Isolated Nodule and Generalized Lymphadenopathy

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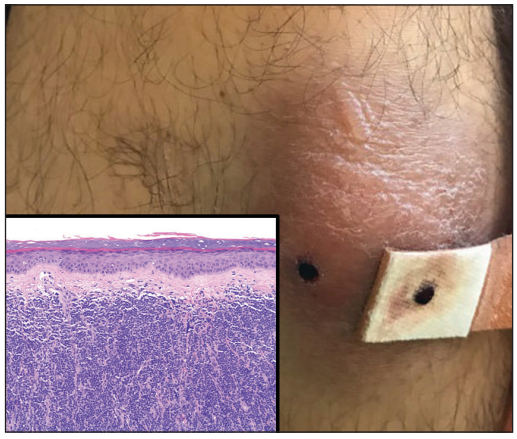

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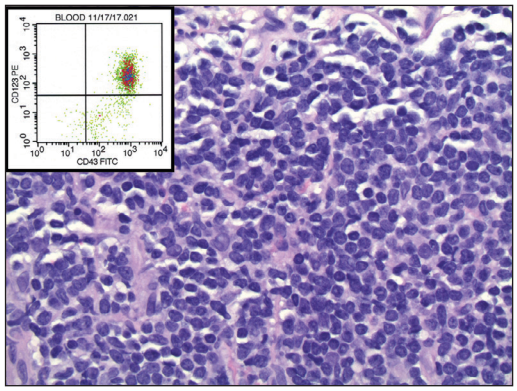

H&E, original magnification ×400.

A 23-year-old man presented with skin that bruised easily, pancytopenia, recent fatigue, fever, and loss of appetite, along with a nontender, brown-purple, left anterior pretibial mass of 2 years' duration (top). Computed tomography showed diffuse lymphadenopathy involving the inguinal, mesenteric, retroperitoneal, mediastinal, and axillary regions. A biopsy of the mass showed a dense monomorphous infiltrate of medium-sized blastoid cells with small or inconspicuous nucleoli (bottom). The lesion diffusely involved the dermis and extended into the subcutaneous tissue but spared the epidermis. Flow cytometry immunophenotyping of peripheral blood neoplastic cells (bottom [inset]) showed high-level expression of CD123 together with expression of CD4, CD56, CD45RA, and CD43 but a lack of expression of any other myelomonocytic or lymphoid lineage–associated markers.

THE BEST **DIAGNOSIS IS:**

a. adult T-cell leukemia/lymphoma
b. blastic plasmacytoid dendritic cell neoplasm
c. diffuse large B-cell lymphoma
d. primary cutaneous γδ T-cell lymphoma
e. T-cell lymphoblastic leukemia/lymphoma

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THE **DIAGNOSIS:** Blastic Plasmacytoid Dendritic Cell Neoplasm

A diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN) was rendered. Subsequent needle core biopsy of a left axillary lymph node as well as bone marrow aspiration and biopsy revealed a similar diffuse blastoid infiltrate with an identical immunophenotype to that in the skin biopsy from the pretibial mass and peripheral blood.

Previously known as *blastic natural killer cell leukemia/lymphoma* or *agranular CD4$^+$/CD56$^+$ hematodermic neoplasm/tumor*, BPDCN is a rare, clinically aggressive hematologic malignancy derived from the precursors of plasmacytoid dendritic cells. It often is diagnostically challenging, particularly when presenting at noncutaneous sites and in unusual (young) patient populations.[1] It was included with other myeloid neoplasms in the 2008 World Health Organization classification; however, in the 2017 classification it was categorized as a separate entity. Blastic plasmacytoid dendritic cell neoplasm typically presents in the skin of elderly patients (age range at diagnosis, 61–67 years) with or without bone marrow involvement and systemic dissemination.[1,2] The skin is the most common clinical site of disease in typical cases of BPDCN and often precedes bone marrow involvement. Thus, skin biopsy often is the key to making the diagnosis. Diagnosis of BPDCN may be delayed because of diagnostic pitfalls. Patients usually present with asymptomatic solitary or multiple lesions.[3-5] Blastic plasmacytoid dendritic cell neoplasm can present as an isolated purplish nodule or bruiselike papule or more commonly as disseminated purplish nodules, papules, and macules. Isolated nodules are found on the head and lower limbs and can be more than 10 cm in diameter. Peripheral blood and bone marrow may be minimally involved at presentation but invariably become involved with the progression of disease. Cytopenia can occur at diagnosis and in a minority of severe cases indicates bone marrow failure.[2-6]

