$CD4^+CD56^+$ Hematodermic Neoplasm and Plasmacytoid Dendritic Cell Tumor: Case Report and Review of the Literature

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$CD4^+CD56^+$ hematodermic neoplasm (HN) is a rare and aggressive neoplasm that has raised controversy regarding its etiology. $CD4^+CD56^+$ HN is thought to be derived from plasmacytoid dendritic cells (pDCs) and most commonly stains with CD4, CD56, CD123, and T-cell leukemia/lymphoma 1 (TCL1). Skin manifestations usually are the presenting signs and vary in appearance. Lymph node involvement also is common at the time of presentation, and the natural course of the disease is a progression to leukemia. Treatment of $CD4^+CD56^+$ HN focuses on multiple chemotherapeutic regimens but none have been proven to successfully impact overall survival.

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A $CD4^+CD56^+$ hematodermic neoplasm (HN) is an uncommon tumor that has received attention from the pathologic community due to an evolving understanding of the neoplasm's cell of origin. Because of the tendency for skin trophism to occur in $CD4^+CD56^+$ HN, the clinical dermatologist must be familiar with the condition's clinical presentation and course. We present a case of a patient with $CD4^+CD56^+$ HN and review the literature regarding the pathologic history, histologic and immunophenotypic features, clinical manifestations, and treatment of $CD4^+CD56^+$ HN.

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CASE REPORT

A 70-year-old woman presented with a rapidly growing, plaquelike mass on her scalp of 2 months' duration. On physical examination, nodular, erythematous, violaceous, ulcerative plaques involving the forehead, as well as the frontal, temporal, and parietal scalp, were noted (Figure 1). The remainder of the cutaneous examination was negative for tumor involvement. Diffuse bilateral cervical and supraclavicular lymphadenopathy and matting of the parotid glands bilaterally also was present. Abdominal examination revealed splenomegaly and hepatomegaly. Three punch biopsies were obtained and sent for analysis.

There was prominent superficial and deep dermal proliferation of highly atypical lymphoid cells (Figure 2A) that showed nuclear enlargement with prominence of nucleoli and mitotic activity (Figure 2B). Staining for CD20 and CD30 was negative. Staining for expression of

Figure not available online

Figure 1. Nodular, erythematous, violaceous, ulcerative plaques were noted at initial presentation involving the forehead, as well as the frontal, temporal, and parietal scalp.

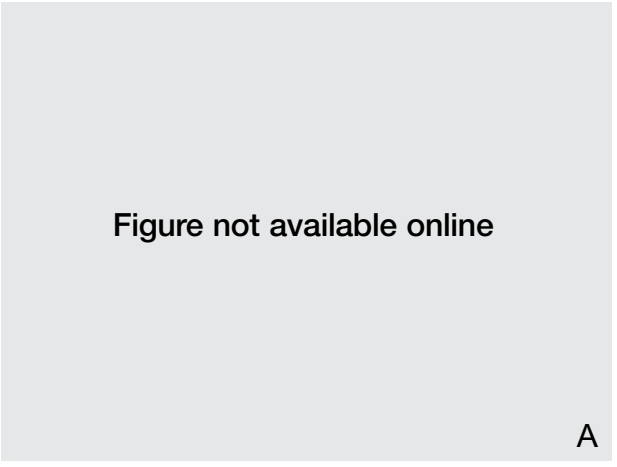

Figure 2. Prominent superficial and deep dermal proliferation of highly atypical lymphoid cells (H&E, original magnification ×200)(A). At higher magnification, the atypical lymphocytic cells demonstrated nuclear enlargement with prominence of nucleoli and mitotic activity (H&E, original magnification ×400)(B).

CD45RO marker was positive. A preliminary diagnosis of a high-grade aggressive T-cell lymphoma was made. Over the next 2 weeks, the neoplasm substantially spread to include cutaneous involvement of the lateral aspects of the face (Figure 3) and the trunk with diffuse plaque and nodular growths.

