

Leukemia Cutis in a Patient with Metastatic Pancreatic Cancer: A Case Report

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Abstract: Background: Leukemia cutis is an extramedullary manifestation of leukemia with infiltration of neoplastic leukocytes into the epidermis, dermis, or subcutaneous tissues. Most often it is associated with myelodysplastic syndrome or acute myelogenous leukemia. Case History: Here we present a patient with new-onset, multiple, non-tender red papules, that were initially concerning for skin metastases of her previously diagnosed pancreatic ductal adenocarcinoma. She was previously diagnosed with pancreatic cancer six years prior and was in remission until one year prior when she was found to have pulmonary metastases. The metastatic pulmonary nodules were successfully treated with radiotherapy, and the patient was in surveillance prior to presenting with a two month history of rapidly growing pink nodules on her skin. Results: Skin biopsies initially indicated this was likely not metastatic pancreatic adenocarcinoma but rather a hematologic malignancy with monocytic blast dermal infiltration. A subsequent bone-marrow biopsy and staining indicated a second primary hematologic malignancy, acute myelogenous leukemia. With the patient's previous chemotherapy history, this new malignancy could have been treatment related. However, genetic analysis revealed this was not likely as it did not harbor known phenotypes or markers of treatment related myelodysplastic syndrome or acute myelogenous leukemia including myelomonocytic leukemia with eosinophils (FAB M4EO) or an inversion in chromosome 16 (p13q22). Instead, cytogenetics and next-generation sequencing showed trisomy 8 and a gain of function missense mutation in U2AF1. Conclusion: Maintaining a broad differential and utilizing sequential diagnostic testing confirmed a blast phase de novo acute myelogenous leukemia, presenting as leukemia cutis. She was treated with decitabine and venetoclax and within a few days of initiation, her skin nodules had already begun to recede.

Keywords: Leukemia, Cutis, Acute, Myelogenous, Leukemia

1. Introduction

Leukemia cutis (LC) - infiltration of neoplastic leukocytes into the epidermis, dermis, or subcutaneous tissue – is an extramedullary manifestation of leukemia that may precede, occur concomitantly with, or follow a diagnosis of leukemia [1]. Herein we present a case of a patient with known metastatic pancreatic ductal adenocarcinoma (PDAC) who presented with a one-month history of skin nodules. Initially concerning for PDAC metastases, evaluation revealed LC arising from new-onset acute myelogenous leukemia (AML).

2. Clinical Case

An 88 year old female with metastatic PDAC was referred to dermatology clinic in October 2020 for a one-month history of sub-centimeter pink nodules on her back and abdomen. (Figure 1). In 2014, she had undergone distal pancreatectomy for adenocarcinoma of the pancreas (pT3N1 with negative margins), after which she received four months of adjuvant chemotherapy (nab-paclitaxel and gemcitabine) [2]. In 2019, she was found to have new pulmonary nodules, and

transthoracic needle biopsy confirmed metastatic PDAC. She was treated with stereotactic radiotherapy, which she tolerated well, and returned to surveillance [3].

During a routine follow-up visit, she reported a recent appearance of several non-painful, non-pruritic skin nodules. She was referred to a dermatologist, who noted multiple, non-tender, 5-8 mm, red papules on her abdomen and back (Figure 1). At that time, the working diagnosis was PDAC metastatic to the skin, a rare but reported manifestation of metastatic PDAC [4–6]. Other possibilities included benign causes, non-melanomatous skin cancer, treatment-related malignancies including leukemia cutis, and cutaneous lymphoma.

A shave biopsy revealed diffuse dermal infiltration of blasts with monocytic differentiation expressing CD45, CD56, CD68 and lysozyme (Figure 2). There was a high proliferative

rate with a Ki-67 index of 70-80%.

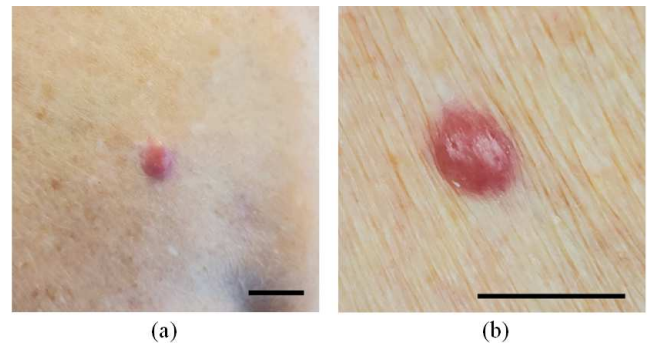


Figure 1. Patient skin findings. (a) Pink nodules on patient's abdomen. Scale bar 1 cm. (b) Nodule on patient's back that was shave biopsied. Scale bar 1 cm.