Skin involvement of BPDCN is thought to be secondary to the expression of skin migration molecules, such as cutaneous lymphocyte-associated antigen, one of the E-selectin ligands, which binds to E-selectin on high endothelial venules. In addition, the local dermal microenvironment of chemokines binding CXCR3, CXCR4, CCR6, or CCR7 present on neoplastic cells possibly leads to skin involvement. The full mechanism underlying the cutaneous tropism is still to be elucidated.[4-7] Infiltration of the oral mucosa is seen in some patients, but it may be underreported. Mucosal disease typically appears similarly to cutaneous disease.

The cutaneous differential diagnosis for BPDCN depends on the clinical presentation, extent of disease spread, and thickness of infiltration. It includes common nonneoplastic diseases such as traumatic ecchymoses; purpuric disorders; extramedullary hematopoiesis; and soft-tissue neoplasms such as angiosarcoma, Kaposi sarcoma, neuroblastoma, and vascular metastases, as well as skin involvement by other hematologic neoplasms. An adequate incisional biopsy rather than a punch or shave biopsy is recommended for diagnosis. Dermatologists should alert the pathologist that BPDCN is in the clinical differential diagnosis when possible so that judicious use of appropriate immunophenotypic markers such as CD123, CD4, CD56, and T-cell leukemia/lymphoma protein 1 will avoid misdiagnosis of this aggressive condition, in addition to excluding acute myeloid leukemia, which also may express 3 of the above markers. However, most cases of acute myeloid leukemia lack terminal deoxynucleotidyl transferase (TdT) and express monocytic and other myeloid markers. Terminal deoxynucleotidyl transferase is positive in approximately one-third of cases of BPDCN, with expression in 10% to 80% of cells.[1]

It is important to include BPDCN in the differential diagnosis of immunophenotypically aberrant hematologic tumors. Diffuse large B-cell lymphoma, leg type, accounts for 4% of all primary cutaneous B-cell lymphomas.[1] Compared with BPDCN, diffuse large B-cell lymphoma usually occurs in an older age group and is of B-cell lineage. Morphologically, these neoplasms are composed of a monotonous, diffuse, nonepidermotropic infiltrate of confluent sheets of centroblasts and immunoblasts (Figure 1). They may share immunohistochemical markers of CD79a, multiple myeloma 1, Bcl-2, and Bcl-6; however, they lack plasmacytoid dendritic cell (PDC)–associated antigens such as CD4, CD56, CD123, and T-cell leukemia/lymphoma protein 1.[1]

Adult T-cell leukemia/lymphoma is a neoplasm histologically composed of highly pleomorphic medium- to large-sized T cells with an irregular multilobated nuclear contour, so-called flower cells, in the peripheral blood. The nuclear chromatin is coarse and clumped with prominent nucleoli. Blastlike cells with dispersed chromatin are present in variable proportions. Most patients present with widespread lymph node and peripheral blood involvement. Skin is involved in more than half of patients with an epidermal as well as dermal pattern of infiltration (mainly perivascular)(Figure 2). Adult T-cell leukemia/lymphoma is endemic in several regions of the world, and the distribution is closely linked to the prevalence of human T-cell lymphotropic virus type 1 in the population. This neoplasm is of T-cell lineage and may share CD4 but not PDC-associated antigens with BPDCN.[1]

