SKIN

BRIEF ARTICLE

Trauma-induced Spread of Acute Myeloid Leukemia to the Skin and Small Intestine: A Potential Form of "Koebnerization" that is More than Skin Deep

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ABSTRACT

Leukemia Cutis (LC) is a form of myeloid sarcoma (MS) that describes the extramedullary spread of leukemic cells to the skin, such as by Acute Myeloid Leukemia (AML). While LC occurs in 3-4% of patients with AML, rarely has it been reported secondary to trauma, a form of isomorphic response or Koebnerization (N=3). Another form of MS that has not been documented, to our knowledge, is surgical-induced trauma leading to AML infiltrating the small intestine. The present case describes biopsy-supported Koebnerization of AML to the skin (LC) and small intestine (MS), both induced by surgical incisions. Overall, trauma-induced dissemination of AML is an important diagnostic consideration and prognostic indicator for non-healing wounds of the skin and, potentially, the gastrointestinal tract in patients with AML.

INTRODUCTION

Myeloid sarcoma (MS) refers to the extramedullary manifestations of leukemias, such as by acute myeloid leukemia (AML).[1,2] Reported sites of AML infiltrates are numerous, including the gastrointestinal tract and skin, where the latter is termed Leukemia Cutis (LC).[1,2] Of all leukemias, LC occurs most often in AML (74%).[3] LC induced by trauma, a form of isomorphic response (Koebnerization), has been rarely reported (N=3).[4,5] What has not been reported, to our knowledge, is spread of AML to the intestines following surgical-induced trauma to the bowel. Here we describe a case of biopsy-supported Koebnerization of AML to the skin (LC) and small intestine (MS), both induced by surgical incisions.

CASE

A 37-year-old female presented to the emergency department for worsening fever, low back and abdominal pain. She was taken to the operating room for suspected appendicitis when a mass was found in the terminal ileum. Labs showed a leukocytosis of 48.88 with 81% blasts and flow cytometry of CD 13, 33, 45, 64, and 117 positive myeloid blasts. The mass was then analyzed by hematopathology with no evidence of

malignancy, only the sequalae of intestinal obstruction (ischemic mucosal injury, mural abscess, diffuse serositis and adhesions; appendix with fibrous obliteration). A bone marrow biopsy confirmed AML with 75% blasts, 46 XX cells with DNMT3A and mutated NPM1. She then developed a worsening small bowel obstruction that required an anastomotic revision. Procedure notes remarked that the previous anastomosis was folded upon itself. Histological analysis of the resected bowel now had evidence of AML cells with mutated NPM1, CD33 and an increased Ki-67 proliferation rate.

During the following week, she developed worsening erythema and pain of the abdominal incision (**Figure 1**) with persistent fevers and negative blood cultures (on vancomycin, meropenem, and micafungin) while not yet on chemotherapy (to facilitate wound healing). Punch biopsies revealed CD 33, 43, 68 and myeloperoxidase (MPO) staining cells consistent with LC (**Figure 2**). Tissue culture was positive for a rare fungus (*Cladosporium*) with infectious disease suspecting a contaminate with growth only at the edge of the plate. Despite a negative tissue culture, the patient was broadened to posaconazole for neutropenic fever.

