5 Leukemia Cutis and Hematologic Malignancies with Cutaneous Manifestation

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Clinical History

In this chapter we present a case of leukemia cutis in an 18-year-old male with a history of monoblastic acute myeloid leukemia (AML) (SAB M5) in second remission. The patient received a matched unrelated donor transplant and had an acute episode of GI GVHD with diarrhea (confirmed with GI biopsy) on day 28, which resolved after treatment with prednisone, budesonide, and beclomethasone. Bone marrow aspirate on day 28 showed no morphologic or flow cytometric evidence of residual acute myeloid leukemia. Beginning on day 30, the patient had developed non-pruritic diffuse subcutaneous lesions over his chest and scalp, which were progressively worsening. Especially prominent on his chest was a raised nodule at several centimeters in diameter with associated erythema at the base of the lesion. Because of the concern of leukemia cutis, a skin punch biopsy of a scapular lesion was performed on day 37 (Figs. 5.1 and 5.2). Immunohistochemical studies of the cellular infiltrate are illustrated in Fig. 5.3. A bone marrow aspirate and biopsy 13 days later showed no morphologic or flow immunophenotypic (with a sensitivity

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C. C. S. Yeung, H. M. Shulman (eds.), *Pathology of Graft vs. Host Disease*,
https://doi.org/10.1007/978-3-319-42099-8_5

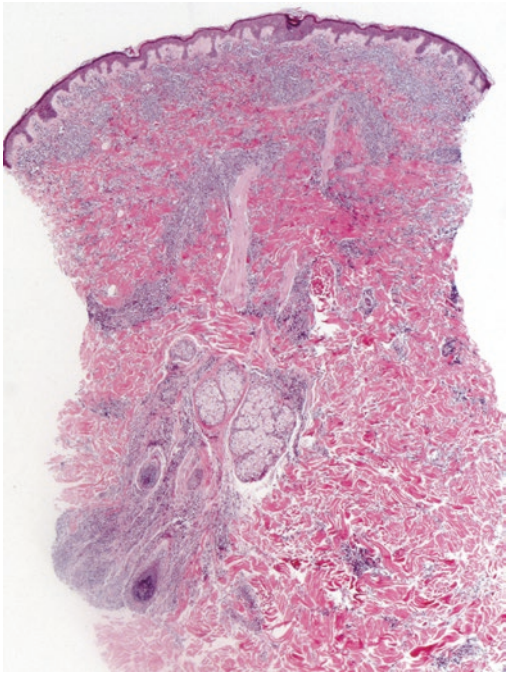

Fig. 5.1 An H&E-stained section shows heavy infiltration of the upper and mid-dermis by immature cells most compatible with leukemic blasts

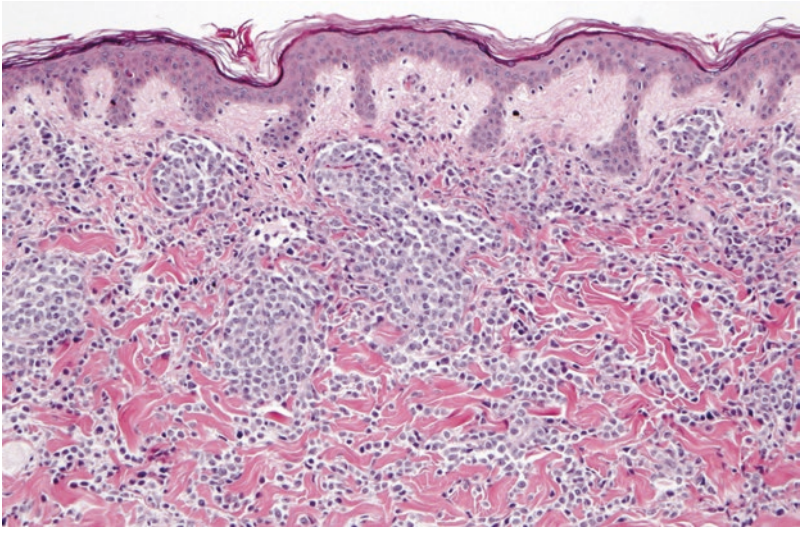

Fig. 5.2 There is a grenz (clear) zone between the dense dermal perivascular monomorphous infiltrates and the overlying epidermis

of detection of 10^{-3}–10^{-4}) evidence of residual acute myeloid leukemia. However, a marrow aspirate and biopsy from day 80 showed 72% monoblasts, which were confirmed by flow cytometry to have a similar immunophenotype to this patient's original leukemia (Fig. 5.4).