Cutaneous involvement by T-cell lymphoblastic leukemia/lymphoma (T-LBL) is a rare occurrence with a frequency of approximately 4.3%.[8] T-cell lymphoblastic leukemia/lymphoma usually presents as multiple skin lesions throughout the body. Almost all cutaneous T-LBL cases are seen in association with bone marrow and/or mediastinal, lymph node, or extranodal involvement. Cutaneous T-LBLs present as a diffuse monomorphous infiltrate located in the entire dermis and subcutis without epidermotropism, composed of medium to large blasts with finely dispersed chromatin and relatively prominent nucleoli (Figure 3). Immunophenotyping studies show an immature T-cell immunophenotype, with expression of TdT (usually uniform), CD7, and cytoplasmic CD3 and an absence of PDC-associated antigens.[8]

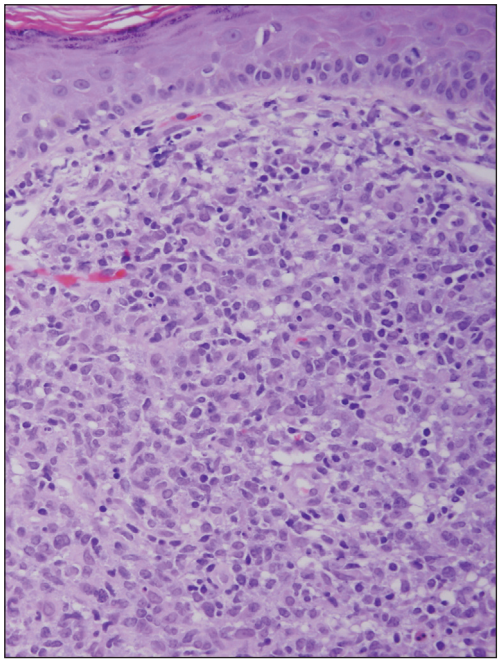

FIGURE 1. Diffuse large B-cell lymphoma, leg type. Monotonous, diffuse, nonepidermotropic infiltrate of confluent sheets of centroblasts and immunoblasts (H&E, original magnification ×400).

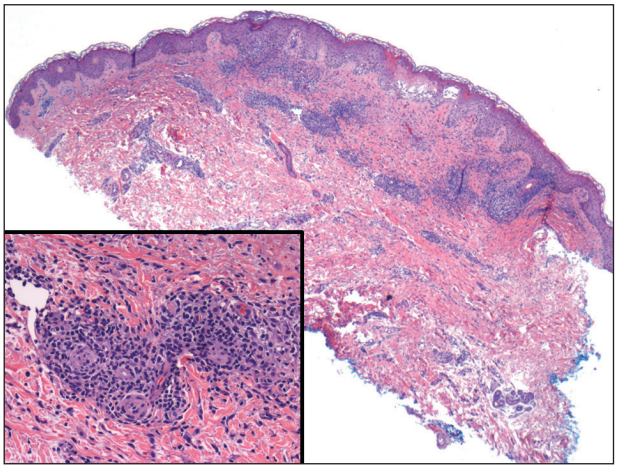

FIGURE 2. Adult T-cell leukemia/lymphoma. Epidermal as well as dermal pattern of skin involvement by highly pleomorphic medium- to large-sized lymphoid cells (H&E, original magnification ×50; inset ×200).