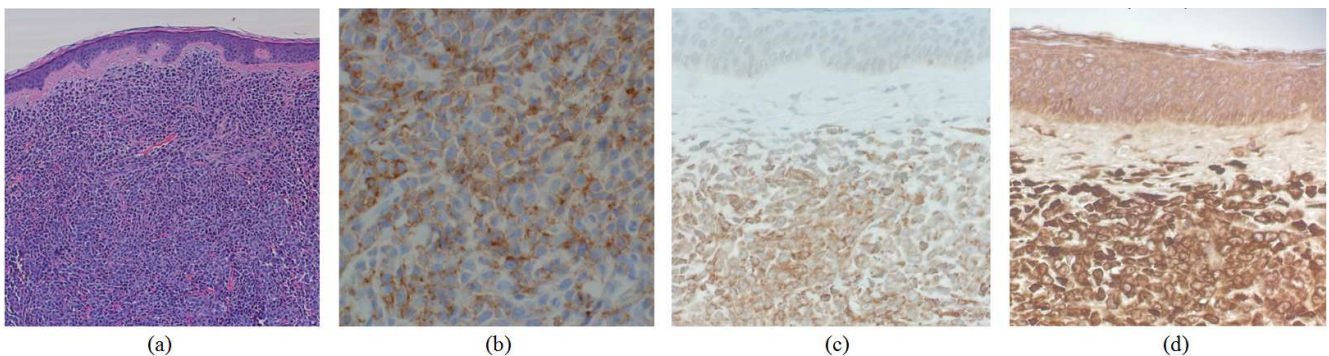


Figure 2. Skin biopsy and stains. (a) Diffuse dermal infiltrate by intermediate to large blasts with scant cytoplasm, round-oval nuclei, and prominent nucleoli. Mitotic figures are numerous. (hematoxylin and eosin stain 40x). (b-d) The neoplastic cells strongly express CD56 (b), CD68 (c), and lysozyme (d).

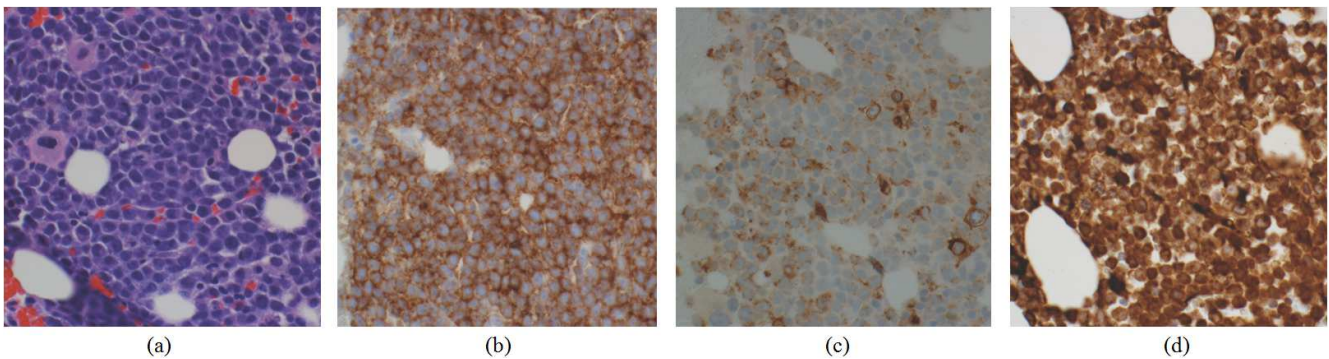


Figure 3. Bone marrow biopsy and stains indicating acute myeloid leukemia with monocytic differentiation. (a) Hypercellular bone marrow clot with blasts admixed with trilineage hematopoietic elements. Blasts show similar morphologic features as those in the skin (hematoxylin and eosin stain 400x). (b-d) The neoplastic cells strongly express CD56 (b), CD68 (c), and lysozyme (d).

Peripheral blood examination showed a normal total white blood cell count, hemoglobin, and platelets with relative monocytosis. Her bone marrow was infiltrated with myeloblasts staining positive for CD68, CD56, and lysozyme (Figure 3). Flow cytometry showed that the blast population expressed cMPO, CD11c, CD64, CD56, and CD4. Taken together, the dermatologic and hematologic evaluations yielded a diagnosis of acute myelogenous leukemia, monocytic variant [7, 8]. The patient received combination therapy with decitabine and venetoclax, and within a few days of starting treatment, her skin nodules were already receding [9].