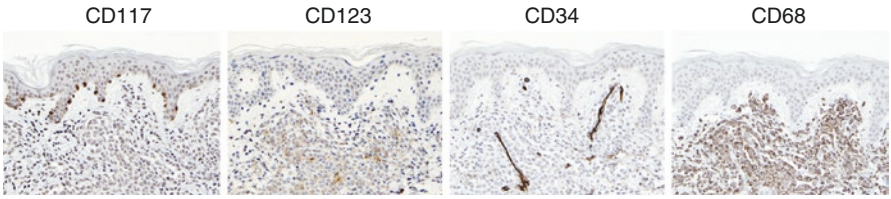

Fig. 5.3 Immunohistochemistry staining of the cellular infiltrate is positive for CD68 (monocytes), weakly positive for CD123 (a marker for plasmablastic lymphoma), and negative for CD34 and CD117 (surrogate for CD34). Typical leukemia markers such as CD34 and CD117 are commonly lost in leukemia cutis

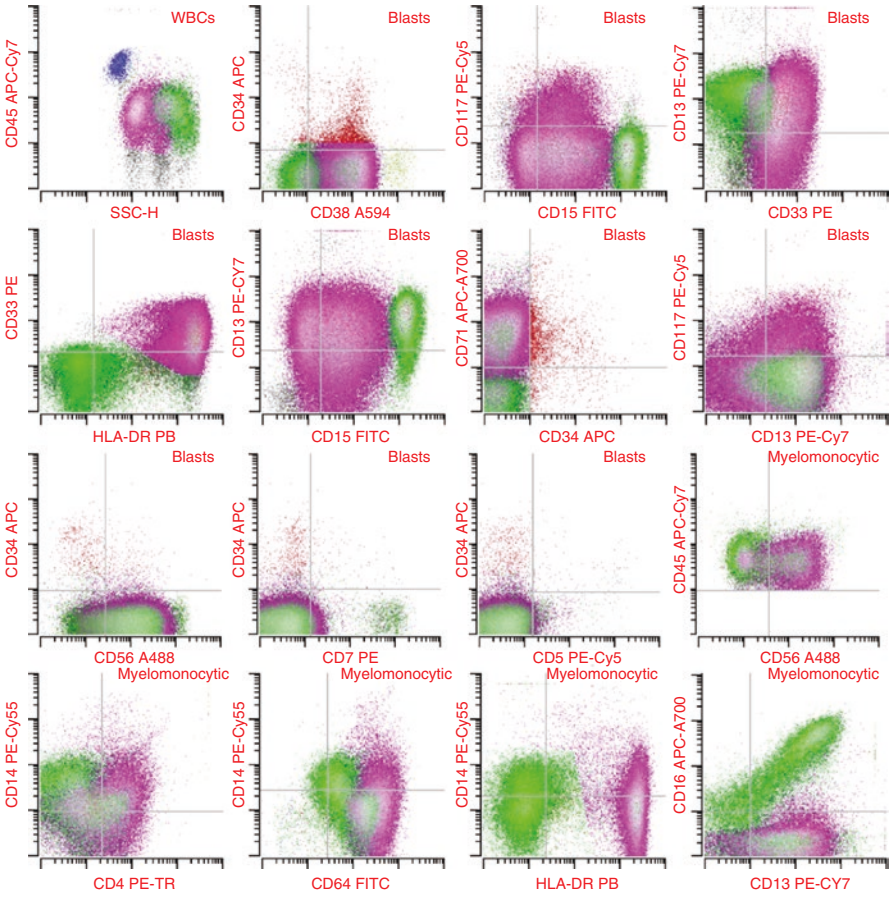

Fig. 5.4 On day 80, an abnormal immature blast population (magenta) in the patient's marrow was detected by flow cytometry that represented 50.5% of the white cells. The blasts abnormally expressed CD4, CD14 (low), CD15, CD34 (absent), CD45 (low), CD56, CD64, CD117 (absent), and HLA-DR (high) with normal expression of CD13, CD33, CD38, CD71, and CD123 without CD5, CD7, CD16, or CD19. This finding is consistent with persistent/recurrent acute myeloid leukemia of monocytic lineage

