Case Report

A 42-year-old male without prior significant medical history presented to the emergency department (ED) with a 3-week history of fever, night sweats, sore throat, cough, and rash. Initial laboratory evaluation in the ED revealed a white blood cell (WBC) count of >90,000/uL. The patient was hospitalized for evaluation and treatment of the significant leukocytosis. Dermatology and Hematology-Oncology were consulted for work-up of the rash and leukocytosis, respectively. On physical examination, the patient had numerous discrete violaceous macules and papules scattered on his face, ears, trunk, and extremities (Figures 1 and 2).

Figure 1:

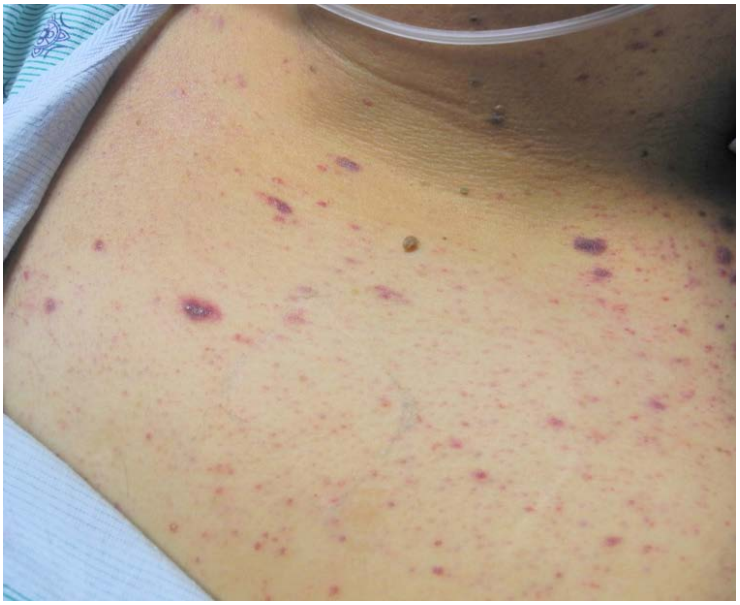
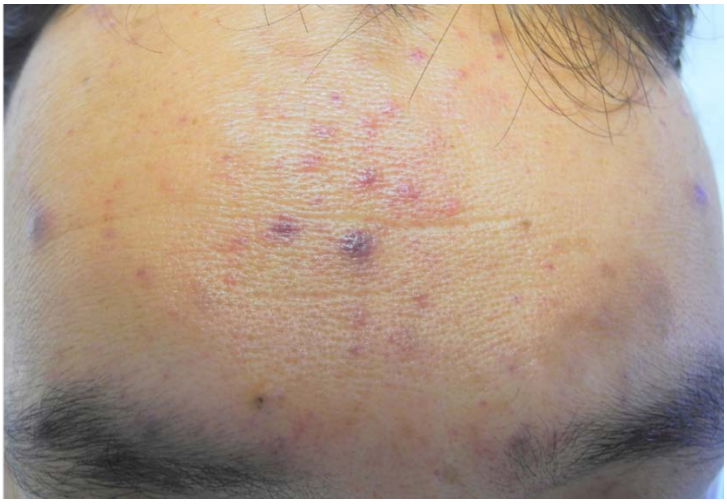


Figure 2:



Microscopic Findings:

A 4-mm punch biopsy was performed from a representative lesion. Hematoxylin-eosin (H&E) staining of the biopsy revealed nodular dermal infiltrates of atypical monocytic cells (Figure 4) and scattered mitotic figures that stained positive for myeloperoxidase (MPO) (Figure 4). A bone marrow biopsy was also completed, which revealed 54% myeloblasts and immature monocytic cells.

