

Atypical Cutaneous Myeloid Infiltrate in Myelodysplastic Syndrome: A Case Report

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We report the case of a 31-year-old man with an atypical myeloid dermal infiltrate manifested by a 1.5-year history of recurrent erythematous plaques over his body that previously were shown to be culture positive for Staphylococcus aureus and had responded well to oral antibiotic treatment. The ultimate diagnosis was refractory anemia with excess blasts-2 (RAEB-2), a myelodysplastic syndrome (MDS). Whether it is a specific or non-specific lesion, cutaneous involvement in MDS is a poor prognostic factor. Leukemia cutis (LC), a specific dermal infiltrate of malignant hematopoietic cells, particularly is associated with progression to acute leukemia. However, the pathology of our patient's lesions revealed a more sparse sprinkling of atypical mononuclear cells indicative of an inflammatory recruitment of leukemic cells to the dermis. Nonetheless, the guarded prognosis of this high-risk subtype of MDS mandates continued monitoring for development of LC and progression to leukemia.

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Case Report

A 31-year-old Hispanic man was in his usual state of good health until January 2004 when he noticed a diffuse blistering rash all over his body. The patient described a continuous cycle of painful bullae that would appear, rupture with bleeding, and then resolve after several weeks, leaving 1-cm areas of hyperpigmentation. Prior cultures of

specimens of these lesions had grown pansensitive *Staphylococcus aureus*, and the patient reported that oral antibiotics would resolve the rash. At the time of his first presentation, the patient denied any other medical problems and denied any systemic symptoms including weight loss, bowel and/or bladder problems, fatigue, fever, nausea or vomiting, cough, night sweats or diaphoresis, and easy bruising or bleeding. He denied any family history of lesions or blistering diseases.

Sixteen months after presentation of the first skin eruptions, the patient was discovered to have anemia (hematocrit level, 25% [reference range, 41%–50%]; hemoglobin level, 8.3 g/dL [reference range, 14–17 g/dL]; in May 2002, his hematocrit level was 47% and hemoglobin level was 16.1 g/dL) and an elevated total bilirubin level of 2.1 mg/dL (reference range, 0.2–1.6 mg/dL). A peripheral smear demonstrated anisocytosis with microcytes, spherocytes, and occasional ovalocytes. The patient remained asymptomatic, denying fatigue, decreased appetite, sleep disturbances, myalgia or arthralgia, headaches, hematuria and/or bloody stool, or changes in bladder and/or bowel movements at the time. However, he did admit to weight loss, recorded as 13.5 kg, over a 6-month period that he attributed to exercise and dietary changes. The patient also denied any recent illnesses or infections. He denied any family history of anemia; thrombocytopenia; leukopenia; bleeding diathesis; or exposure to radiation, chemicals, and biologic agents. Results of a physical examination at that time demonstrated only minimal scleral icterus and lack of generalized lymphadenopathy; no palpable hepatosplenomegaly; and no skin petechiae, ecchymosis, or purpura. Results of further hematologic workup confirmed pancytopenia (white blood cell count, $2.6 \times 10^9/L$ [reference range, $4.5\text{--}11.0 \times 10^9/L$]; segmented neutrophil count, 65% [reference range, 54%–62%]; basophil