The patient was referred to hematology and oncology for further evaluation. Computed tomography of the chest and abdomen showed hepatosplenomegaly, extensive lymphadenopathy, and thickening of the bronchovascular structures consistent with a lymphoproliferative disorder. Computed tomography of the neck demonstrated extensive adenopathy with enlargement of the adenoidal tissue with the parotid glands. A blood smear test showed evidence of anemia, thrombocytopenia, and circulating neoplastic cells. Bone marrow biopsy revealed a blastlike

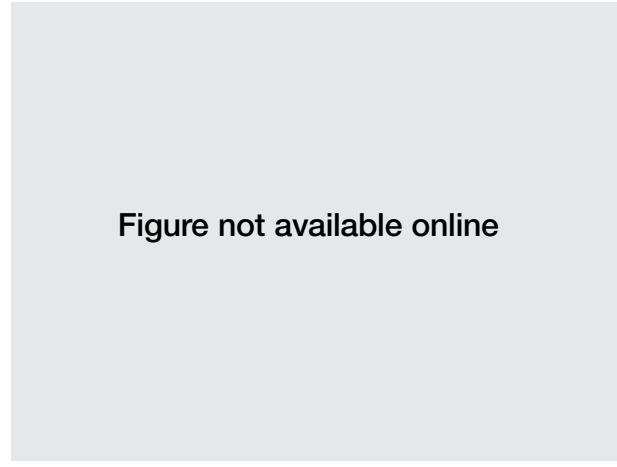

Figure 3. Extension of cutaneous involvement of the lateral aspects of the face 2 weeks following initial presentation.

aggressive neoplasm positive for CD2, CD4, CD33, and HLA-DR antigen. Flow cytometry immunophenotyping demonstrated positivity for CD56. She was subsequently diagnosed with a $CD4^+CD56^+$ HN. Systemic chemotherapy was suggested, but her family declined. She died a few weeks later, 22 days following her initial presentation to our clinic.

COMMENT

History

Several decades ago, when the application of CD cell markers was new and limited, there were numerous $CD4^+CD56^+$ pathologic entities that exhibited overlap and lacked distinction.[1] Initially, most $CD4^+CD56^+$ neoplasms were considered to be of T-cell origin because of their CD4 expression. Consequently, some cases were classified with plasmacytoid T-cell lymphomas.[2] However, as the erudition of CD cell markers expanded, a natural killer (NK) cell origin came into favor that was supported by the expression of CD56 and the lack of T cell and myeloid lineage antigens. The World Health Organization classified $CD4^+CD56^+$ neoplasms as blastic NK cell lymphoma in 1999.[3]

As the debate continued, advances were made to further distinguish $CD4^+CD56^+$ neoplasms and their cell of origin. A myelomonocytic precursor was thought to be plausible based on several shared characteristics between monocytes and $CD4^+CD56^+$ HN. Although CD4 is considered a T-cell marker, it also frequently is expressed by monocytes. In addition, CD56 is found on monocytic leukemia blast cells in approximately 20% to 40% of cases. Moreover, CD68, which also is a monocyte marker, is found in approximately 75% of $CD4^+CD56^+$ HN cases.[4-6]

A development to further support this theory was recognized when CD4+CD56+ tumors were found to express CD123, a cell marker that is relatively specific for plasmacytoid dendritic cells (pDCs).[7,8] In addition, CD4+CD56+ neoplasms also were shown to express T-cell leukemia/lymphoma 1 (TCL1), another cell marker for pDCs.[9] Consequently, the World Health Organization–European Organization for Research and Treatment of Cancer replaced the term *blastic NK cell lymphoma* with *CD4+CD56+ HN* and *early plasmacytoid dendritic cell leukemia/lymphoma*.[10]

Pathologic Features

Histogenesis—Plasmacytoid dendritic cells, which are now thought to be the progenitor cells of CD4+CD56+ HN, are generated by hematopoietic stem cells in the bone marrow and are an essential part of the immune system. They belong to the larger category of immune cells called dendritic cells (DCs); stain positively for CD4, CD123, and HLA-DR antigen; and do not stain for lineage-specific CD cell markers. Plasmacytoid dendritic cells also weakly express CD43 and CD68. CD4+CD56+ HN shares this immunophenotypic profile with pDCs.[9,11] In addition, a study performed on voluntary donors demonstrated that a small subset of pDCs also expressed CD56,[7] which Petrella et al[7,12] hypothesized may be the normal physiologic counterpart of CD4+CD56+ HN tumor cells. When exposed to IL-3 and CD40 ligand, pDCs can differentiate into DCs, a property also shared by CD4+CD56+ HN cells and demonstrated by Chaperot et al.[13] The immunophenotypic and functional similarities between pDCs and CD4+CD56+ HN support evidence of pDCs as the cell of origin. However, because both subsets of DCs have considerable plasticity, which means they can mature into different immune cells depending on the molecular environment and antigenic stimulus, the prospect of creating a definitive immunophenotypic classification of tumors derived from DCs may be fraught with challenging and unrealistic expectations.