Figure 3:

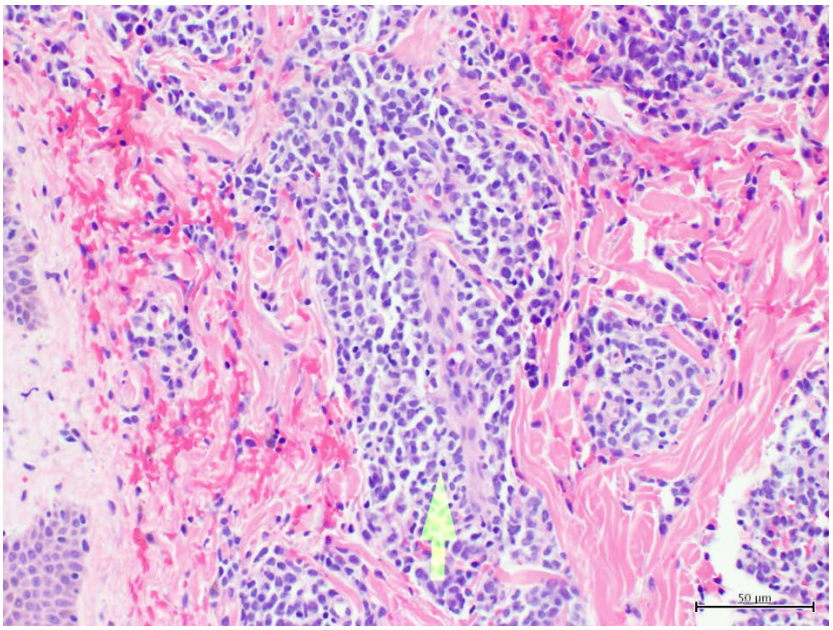
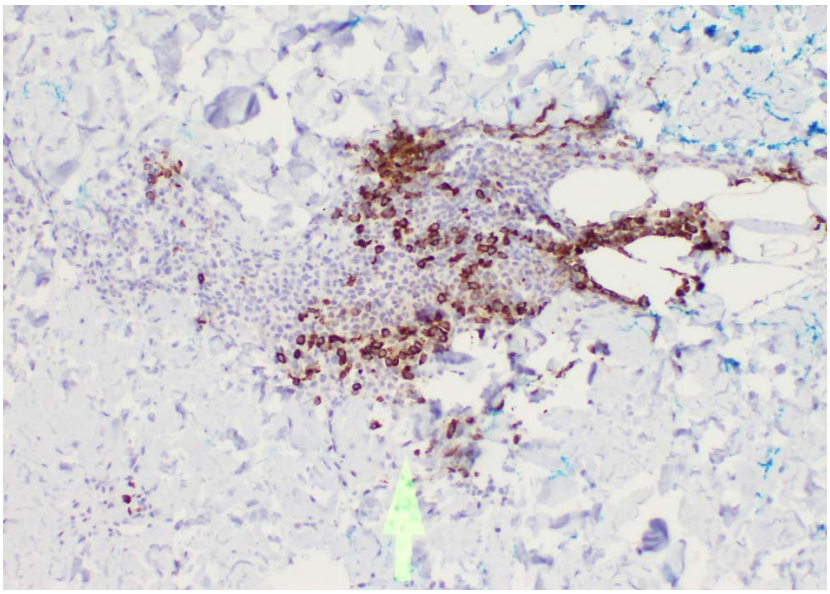


Figure 4:



What is your diagnosis?

Answer: Leukemia cutis secondary to acute myelogenous leukemia.

Discussion

Leukemia cutis is a rare manifestation of hematologic malignancy caused by the metastatic spread of leukocytes into the skin. Leukemia cutis may present with varied morphologies, such as macular and papular lesions, that clinically have a characteristic violaceous color[1]. Biopsy is required for diagnosis. Generally, patients with leukemia cutis have underlying leukemia. However, the presentation of leukemia cutis may precede diagnosis of underlying leukemia or represent recurrence after disease remission[2]. Histologically, leukemia cutis secondary to AML appears as large, myeloperoxidase (MPO) positive-staining cells with a high nuclear to cytoplasmic ratio and finely dispersed chromatin infiltrating into the subcutis, dermis, or epidermis[3]. Staining with MPO identifies myeloid cells due to the presence of azurophilic granules during the promyelocytic stage of differentiation[4]. Our patient's skin biopsy was consistent with leukemia cutis secondary to AML. Bone marrow biopsy, which is the gold standard for diagnosis of hematologic malignancy, was later performed to confirm the diagnosis of AML.