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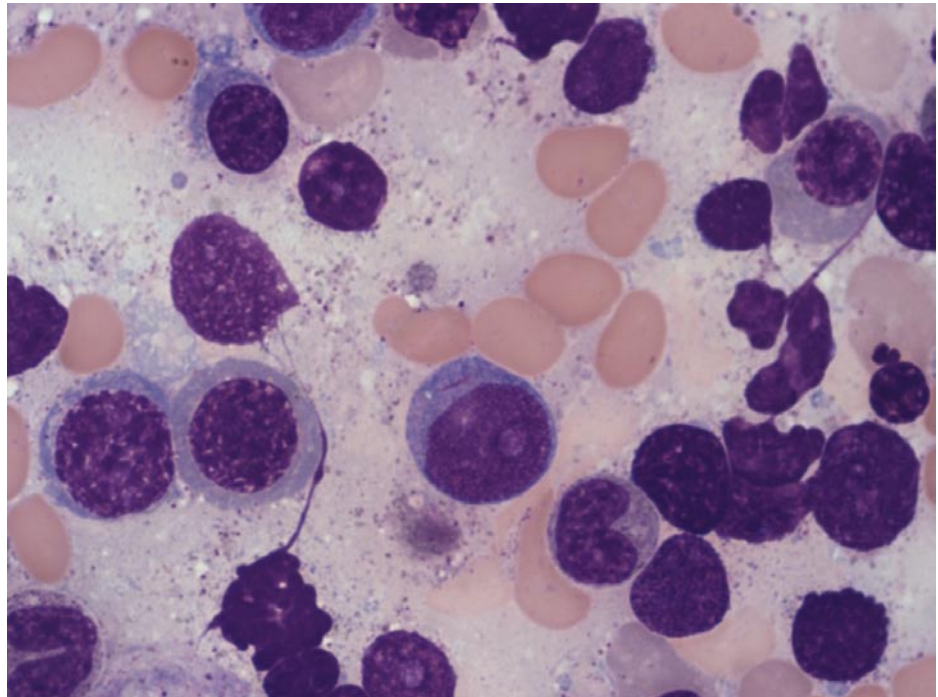


Figure 1. Auer rods in a blast cell (Wright-Giemsa, original magnification $\times 1000$).

count, 2% [reference range, 0%–1%]; lymphocyte count, 28% [reference range, 26%–40%]; atypical lymphocyte count, 3% [reference, 0%]; hematocrit level, 18% [reference range, 41%–50%]; reticulocyte count, 5.6% [reference range, 0.5%–1.5%]; mean cell volume, 112.4 fL [reference range, 80–100 fL]; platelet count, 37,000/mm³ [reference range, 140–400 $\times 10^3$ /mm³]).

A biopsy was performed on a bone marrow specimen and the results showed a hyperplastic bone marrow for age, with a population of myeloblasts, some of which contained Auer rods that comprised approximately 5% of the bone marrow cellularity; also, there was dysmegakaryopoiesis, hyperplastic dyserythropoiesis with late maturation defects, megaloblastoid change, and markedly decreased and mildly left-shifted granulocytopenia (Figure 1). By flow cytometry, the myeloid cells expressed dim CD45, CD13, CD15, CD33, and CD117. These results were consistent with a myelodysplastic syndrome (MDS), specifically refractory anemia with excess blasts-2 (RAEB-2) as described by the World Health Organization. Cytogenetic analysis also was performed and revealed a deletion in chromosome arm 9p, which sometimes is associated with acute myelogenous leukemia (AML) and Auer rods.

The patient was treated with 5-azacytidine (a demethylating agent) therapy and epoetin alfa, with noted improvement in his anemia and normalization of his platelet count.

As previously described, the patient's skin lesions appeared 16 months prior to the diagnosis

of MDS and to any chemotherapy treatment. These skin lesions previously had been cultured, had grown *S aureus*, and were effectively treated with oral antibiotics.

A few months after the patient was diagnosed with MDS, he was referred to dermatology from the hematology/oncology clinic because of a recurrence of his skin lesions. A 10-cm targetoid plaque was present on his right thigh, with 3-cm central, necrotic, erythematous bullae with active bleeding. The lesion appeared to have a central area of necrosis overlying a dusky violaceous slightly raised plaque (Figure 2).

The right axilla had 2 similar lesions that, according to the patient, were resolving. The left thigh had multiple 1.3-cm hyperpigmented round scars that the patient identified as sites of prior lesions. The initial differential diagnoses included leukemia cutis (LC) as well as the neutrophilic dermatoses Sweet syndrome and pyoderma gangrenosum, all of which have been associated with MDS.