Histology—The overall initial histologic picture of CD4+CD56+ HN typically is a diffuse monomorphic dermal infiltrate of medium-sized lymphoid cells. Epidermotropism is rare[1,14] and the cytoplasm is scant and agranular.[12] An inflammatory infiltrate may accompany the neoplastic process and typically consists of small T lymphocytes. Mitoses usually are seen. Plasma cells and eosinophils usually are not found.

There are different histologic patterns based on 2 types of clinical appearance. The clinical nodular pattern shows a dense large monomorphic infiltrate focused in the dermis.[12] Sparing of the epidermis often occurs with a grenz zone. Appendageal structures are eroded by tumor invasion, but the vasculature usually is spared. The clinical patch or ecchymotic lesions show a less dense infiltrate that tends to concentrate around blood vessels and/or form scattered nodules. Again, the epidermis is spared.[12]

Immunophenotype, Diagnostic Criteria, and Differential Diagnosis

The diagnosis of CD4+CD56+ HN predominantly relies on the immunophenotype of CD4 and CD56 positivity. CD4+CD56+ HNs are defined by the expression of CD4 and CD56 in the absence of lineage-specific markers for T cells, B cells, or myelomonocytic cells.[1,12] However, expression of CD4 or CD56 may be weak. In many cases, CD4+CD56+ HN will demonstrate coexpression of CD43, HLA-DR antigen, and a CD45RA marker.[1] In addition, skin lesions stain positive for the selectin ligand, also known as cutaneous lymphocyte antigen (CLA).[11] There also have been a few cases of CD4+CD56+ HN that expressed CD68 and CD3.[12]

The most recent progress in the diagnosis of CD4+CD56+ HN lies in immunomarkers specific to pDCs. CD123, the IL-3Rα chain, currently is the most significant and is found in more than 90% of CD4+CD56+ HNs. Identification of CD123 is achieved through paraffin sectioning with immunostaining or flow cytometry, which typically shows a uniform and strong pattern in CD4+CD56+ HN.[7,9]

T-cell leukemia/lymphoma 1 is another important CD cell marker that also is found in 90% of CD4+CD56+ HNs and helps to distinguish it from other tumors.[9,11] T-cell leukemia/lymphoma 1 is a lymphoid proto-oncogene and an Akt kinase regulator[15,16] in which nonneoplastic expression is limited to pDCs and B cells.[17,18] Some emerging useful pDC markers include blood DC antigens 2 and 4, which are present on a mature subset of CD4+CD56+ HN,[19] and terminal deoxynucleotidyl transferase, a lymphoblast marker that was found in up to 50% of CD4+CD56+ HNs and was likely to have prognostic significance. Marafioti et al[20] suggested that the use of the adaptor protein CD2AP (CD2-associated protein) and the transcription factor ICSBP/IRF8 (interferon consensus sequence binding protein/interferon regulatory factor 8) may be more specific for pDC neoplasms, particularly CD4+CD56+ HN.

CD4+CD56+ HN is diagnosed based on several factors, such as clinical presentation, morphologic features, and cytogenetic and molecular data. Morphologically, the differential diagnosis of CD4+CD56+ HN includes cutaneous T-cell lymphoma, nasal-type NK cell lymphoma, and

acute lymphoblastic leukemia or acute myeloblastic leukemia. Prototypic cases of CD4+CD56+ HN can be readily distinguished from these differential diagnoses based on positive staining for CD123 and TCL1. When some cases of CD4+CD56+ HN are less obvious, other distinguishing features between the different types of neoplasms can be used.

Overall, to diagnose CD4+CD56+ HN, staining for CD4, CD56, and CD123 should be positive and staining for CD3, CD20, myeloperoxidase, and lysozyme should be negative. Additional stains such as cutaneous lymphocyte antigen, CD45RA, CD43, and TCL1 also can be used to support the diagnosis of CD4+CD56+ HN when the staining is weak or exhibits an ambiguous pattern. Other markers, such as blood DC antigens 2 and 4, terminal deoxynucleotidyl transferase, and CD2AP require further investigation and consensus regarding their usefulness.