Diagnosis

Skin with leukemia cutis of AML with monocytic differentiation

Key Pathology Features

- Monotonous infiltrate
- Presence of a grenz zone
- Potential loss of original myeloid blast immunophenotypic markers
- Lack of epidermotropism

Differential Discussion

Following HSCT for hematopoietic malignancy and new-onset rashes with a mononuclear dense dermal infiltrate, diagnosis of leukemia cutis must be excluded. Our patient has leukemia cutis of AML (lesions are generally referred to as chloromas) with monocytic differentiation, which may have morphologic features overlapping with those of acute graft-versus-host disease (aGVHD). The infiltrate in leukemia cutis will be monomorphic, commonly have a grenz zone (a clear zone between the epidermis and the perivascular dermal infiltrate), and lack the prominent epithelial changes seen in GVHD. Our patient's biopsy showed dense perivascular collections of cells, but the leukemic infiltrate can also form a dense mass infiltrating the dermal collagen.

Leukemia cutis occurs in approximately 10% of myeloid leukemia, most commonly with monocytic subtypes and generally has poor prognosis [1]. Lesions of leukemia cutis can have varied appearances ranging from single to multiple violaceous-, red-, or skin-colored lesions. Often skin biopsies may arrive in pathology with other differentials [2]. The skin is rarely the only site of involvement in leukemia. In 50–90% of acute leukemia patients, there has been a prior established diagnosis of leukemia. The term chloroma is often used to encompass extramedullary manifestations of leukemia and refers to the green sheen seen on fresh-cut surfaces of the neoplastic tissue due to myeloperoxidase. This special feature provides stronger support for leukemic involvement of cutaneous sites [3].

Challenges in Diagnosing Leukemia Cutis in the Post-transplant Setting

Leukemias with monocytic differentiation more commonly involve the skin [4]. Often when myeloid leukemia involves the skin, characteristic expression of CD34, MPO, and CD117 is lost while maintaining expression of antigens more indicative of monocytic differentiation, such as CD68, CD163, and CD4 [4].

Benet et al. demonstrated that by using a combination of CD68, CD33, and MPO they could detect 100% of myeloid leukemia cutis in their study of 173 specimens [5]. In a smaller cohort, Cronin et al. had similar findings and showed that often the immunophenotype changed between the blasts in the marrow and the skin [2]. The mixed infiltrate of lichenoid GVHD may show varying degrees of monocytes and lymphocytes, which overlap with leukemia cutis (see Chap. 6). Further complicating the problem is that in many instances, when a skin biopsy is performed a sample for flow cytometry was not taken (flow cytometry allows us to identify immunophenotypic abnormalities that may confirm the neoplastic nature of an infiltrate). This often complicates the diagnosis of leukemia cutis, especially if the blasts have lost the characteristic progenitor markers of CD34 and CD117. Without flow cytometric data, it can be very difficult to distinguish with certainty between a monocytic infiltrate and monoblastic leukemia infiltrate. It is recommended that when there is strong clinical suspicion for leukemia cutis, a fresh biopsy of skin should always be collected and submitted in Roswell Park Memorial Institute medium or similar cell culturing media for flow cytometry.

GVHD with Abundant Monocytes

One morphologic presentation of aGVHD in skin biopsies when obtained near the onset of a rash is an abundance of monocytes within a pleomorphic infiltrate. Key features of florid GVHD not seen in leukemia cutis include epidermotropism with apoptosis and the absence of a grenz zone. Nishiwaki et al. (2009) performed a study of early skin biopsy near the onset of skin GVHD using IHC markers for T lymphocytes (CD3) and monocytes (CD163). They found that biopsies with dense cutaneous infiltrates in GVHD were monocyte-predominate. Moreover, they were associated with steroid-refractory GVHD and poorer overall survival in aGVHD [6]. A subsequent study by the same group shows that treatment with dexamethasone may ameliorate the effects of the macrophages on exacerbating GVHD [7]. Terakura et al. (2015) performed a case-controlled study using a CD163 semiquantitative score for dermal macrophage infiltration. They found a significant association between cases with many macrophages and increased risk of death. Nonetheless, the association between high macrophage infiltrate and severe GVHD or increased risk of death was not strong enough to apply as an independent prognostic indicator [8]. Further studies are needed to elucidate the effect that heavy macrophage infiltration has on the severity of GVHD.