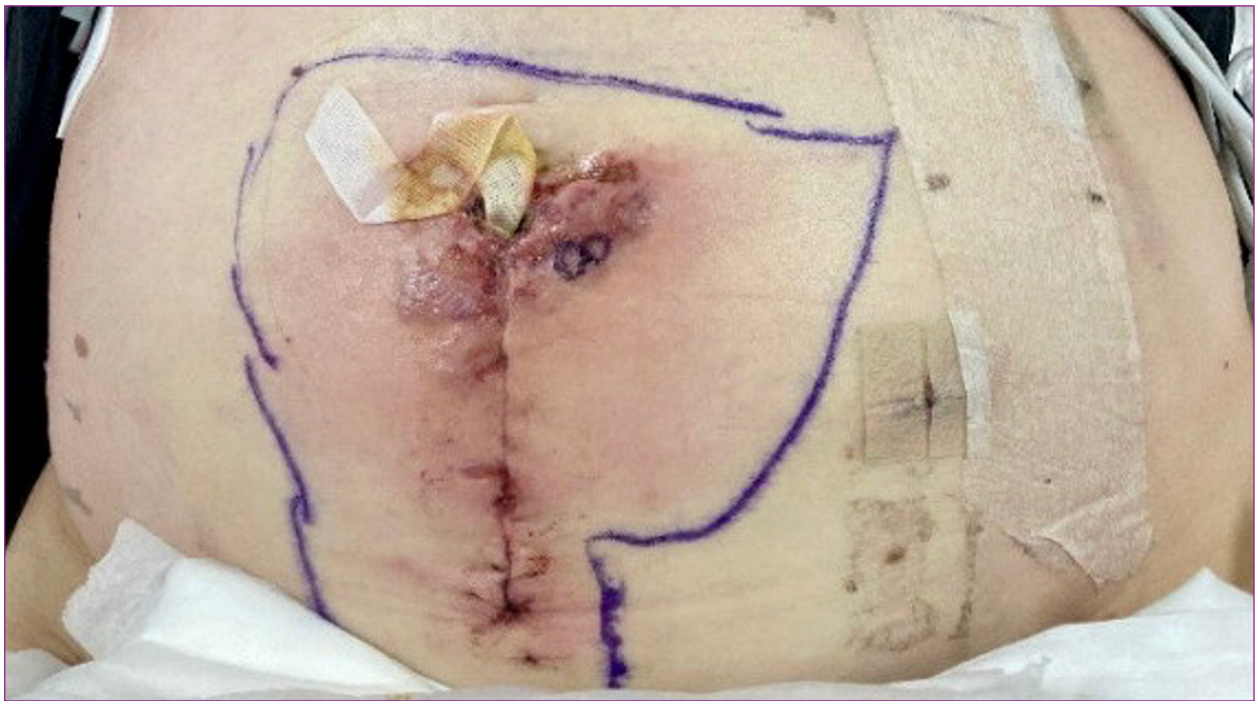

Figure 1. Postsurgical Abdominal Wound Incision: Image taken at time of punch biopsies (small purple circles) following two laparotomies (most recent one week prior) while NOT on chemotherapy (only broad-spectrum antimicrobials for one week).

A week after the second surgery, she began chemotherapy with a 7+3 regimen of cytarabine and daunorubicin. Around day 2-3 of chemotherapy, she noticed vesiculobullous lesions at sites of IV and line insertions on the dorsal hands, antecubital fossae, medial arm, and anterior shin (where she shaved). A previously deroofed lesion was swabbed for VZV/HSV (negative) and empiric acyclovir was begun. With continued chemotherapy, the vesiculobullous lesions flattened and the incisional erythema and pain improved. Of note, the patient also developed a pruritic rash that was consistent