Genetic Features

Although recurrent, reciprocal, chromosomal translocations or inversions have not been found in CD4+CD56+ HN, Petrella et al[5] reported an increased frequency in the deletion of 5q as an isolated event or in concordance with other karyotypic abnormalities. Other dysfunctions have been detected in 13q, 12p, and 6q, and in some cases of CD4+CD56+ HN, there have been losses of chromosomes 15 and 9.[5,21-26] Clonality with T-cell receptor gene rearrangement is a feature that usually is not seen in CD4+CD56+ HN and has only been reported in a few cases.[27,28]

Clinical Features

Due to the rare nature of CD4+CD56+ HN and its evolving pathologic criteria, epidemiologic data are limited and may be somewhat skewed. The number of cases reported in the literature that meet the diagnostic criteria for CD4+CD56+ HN are estimated to be more than 100, with some reports estimated to be as many as 150 cases.[1,12]

According to Herling and Jones[1] who reviewed a total of 92 cases, CD4+CD56+ HN has a predilection for women over men with a ratio of 3 to 1; CD4+CD56+ HN also appears to be a disease that affects the elderly population. In a review of 30 cases from Petrella et al,[12] the median age of onset was 65.3 years. However, 30% of CD4+CD56+ HN cases involved patients younger than 50 years[1] and there have even been reports of pediatric cases of CD4+CD56+ HN.[29]

Clinical presentation of CD4+CD56+ HN varies, but skin lesions usually are the initial presenting sign; in approximately 50% of CD4+CD56+ HN cases, cutaneous lesions are the only extramedullary sign.[1] Skin manifestations of CD4+CD56+ HN differed but included nodules, plaques, patches, and ecchymotic lesions[12] with solitary or multifocal involvement.[1] Skin lesions may appear somewhat benign and exhibit erythema, purpura, hyperpigmentation, and ulceration.[1] Most CD4+CD56+ HNs are clinically thought to be lymphomas based on shared morphologic features. Skin involvement tends to worsen with time. There have been instances of CD4+CD56+ HN without cutaneous manifestations, as reported by Feuillard et al.[30] This finding contributes to the debate of whether CD4+CD56+ HN is a primary or secondary cutaneous tumor. Petrella et al[12] maintain that CD4+CD56+ HN may be a primary cutaneous tumor. All of the cases the authors reviewed had initial cutaneous involvement and demonstrated lymph node activity in the lymphatic basin that corresponded to the area of tumor involvement.[12]

Extracutaneous involvement is common at the initial evaluation. About one-half of patients present with affected lymph nodes. Involvement of the spleen and mucosal sites is uncommon at presentation. There have been rare reports of central nervous system involvement.[31] Fulminant leukemia at the time of presentation is rare, though up to 90% of patients present with low-level bone marrow and peripheral blood involvement.[1] Progression to leukemia seems inevitable and is part of the natural progression of the disease.

Treatment and Prognosis

Long-term prognosis for CD4+CD56+ HN is poor with an estimated time of survival of approximately 12 to 14 months. Although the initial disease pattern seems to have no prognostic significance, advancing age is a poor prognostic indicator.[1,13] Younger patients (<40 years) had a median survival of 38 months in comparison to older patients (>40 years) who had a median survival of 10 months.[13] In addition, long-term remission has been reported in younger patients who received acute leukemia–type induction therapy and an allogenic stem cell transplant.[12,29-33]

In general, treatment has focused on multiple systemic chemotherapeutic regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, an allogenic stem cell transplant, and radiotherapy. There have been isolated cases of complete clinical response in 2 patients, one treated with CHOP chemotherapy and the other with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) chemotherapy.[34] There was a promising case report of the use of pralatrexate for tumor reduction in a case of CD4+CD56+ HN, but its impact on overall survival is not

known.[35] Due to the poor prognosis and comorbidities of most patients, many treatment efforts focus on palliative treatment.

CONCLUSION

$CD4^+CD56^+$ HN exemplifies the use of CD cell markers in cutaneous oncology and the need for the clinical dermatologist to become more aware of this disease. As more research is done, $CD4^+CD56^+$ HN will continue to be defined. Currently, it appears that pDCs are the cell of origin, but several other issues surrounding $CD4^+CD56^+$ HN, such as its definition as a primary or secondary skin neoplasm, have yet to be resolved. Nevertheless, the highly aggressive and ultimately fatal course of $CD4^+CD56^+$ HN warrants early diagnosis and treatment to better serve patients affected by this devastating disease.

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