Other Hematologic Malignancies Involving the Skin

A number of hematologic malignancies may present in the skin concurrently with GVHD, including AML. Clinically, the cutaneous T-cell malignancies mycosis

fungoides or Sézary syndrome (MF/SS) may mimic features of GVHD. Patients can present with scaly rashes, multiple plaques, or raised lesions. Early stages are typically limited to the skin and are often initially misdiagnosed as psoriasis. The disease has a predominantly indolent course in most patients and eventual disease dissemination to the lymph nodes and marrow. Ulceration and erythroderma can also be presenting features of the cutaneous lesions. The neoplastic infiltrate in the skin of these patients is epidermotropic and comprises small- to medium-sized atypical lymphocytes with cerebriform nuclei. In approximately a quarter of patients, circulating atypical lymphocytes are seen in the peripheral blood. Large cell transformation is generally associated with progression of the disease, but rare stage 1 cases will feature significant large cells morphology at diagnosis. The workup of MF/SS can be challenging, and often definitive diagnosis of a T-cell lymphoma is not possible in the early stages. Having a clinical suspicion of GVHD in the post-transplant setting can further confound the situation. The immunophenotype of MF/SS is generally CD4 positive although up to 20% are CD8 positive. There is often loss of one or more of the remaining T-cell antigens including CD2, CD3, CD5, and CD7. Molecular studies for T-cell clonality are not required for diagnosis and may in certain cases be misleading as inflammatory skin disorders as well as GVHD can show clonal signatures. In the patient scenario, where a clonal T-cell molecular signature is known from another definitive lesion, a comparative T-cell clonality study in the skin can be helpful in confirming skin involvement by T-cell lymphoma.

MF/SS comprise approximately half of the cutaneous T-cell lymphomas. Other common T-cell lymphomas that present in the skin include primary cutaneous γδ T-cell lymphoma NOS, primary cutaneous CD30+ lymphoproliferative disorders (lymphomatoid papulosis and cutaneous anaplastic large cell lymphoma), peripheral T-cell lymphoma, NOS, as well as other provisional entities highlighted in the updated 2016 WHO [9]. Less likely to confound the diagnosis of GVHD are B-cell lymphomas as these are generally associated with infiltrates that are more dense and monotonous, with some identifiable morphologic features (such as nodular proliferative pattern, sheets of large atypical cells, or plasmablastic morphology) or immunohistochemical markers. B-cell lymphomas which may involve the skin include primary cutaneous follicular center lymphoma, cutaneous marginal zone lymphoma, primary cutaneous diffuse large B-cell lymphoma leg type, and plasmablastic lymphoma.

Teaching Points

1. Leukemia cutis most commonly occurs with AML with monocytic differentiation.
2. AML leukemia cutis commonly loses expression of canonical markers CD34, MPO, and CD117, retaining CD68, CD4, and CD163, taking on an immunophenotype very similar to monocytes.

3. Morphologic features of aGVHD may include a dense inflammatory infiltrate that can have a high monocytic component which may overlap with leukemia cutis.
4. The features distinguishing GVHD from leukemia cutis are:
   (a) GVHD may include more frequent apoptotic basal keratinocytes; apoptotic change is not a feature of leukemia cutis.
   (b) Leukemia cutis has more monotonous dense infiltrate.
   (c) Leukemia cutis has a grenz zone between the infiltrate and the epidermis.
5. Immunophenotyping of dermal macrophages with IHC demonstrates a range of macrophages from few to many. Cases of aGVHD with increased dermal monocytes may be associated with more severe disease, treatment refractoriness, and increased risk of death.

Questions

1. A 30-year-old woman presents on day 50 post-transplant with a diffuse rash over her arm, back, and chest. The biopsy performed on the left arm shows a monocytoid cell-rich infiltrate with expression of CD68 and CD163. What would your differential include?
   A. GVHD
   B. Leukemia cutis
   C. Infection
   D. Macrophage activation syndrome
   E. All of the above

2. The first manifestation of relapsed acute leukemia may be in an extramedullary location.
   A. True
   B. False

3. When leukemia involves the skin, what markers are commonly lost?
   A. CD34
   B. CD117
   C. CD68
   D. CD123
   E. A and B
   F. All of the above

Answers

1. Answer: E
2. Answer: A
3. Answer: E

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