Two 4-mm punch biopsies were performed on specimens from the edge of the lesions on the right lateral thigh. One specimen was sent for bacterial, fungal, and acid-fast bacilli cultures, and the other specimen was sent for histologic evaluation. Biopsy results showed a spongiotic epidermis with marked neutrophilic exocytosis, papillary edema, and red cell extravasation. An atypical infiltrate of mononuclear cells was present around the adnexa and dermal vessels and between collagen bundles. This infiltrate consisted of neutrophils, eosinophils, and



Figure 2. A 10-cm targetoid violaceous plaque on the right thigh, with a central granulating ulcer and overhanging border that previously was a purulent bullous lesion.

lymphocytes, as well as early myeloid precursors (Figure 3). Large immature forms also were noted, with high nuclear-cytoplasmic ratios and prominent nucleoli. Auer rods were not noted in the blast cells. These atypical cells stained strongly for myeloperoxidase, with scattered cells staining for CD68 (Figure 4). The cells of interest were negative for CD3 (T-cell marker), CD20 (B-cell marker), CD30 (T-cell and B-cell markers), CD34 (marker of stem and progenitor hematopoietic cells), and CD117 (hematopoietic stem cell factor receptor marker).

Comment

MDS refers to a diverse group of hematopoietic disorders defined by a defect in maturation at the clonal

level. This intrinsic disorder of the hematopoietic pluripotent stem cell or early myeloid progenitor cell in MDS typically results in a hypercellular bone marrow with trilineage dysplastic changes. Our patient more specifically was diagnosed with RAEB-2, the MDS subtype characterized by 5% to 19% blasts in the bone marrow or the presence of blasts with Auer rods, as in this case. RAEB-2 is associated with a higher risk of leukemic transformation and overall higher morbidity or mortality secondary to complications of bleeding and infections that result from its intrinsically debilitating cytopenia.

Cutaneous lesions in MDS can take the form of either specific cutaneous lesions, such as LC, or the more common nonspecific lesions, including

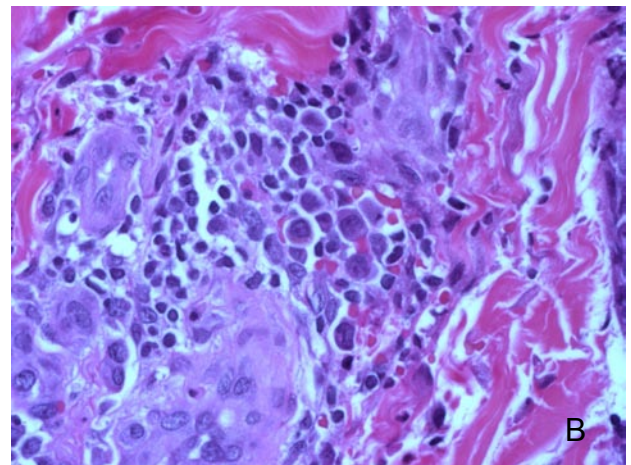
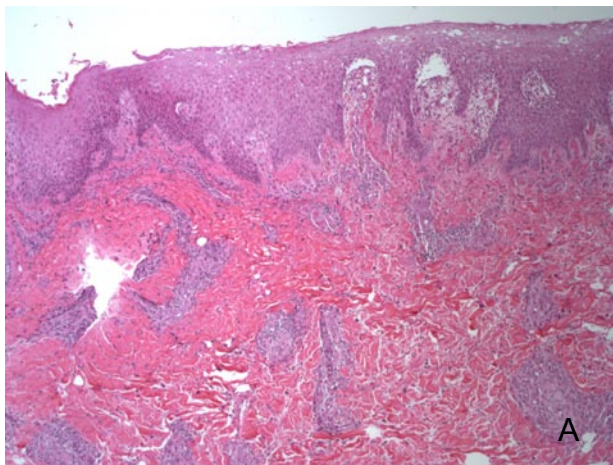


Figure 3. Perivascular infiltrate composed of scattered neutrophils, lymphocytes, eosinophils, early myeloid precursors, and large atypical mononuclear cells (A and B)(H&E; original magnifications $\times 40$ and $\times 400$, respectively).