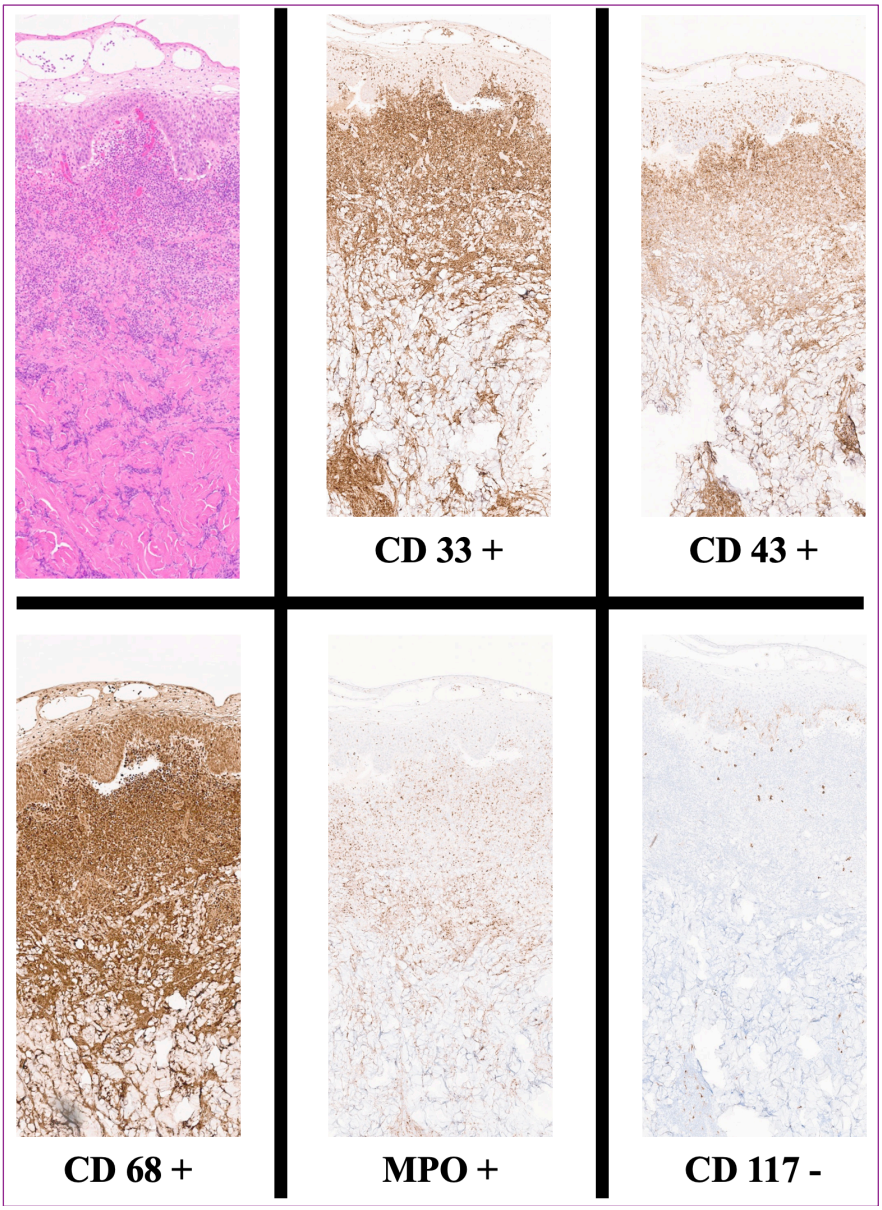

Figure 2. Histopathology supporting Leukemia Cutis. Representative sections of the punch biopsy from the abdominal skin incision (Figure 1) are shown here at 20 x magnification. The hematoxylin and eosin stain in the upper left demonstrates marked parakeratosis with serum overlying an epidermis with granular layer loss, acanthosis, spongiosis, and ballooning degeneration in the upper epidermis. The underlying dermis shows a diffuse infiltrate of atypical mononuclear cells that have fine chromatin and scant cytoplasm, intermixed with neutrophils, lymphocytes and histiocytes. The atypical cells intercalate between the collagen fibers of the reticular dermis. Staining shows positivity for CD 33, 43, 68 and Myeloperoxidase (MPO) (all markers associated with acute myeloid leukemia) but negative for CD 117 (marker for blasts).

with an exanthematous drug reaction. This quickly responded to topical triamcinolone 0.1% ointment. To date, the patient is alive, pursuing genetic testing and is being considered for clinical trials. To our knowledge, without any additional trauma to the skin, she has remained free of further lesions.

DISCUSSION

Koebner's phenomenon refers to the development of new skin lesions at sites of trauma that are "isomorphic" or the same as the underlying cutaneous disease (ie, psoriasis → trauma → psoriasis). [4,5] In contrast, pathergy is the development of "non-isomorphic" skin lesions at sites of trauma that are not the same as the underlying cutaneous disease (ie, Sweet syndrome → trauma → nonspecific papule, pustule, ulcer).[4,5,6,7] While LC occurs in 3-4% of patients with AML, trauma-induced isomorphic response (Koebnerization) has only been reported three times (**Table 1**).[1,3,4,5,8,9]

Table 1. Reported Cases of Trauma-Induced Isomorphic Response (Koebnerization) of Leukemia Cutis in Acute Myeloid Leukemia Patients