AML is a group of blood cell cancers originating from malignant clonal expansion of blood cell precursors in the bone marrow. A recent comparative study by Agis et al. revealed a 4% prevalence of leukemia cutis secondary to AML[5]. Other malignancies such as acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL) can also present with leukemia cutis. ALL generally presents in children and neither ALL nor CLL stain positive for MPO histologically[6,7]. Clinically, leukemia cutis presents with firm nodules and papules which become hemorrhagic on the head, neck, and trunk. In addition to leukemia cutis, AML frequently displays a variety of skin manifestations such as hemorrhagic diathesis, vasculitis, infectious lesions, and drug reactions[8]. Additional cutaneous manifestations of AML include Sweet Syndrome (SS), pyoderma gangrenosum (especially bullous type), neutrophilic eccrine hidradenitis, and erythema nodosum. AML is the most common malignant cause of these cutaneous findings.

The clinical differential diagnosis for our patient’s violaceous macules and papules included SS, cutaneous pseudolymphoma (PSL), hemorrhagic folliculitis, and leukocytoclastic vasculitis. Given that the patient had an elevated WBC count of >90,000/µL on presentation, a malignant process was favored as the underlying cause of the patient’s cutaneous lesions. Biopsy of the skin lesions did not show histologic vascular disruption or extravasation of red blood cells that characterize hemorrhagic folliculitis or leukocytoclastic vasculitis[9].

Sweet Syndrome, or acute febrile neutrophilic dermatosis, is a reactive syndrome of unknown etiology that is associated with hematological malignancies including AML, solid malignant neoplasms, medications, autoimmune diseases, viral infections, pregnancy, inflammatory bowel disease, and idiopathic etiologies[10]. SS presents with painful, violaceous papulonodules on the face and extremities that coincides with onset of systemic symptoms of fever and leukocytosis. On histological examination, SS appears as a neutrophilic infiltrate in the dermis with papillary dermal edema[11]. In the histiocytoid type, cells appear as immature myeloid cells that look similar to histiocytic mononuclear cells that also often stain positive for MPO[10]. Although this aspect is similar to leukemia cutis secondary to AML, the diffuse presentation of asymptomatic violaceous lesions favored the diagnosis of leukemia cutis.

PSLs, additionally known as cutaneous lymphoid hyperplasia, are lymphoid infiltrates into cutaneous tissue that simulate lymphomas[12]. Medications, tattoos, infections, and idiopathic causes have all been reported to cause PSLs. PSLs can be divided into several patterns such as nodular, epidermotropic, dermal diffuse, subcutaneous, or intravascular, however they generally present

clinically as a solitary nodule with occasional occurrence of multiple nodules. These may appear similar to cutaneous T- or B-cell lymphomas histologically. PSLs can additionally occur in cutaneous lupus erythematosus and portray a broad spectrum of histological presentations, therefore clinical correlation is vital to making an accurate diagnosis[13]. Lymphomatoid drug eruptions can occur with the use of certain medications and are reversible with discontinuation of the drug. These lesions generally contain T cell lymphocytic infiltrates on histology examination[14].

AML patients with skin lesions typically have a more aggressive underlying malignancy and a significantly lower survival rate than those without skin lesions[15]. However, additional studies are needed to further understand if leukemia cutis as a presenting sign is associated with a worse prognosis versus manifestation later in the disease course. Although there is no treatment specifically for leukemia cutis, the condition improves with treatment of the underlying malignancy. The current standard induction treatment for AML is the "7+3" regimen, which involves 7 days of cytarabine treatment and 3 days of treatment with an anthracycline (such as daunorubicin or idarubicin). This is associated with a complete remission rate of approximately 80% in younger patients[16]. Autologous bone marrow transplantation in addition to chemotherapy has shown to decrease the risk of relapse[17]. Hydroxyurea prior to initiation of chemotherapy in AML patients with extremely high WBC count has shown to decrease incidence of early death[18]. In our patient, the rash began to resolve within one week after treatment with hydroxyurea, cytarabine, and idarubicin.