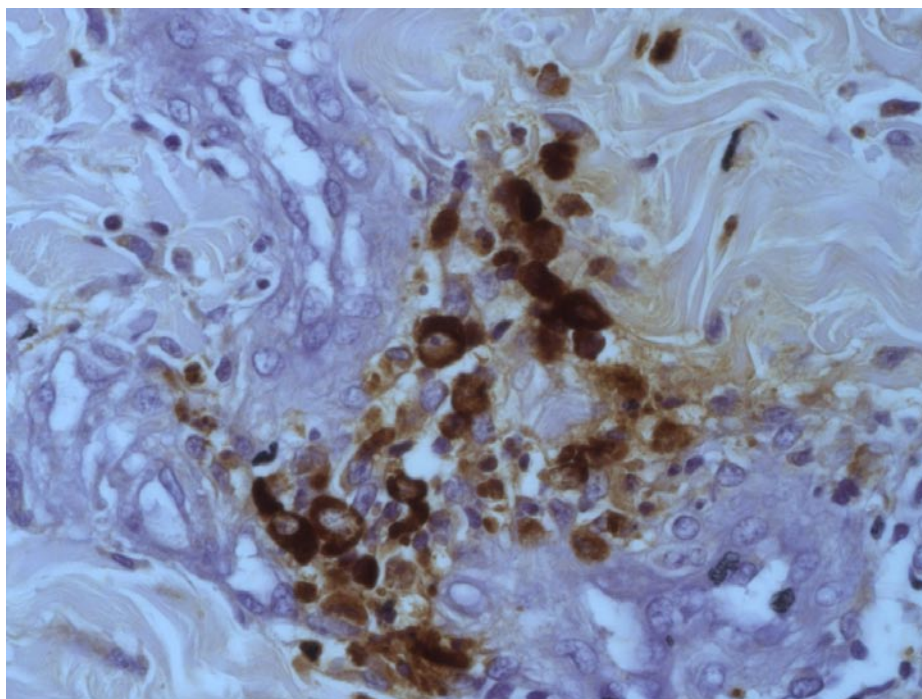


Figure 4. Large cells with strong cytoplasmic staining and prominent nucleoli consistent with immature myeloid precursors (immunohistochemical stain against myeloperoxidase using a streptavidin-biotin complex immunoperoxidase method, original magnification $\times 400$).

neutrophilic dermatoses (NDs), cutaneous infections, and cutaneous vasculitis.¹ In particular, LC and ND are poor prognostic factors in MDS. LC more specifically has been closely linked to a rapid progression to AML.

LC in MDS has a wide spectrum of presentations, which underscores the importance of early evaluation and biopsy of any suspicious skin lesions in hematologic patients. The clinical presentation of LC in MDS consists mainly of papules, nodules, and tumors, but Aractingi et al² also reported ecchymotic macules, necrotic black plaques, ulcerated lesions, and prurigo-like papules. LC also can manifest as seemingly benign lesions, including generalized pruritic papules,³ or mimic inflammatory dermatoses, such as stasis dermatitis.⁴

NDs similarly encompass a large pool of skin diseases, but 2 of the more common entities that present in MDS are Sweet syndrome and pyoderma gangrenosum. Both conditions are characterized by neutrophilic dermal infiltrates without the presence of leukemic cells or microorganisms, and by clinical improvement on systemic steroid treatment.⁵ Sweet syndrome typically presents as edematous erythematous papules or plaques that may form pustules over time, while pyoderma gangrenosum is characterized by painful nodules or pustules that ulcerate and are surrounded by raised, poorly defined borders. Clinically, both conditions also may be accompanied by systemic symptoms, such as fever and fatigue.¹

In general, skin involvement is regarded as a sign of disseminated disease and thus tends to occur late in the course of established AML. However, in the setting of MDS, LC, which is the specific infiltration of malignant myeloid cells into the skin, often is viewed as a harbinger of transformation to AML.^{1,3,6-8} In a study by Longacre and Smoller,⁹ MDS-associated LC preceded blood and bone marrow manifestations of AML in 9 patients, with a time to transformation varying from 3 weeks to 20 months; MDS-associated LC occurred concomitantly with AML presentation in 7 patients; and MDS-associated LC did not progress to AML in only 2 patients. LC in refractory anemia with excess blasts in transformation, which is another subtype of MDS, has been more commonly reported than RAEB-2 as a herald sign of precipitous transformation to leukemia,^{1,4,8} but both conditions portend poor prognoses.

