back and both legs were present. These showed a reddish ulcerative center (Figure 3). The umbilicus was not involved. The histological grade of differentiation of the tumor varied in the diverse metastases. The neoplasm was ductal, well differentiated in the brain and poorly differentiated in the skin and in the rest of the organs. The cutaneous nodules examined at the autopsy showed nests and thread-like strands of adenocarcinoma cells high in the dermis extending into the deepest reticular dermis and hypodermis. The renal allograft showed no significant alterations.

## Discussion

The present case fulfills pathological criteria for primary ductal adenocarcinoma of tail of pancreas with



FIGURE 1B. The neoplasm consists of large cells with minimal pleomorphism arranged in nests and cords. Abundant clear cells can be seen (H&E stain; 100x).

multiple metastases, including the skin. The clinical presentation of the tumor was that of multiple cutaneous nodules that had appeared recently in various areas of the body. Ductal adenocarcinoma is the most common tumor in the pancreas. It comprises 85% to 90% of all pancreatic tumors.

Cutaneous metastases are classified into three groups according to their appearance: 1) nodular, 2) inflammatory, and 3) sclerodermoid.<sup>7</sup> Generally, the nodular type represents metastasis by blood stream, the inflammatory type by lymph flow, and the sclerodermoid type by direct infiltration.<sup>8</sup> Remote skin metastases, especially if they appear before invasion of local lymph nodes, can be regarded as hematogenous metastases. Cutaneous metastases often show a lesser degree of differentiation than those of the primary neoplasm.<sup>7</sup> In the experience of McKee,<sup>9</sup> a significant number of metastatic tumors in the skin show no distinctive histopathological features, and can only be reported as metastatic anaplastic carcinoma. Usually, pancreatic carcinomas metastasize rapidly to the lymphatic system by permeation, embolization, and retrograde spread in the presence of lymphatic obstruction. The most common site of cutaneous metastases from pancreatic carcinoma is the umbilicus.<sup>5</sup> This structure may be reached by the tumor by contiguous extension, and via lymphatic and venous channels associated with

embryological vestiges in this region. The multiple skin nodules present in our case are considered hematogenous metastases with atypical presentation.<sup>10</sup>

Tumor incidence in human allograft recipients varies from 3% to 11% within the first year, and up to 24% after 5 years.<sup>11</sup> The mean age when the malignancy is diagnosed is 52.9 years.<sup>12</sup> The most common malignancies are skin and

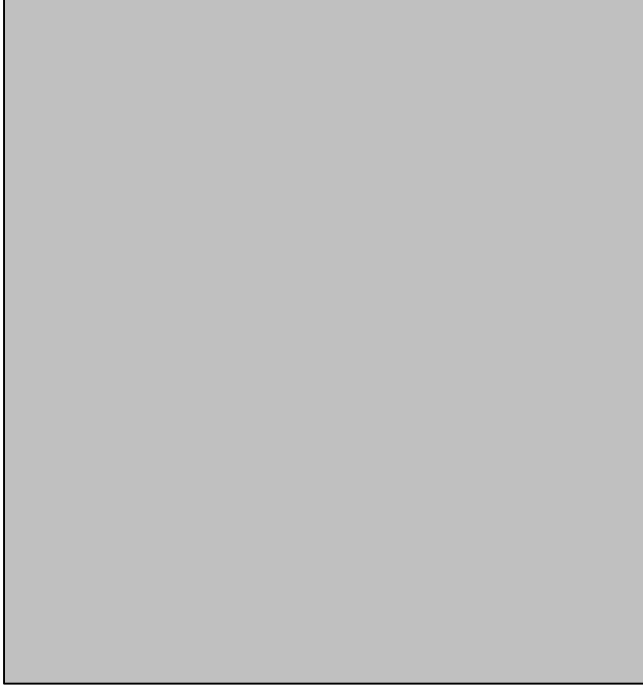


FIGURE 2. Representative section of the primary tumor at autopsy. Poorly differentiated ductal carcinoma of pancreas showing pleomorphism, mitoses, and intracytoplasmic mucin vacuoles. Note absence of clear cells in the field (H&E stain, 64x).



FIGURE 3. Nodular and ulcerative tumor, 3.6 cm in diameter in the abdominal skin at autopsy.

lip carcinoma, lymphoproliferative disease, Kaposi's sarcoma, cervical carcinoma, and carcinomas of the anogenital area.<sup>13,14</sup> Compared to a regional cancer registry, the risk of developing *de novo* malignancy is 3 to 3.5 fold for males and females.<sup>12</sup> Furthermore, the cumulative risk of developing a malignancy within a 10-year interval is 13.5%.<sup>12</sup> If the cause of the development of a neoplasm were simply due to the suppression of the immune surveillance, one would expect a general increase in all tumors rather than this selective increase that occurs. This selection suggests that there must be other factors responsible.<sup>13</sup> One of these factors is the oncogenic viruses. Viral infections are common in transplant patients, especially cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. Other potentially carcinogenic viruses include hepatitis B and C, herpes Zoster, human papilloma, and other as yet unidentified viruses.<sup>14,15</sup> In the genesis of a tumor, the virus needs a cofactor. This may be the chronic immune stimulation by the allograft.<sup>13</sup>

Exocrine pancreatic carcinoma is very uncommon in solid organ transplant recipients. In a total of 2372 patients with 2725 renal allografts, Behrend et al.<sup>6</sup> observed 210 malignant tumors in 147 patients (6.2% of the patients). Malignancies of the pancreas were only three (1.4% of the tumors). To our knowledge ductal adenocarcinoma of the pancreas presenting as cutaneous metastases has not been described in a transplant recipient. Sinicco et al.<sup>16</sup> reported a case of eruptive metastases to the skin from an occult gastric carcinoma occurring in a 52-year-old man, about 6 months after he contracted human immunodeficiency virus infection. This case and ours show that visceral carcinoma may present atypically in the immunocompromised patient. Pathologically, a diagnosis of metastatic clear cell adenocarcinoma should be considered in the present case. Sources of such a primary tumor include kidney, lung, liver, stomach, intestine, adrenal, bladder, ovary, endometrium, cervix and vagina, and others. Clear cell carcinoma of pancreatic origin is rare.<sup>17,18</sup> This tumor shows positivity for mucin stains and negativity for fat stains. However, an incomplete clear cell change is occasionally seen in ductal adenocarcinoma, as occurred in the cutaneous metastases of our patient. On the other hand, the cells of a metastatic sebaceous carcinoma manifest foamy rather than clear cytoplasm, and show positive reaction for EMA but not for CEA.

In conclusion, the incidence of malignancies after solid organ transplantation is higher when compared with expected cancer in control patients. We have described a pancreatic exocrine carcinoma presenting as multiple cutaneous metastases three years after renal transplantation. Skin metastases can be the revealing sign of visceral carcinoma in renal transplant recipients.

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