Cases	AML Type	Trauma	Response to Trauma
***Satter et al (2004) Female Infant**	**AML** (Acute Monocytic Leukemia FAB class M5, 46 XX, t (3;22;8) p (21; q13; p11.2)	**Excoriation**	**Leukemia Cutis at Birth** → resolved with chemotherapy → **excoriation** → white-linear papules → shave biopsy → **linear calcinosis cutis** *(case does not actually represent Koebnerization*)*
Tendas et al (2010) 56-year-old Female	**AML** (46 XX t (6:9) (p23; q34), FAB M1, Dek/Kan rearrangement positive)	**Central Venous Catheter** (CVC) Placement with presumed Infection	Large erythematous infiltrative papular lesion at CVC site → **limited response to antibiotics** → Biopsy → MPO positive myeloid blasts = **Leukemia Cutis** → not eligible for further chemotherapy
Tendas et al (2010) 52-year-old Female	**AML** (46 XX, FAB M1 positive, NPM1 negative)	**Central Venous Catheter** (CVC) Placement with presumed Infection	Large Papular infiltrative lesion at CVC site→ **limited response to antibiotics** → Biopsy → CD 43 and MPO positive immature myeloid cells = **Leukemia Cutis** → chemotherapy → resolution of skin lesion
Nobeyama et al (2014) 74-year-old Male	**AML-MDS** (46 XY, del(5) (pter→q11)	**Excoriation**	MDS 3 years → pruritic erythematous eruption to thigh/groin → excoriation → **linear papules** → Biopsy → myeloid blast cells = **Leukemia Cutis** → AML-MDS → chemotherapy → improvement with residual hyperpigmentation

Present Case 37-year-old Female	**AML** (46 XX, DNMT3A and NPM1 positive)	**Laparotomy Abdominal Incision** with presumed Infection	Erythematous plaques boarding the incisional site + vesiculobullous lesions to IV and line insertion sites → **limited response to antibiotics** → Biopsy of abdominal incision → CD 33, 43, 68 and MPO positive myeloid cells = **Leukemia Cutis** → chemotherapy → sustained improvement

*Case description does not represent Koebner's phenomena as calcinosis cutis is unrelated to the primary skin disease (ie, not leukemia cutis) so it cannot be an isomorphic response secondary to trauma.

Morphologically, 80% of LC lesions present as nodules, papules, and plaques.[3,8] While the plaques along the site of surgical skin incision are clinically and histologically (**Figures 1, 2**) consistent with LC, the vesiculobullous lesions this patient developed at other sites of trauma (IV/line insertions and shaving) are less typical.[3,8] Importantly though, LC presenting as vesiculobullous lesions that are coin sized with purulent, clear, and hemorrhagic appearances have been reported.[8] In our patient, it appears that her vesiculobullous lesions were induced by trauma and began to resolve with chemotherapy, thus suggesting Koebnerization of LC; however, the possibility of bullous Sweets syndrome cannot be excluded given its association with hematological malignancies and pathergy.[7] Overall, the importance of keeping LC in the differential for non-healing wounds (along with post-surgical pyoderma gangrenosum and infectious etiologies) cannot be understated as it can spare the patient from unnecessary treatments (steroids and/or antibiotics) and provides prognostic information (6% survival at 2 years).[3,7,8,10]

The linkage of trauma-induced cutaneous and intestinal manifestations is demonstrated in Behçet's disease whereby bowel resections have been related to the development of intestinal ulcers.[6] Interestingly, the dissemination of AML to the gastrointestinal tract, a form of MS, most commonly occurs in the small intestine (63% of cases).[2] This can lead to bowel obstructions and intussusception.[2,11,12] Our patient's presenting small bowel mass did not show AML; however, the biopsy at the time of the second surgery (anastomotic revision) at the original intestinal incisional site did, supporting MS. It can be argued that this is a trauma-induced spread of AML or an "isomorphic response", an "intestinal Koebnerization". After all, Koebner's phenomenon is hallmarked by inflammation induced recruitment to sites of trauma, such as surgical sites.[4,5] Conversely, the original small bowel mass could have represented MS with the biopsy not capturing AML (misdiagnoses have been reported in similar scenarios).[2] It is important to note that the original small bowel mass was examined by a hematopathologist with biased knowledge that the patient had leukemia. This speaks strongly to the possibility of MS not being present until it was induced by the trauma of the first surgery.

CONCLUSION

Trauma-induced isomorphic response (Koebnerization) is a rarely reported mechanism of LC. To our knowledge, we presented the 4th reported case. Similarly, we proposed a novel description of trauma-induced spread of AML, a form of MS, to the small intestine following surgical trauma that

may be considered an "intestinal Koebnerization." Overall, the importance of considering leukemia cutis in the differential for nonhealing wounds is critical to spare patients from unnecessary treatments and to provide prognostic information.

Conflict of Interest Disclosures: None

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