Less well-documented is the malignant potential represented by the nonspecific ND. ND clearly has an association with malignancy and has been observed to occur before, simultaneously with, and after the development of AML.¹⁰ However, most cases of Sweet syndrome are idiopathic,¹¹ and only 10% to 20% of cases are associated with malignancy (50% of these cases are associated with AML).¹² Nevertheless, in a review of the association between Sweet syndrome and malignancy, Cohen and Kurzrock¹³ found that the diagnosis of Sweet syndrome often was the presenting

sign (11% diagnosed before the malignancy; 62% diagnosed concurrent with malignancy) of a new or recurrent malignancy, especially leukemia. In addition, Cohen and Kurzrock¹³ noted that two thirds of these patients usually had a recurrence of the lesions of Sweet syndrome, which generally occurred at the same time or before a hematologic relapse. Thus, in the context of low platelets or known chronic anemia, the appearance of ND becomes more concerning for leukemia or MDS; as such, all patients with ND should be screened for possible hematologic abnormalities.¹³

Our patient's lesions were first thought to be infectious and grew *S aureus*; he also appeared to respond to antibiotic therapy. As shown by pathology and the positive bacterial culture results, his lesions were not NDs. The presence of an atypical myeloid infiltrate was disturbing for possible LC, despite the positive *S aureus* cultures. However, the pathology did not demonstrate the usual dense myeloid cell infiltrate characteristic of LC. Instead, there was a more sparse sprinkling of atypical mononuclear cells among the eosinophils, neutrophils, and lymphocytes. The question of whether this was a reactive process complicated by the recruitment of leukemic cells to the site of inflammation thus was considered. Wintzen et al¹⁴ described a similar case of a patient with chronic myelomonocytic leukemia, another subtype of MDS; the authors believed the patient's biopsy-proven LC was provoked by an *S aureus* folliculitis rather than an autonomous tumor growth in the skin. Because the patient's lesions seemed to resolve more effectively with antibiotics than chemotherapy, the authors proposed that the leukemic infiltrate in the skin was a reactive recruitment of circulating leukemic monocytes.¹⁴ Chang et al⁴ also reported a case of a benign-appearing stasis dermatitis that turned out to be LC and suggested that the cellulitis may have initiated the LC. Finally, Aractingi et al² hypothesized that the specific prurigo-like papules that turned out to be biopsy-proven LC in one patient with chronic myelomonocytic leukemia may have been secondary to a leukemic cell infiltration from skin injury initiated by self-excoriation from a different cause, and cited that LC has been reported in surgery scars, trauma, and burns. Therefore, it is possible that the skin lesions in our patient represent an appropriate inflammatory response to a localized skin infection whereby the myeloid infiltrate is composed of atypical leukemic mononuclear cells. There also are a few reports of simultaneous LC and ND^{10,15,16} where the primary dermal infiltrate was neutrophilic but also contained a few leukemic cells. In fact, these cases may have

represented something akin to that of our patient. More specifically, as Tomasini et al¹⁵ speculate, it is likely that these leukemic cells may be "innocent" spectators and may not represent true LC but rather a chemotactic recruitment of malignant cells to the site of a dermal inflammatory process. Therefore, the *S aureus* infection in our patient also may have been the inflammatory nidus around which the malignant leukemic cells gathered. Yet, at the same time, it may not be prudent to dismiss our patient's lesions as a mere reactive nonspecific process. Tomasini et al¹⁷ and Baksh et al¹⁸ both reported rare cases in which a more prominent inflammatory process manifested by granulomas and giant cells, respectively, obscured and overshadowed a true presentation of LC. It would be interesting to consider that if our patient had not been treated appropriately with antibiotics, the reactive leukemic cells may have taken a greater hold in the skin and become an autonomously growing specific tumor.

It would have been easy for this patient to dismiss his rash as a simple infection because of his good health, his credible diagnosis of *S aureus* from cultures, and his response to oral antibiotic treatment. However, after the diagnosis of MDS, it was important for the hematology/oncology clinic to refer the patient to dermatology for a workup of these recurrent skin lesions, despite the plausible history of *S aureus* infection. All skin lesions in patients with MDS should be regarded with a higher degree of suspicion because they may take on a multitude of morphologies, including those of a deceptively benign-appearing nature. LC may signal increased morbidity from impending blastic transformation and thus should be treated as an early sign of acute leukemia. It is crucial to identify these lesions as quickly as possible so that aggressive therapy that includes not only chemotherapy but also consideration for bone marrow transplantation may be instituted.

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