References

1. Su WP, Buechner BA, Li CY, et al. Clinicopathologic Correlations in Leukemia Cutis. Journal of the American Academy of Dermatology, vol. 11, no. 1, 1984, pp. 121–128.
2. Rao, Angoorig, and Indira Danturty. Leukemia Cutis. Indian Journal of Dermatology, vol. 57, no. 6, 2012, p. 504.
3. Hale CS. Leukemia cutis. PathologyOutlines.com website. Caution-http://www.pathologyoutlines.com/topic/skintumornonmelanocyticleukemias.html. Accessed May 16th, 2020.
4. Tsuruta T, Tani K, Hoshika A, et al. Myeloperoxidase Gene Expression and Regulation by Myeloid Cell Growth Factors in Normal and Leukemic Cells. Leukemia & Lymphoma, vol. 32, no. 3-4, 1999, pp. 257–267.
5. Agis H, Wellermann A, Fonatsch C, et al. A Comparative Study on Demographic, Hematological, and Cytogenetic Findings and Prognosis in Acute Myeloid Leukemia with and without Leukemia Cutis. Annals of Hematology, vol. 81, no. 2, 2002, pp. 90–95.
6. Tsang, P. Acute lymphocytic leukemia (ALL). PathologyOutlines.com website. Caution-http://www.pathologyoutlines.com/topic/lymphnodesALL.html. Accessed May 15th, 2020
7. Sangle N. CLL / Chronic lymphocytic leukemia. PathologyOutlines.com website. Caution-http://www.pathologyoutlines.com/topic/lymphomaCLL.html. Accessed May 15th, 2020.
8. Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. J Cutan Pathol. 1993 Oct;20(5):407-410.
9. Carlson, J Andrew. The Histological Assessment of Cutaneous Vasculitis. Histopathology, vol. 56, no. 1, 2010, pp. 3–23.

10. Requena L, Kutzner H, Palmedo G, et al. Histiocytoid Sweet Syndrome. Archives of Dermatology, vol. 141, no. 7, 2005.
11. Hamodat M. Sweets Syndrome. PathologyOutlines.com website. Caution-http://www.pathologyoutlines.com/topic/skinnontumorsweetssyndrome.html. Accessed May 16th, 2020.
12. Mitteldorf, Christina, and Werner Kempf. Cutaneous Pseudolymphoma—A Review on the Spectrum and a Proposal for a New Classification. Journal of Cutaneous Pathology, vol. 47, no. 1, 2019, pp. 76–97.
13. Pereira A, Ferrara G, Calamaro P, et al. The Histopathological Spectrum of Pseudolymphomatous Infiltrates in Cutaneous Lupus Erythematosus. The American Journal of Dermatopathology, vol. 40, no. 4, 2018, pp. 247–253.
14. Magro CM, Olson LC, Nguyen GH et al. CD30 Positive Lymphomatoid Angiocentric Drug Reactions. The American Journal of Dermatopathology, vol. 39, no. 7, 2017, pp. 508–517.
15. Kaddu S, Zenahlik P, Beham-Schmid C, et al. Specific Cutaneous Infiltrates in Patients with Myelogenous Leukemia: A Clinicopathologic Study of 26 Patients with Assessment of Diagnostic Criteria. Journal of the American Academy of Dermatology, vol. 40, no. 6, 1999, pp. 966–978.
16. Dombret H, Gardin, C. An Update of Current Treatments for Adult Acute Myeloid Leukemia. Blood, vol. 127, no. 1, 2016, pp. 53–61.
17. Burnett A, Goldstone A, Stevens R et al. Randomised Comparison of Addition of Autologous Bone-Marrow Transplantation to Intensive Chemotherapy for Acute Myeloid Leukaemia in First Remission: Results of MRC AML 10 Trial. The Lancet, vol. 351, no. 9104, 1998, pp. 700–708.
18. Mamez AC, Raffoux E, Chevret S, et al. Pre-Treatment with Oral Hydroxyurea Prior to Intensive Chemotherapy Improves Early Survival of Patients with High Hyperleukocytosis in Acute Myeloid Leukemia. Leukemia & Lymphoma, 5 Feb. 2016.