3. Discussion

This case presented an intellectual diagnostic work-up as a differential narrowed to eventual de-novo AML presenting as leukemia cutis. Initially, given the patient's history, the skin findings were most concerning for cutaneous metastases of her previous pancreatic cancer.

In general, the overall incidence of cutaneous metastases from internal malignancies ranges from 2-10% [10, 11]. Cancers most likely to metastasize to the skin vary between the sexes and age. In women, breast cancer accounts for

nearly 70% of cutaneous metastases followed by colorectal, melanoma, and ovarian [10, 11]. In males, lung accounts for 25% followed by colorectal at 20% [10, 11]. Given the high incidence of cutaneous metastases from breast cancer, common sites of skin findings include the chest and abdomen, which is where our patient also had new onset rapidly growing papules [10, 12]. Histologically, cutaneous metastases resemble primary cancers with variable degrees of differentiation, and often there is a time delay between the diagnosis of a primary malignancy and skin metastases [12].

While uncommon, there are multiple reports of cutaneous metastasis from pancreatic cancer [4–6]. The most common site for cutaneous metastases of pancreatic cancer is the umbilicus with multiple reviews indicating the umbilicus lesions as one of the initial signs of pancreatic cancer in 55–93.9% of patients [6, 13, 14]. Non-umbilicus cutaneous nodules have been reported on the scalp, neck, temple, thorax and epigastric regions. Often, metastatic lesions were associated with seeding events as sites of surgical procedures or drain placements [6, 15–19].

A recent review of cutaneous metastases of pancreatic cancers indicated an average age of 63.9 years manifesting as a nodule or mass on non-umbilicus skin [6]. The most common subtype was adenocarcinoma, and histology from these cases indicated poorly differentiated tumors that were nearly 100% positive for Ck-7 and Ck-19 [6]. In this case report, the patient's initial shave biopsy did not resemble pancreatic adenocarcinoma. Instead, it showed a myeloid lineage infiltrate indicating a hematologic malignancy. A subsequent bone marrow biopsy led to the diagnosis of AML and leukemia cutis.

Leukemia cutis may present with papules, macules, nodules, or plaques and occurs in 2–13% of patients with acute monocytic and acute myelomonocytic leukemias [20, 21]. A minority (23–38%) of LC cases present as the first sign of AML, and LC is associated with meningeal involvement, expression of CD4 and CD56, and certain molecular features, including t (8; 21), and inv (16) [21].

With the patient's previous cancer treatments, there was a possibility that her new hematologic malignancy could have been treatment related. Treatment-related MDS/AML, which accounts for 10–20% of all MDS/AML cases, occurs most frequently after exposure to alkylating agents and anthracyclines [21]. This particular patient had received gemcitabine and nab-paclitaxel 5 years prior. While gemcitabine is not considered a risk factor for MDS/AML, taxanes have been implicated in causing treatment-related MDS/AML [21–23], in particular myelomonocytic leukemia with eosinophils (FAB M4EO) and those harboring an inversion in chromosome 16 (p13q22) [22, 23]. Leukemic cells in our patient's bone marrow and skin stained positive for CD4 and CD56 (cellular markers associated with LC), and their immunophenotype was consistent with M4 (monocytic) AML. However, molecular testing was not consistent with treatment-related MDS/AML. Cytogenetic analysis showed trisomy 8, consistent with a diagnosis of blast-phase chronic myelomonocytic leukemia [24]. Next generation sequencing

revealed a gain-of-function missense mutation in U2AF1, which is found in 10% of CMML cases and is associated with resistance to traditional “7+3” induction chemotherapy (7 days cytarabine and 3 days of anthracycline antibiotic) [25]. Since the elderly patient was treatment naïve for her AML, she was treated with venetoclax with decitabine which led to her skin papules receding within a few days of initiating treatment.

4. Conclusion

The diagnosis of *de novo* AML in this patient reinforces the importance of maintaining a broad differential diagnosis when new data emerge. With her history of metastatic pancreatic ductal adenocarcinoma, a diagnosis of cutaneous metastases of her previous cancer was high on the differential. A shave biopsy quickly ruled this out. Histopathology and bone marrow biopsies resulted in the eventual diagnosis of leukemia cutis, however questions remained whether this was treatment related or not. Subsequent molecular testing and next-generation sequencing was able to confirm this was not likely to be treatment related, and instead a *de novo* AML. In this case, Occam's razor did not provide the clean-cut “shave” we expected.

Conflicts of Interest

All of the authors do not have any possible conflicts of interest.

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