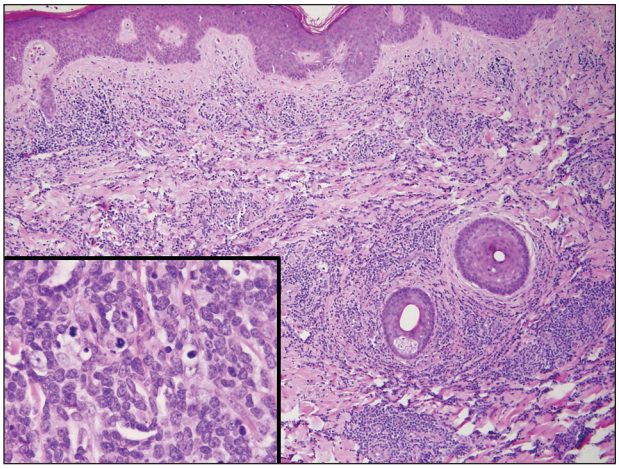

FIGURE 3. Cutaneous T-cell lymphoblastic leukemia/lymphoma. Diffuse monomorphous infiltrate located in the entire dermis and subcutis without epidermotropism composed of medium to large blasts with finely dispersed chromatin and relatively prominent nucleoli (H&E, original magnification ×200; inset ×400).

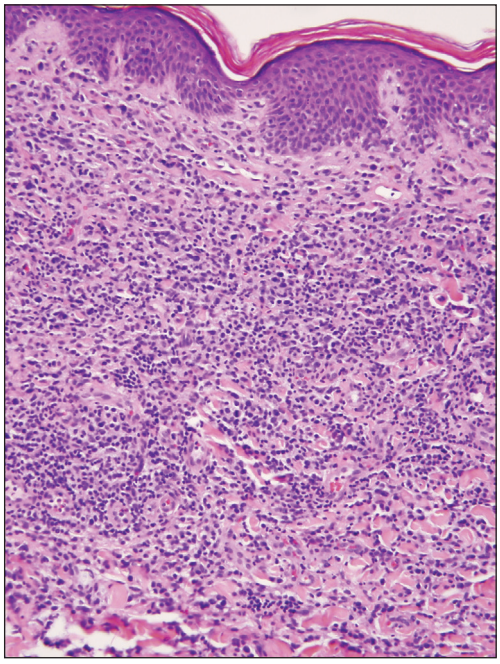

FIGURE 4. Cutaneous γδ T-cell lymphoma. Variable epidermotropism and dermal and subcutaneous involvement by medium to large cells with coarse clumped chromatin (H&E, original magnification ×200).

Primary cutaneous γδ T-cell lymphoma (PCGDTL) is a neoplasm primarily involving the skin. Often rapidly fatal, PCGDTL has a broad clinical spectrum that may include indolent variants—subcutaneous, epidermotropic, and dermal. Patients typically present with nodular lesions that progress to ulceration and necrosis. Early lesions can be confused with erythema nodosum, mycosis fungoides, or infection. Histologically, they show variable epidermotropism as well as dermal and subcutaneous involvement by medium to large cells with coarse clumped chromatin (Figure 4). Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. In contrast to BPCDN, the neoplastic lymphocytes in dermal and subcutaneous PCGDTL typically are positive for T-cell intracellular antigen-1 and granzyme B with loss of CD4.[9]

At the time of presentation, 27% to 87% of BPDCN patients will have bone marrow involvement, 22% to 28% will have blood involvement, and 6% to 41% will have lymph node involvement.[1-4,6,7,10,11] The clinical course is aggressive, with a median survival of 10.0 to 19.8 months, irrespective of the initial pattern of disease.[1] Most cases have shown initial response to multiagent chemotherapy, but relapses with subsequent resistance to drugs regularly have been observed. Age has an adverse impact of prognosis. Low TdT expression has been associated with shorter survival.[1] Approximately 10% to 20% of cases of BPDCN are associated with or develop into chronic myelogenous leukemia, myelodysplastic syndrome, or acute myeloid leukemia.[1,4] Pediatric patients have a greater 5-year overall survival rate than older patients, and overall survival worsens with increasing age. The extent of cutaneous involvement and presence of systemic involvement at initial presentation do not seem to be strong predictors of survival.[1,2,5-7,10-12] In a retrospective analysis of 90 patients, Julia et al[12] found that the type of skin disease did not predict survival. Specifically, the presence of nodular lesions and disseminated skin involvement were not adverse prognostic factors compared with macular lesions limited to 1 or 2 body areas.[12]

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