Cutaneous $CD4^+$ $CD56^+$ hematologic malignancies

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Background: Hematologic malignancies expressing CD4 and CD56 are most commonly associated with the recently described $CD4^+$ $CD56^+$ hematodermic neoplasm.

Methods: Thirteen cases of $CD4^+$ $CD56^+$ hematologic malignancies were prospectively encountered in the routine and referral practices of the authors.

Results: Patients 1 and 2 were elderly men exhibiting an acute onset of skin, bone-marrow, and peripheral blood involvement, both dying of their disease within less than 12 months. $CD3^+$ phenotype and a clonal T-cell receptor β rearrangement indicated categorization as a $CD4^+$ natural killer T-cell lymphoma. Patient 3 developed a $CD56^+$ anaplastic large cell lymphoma and is without disease after excision and radiation. Indolent $CD4^+$ $CD56^+$ poikilodermatous mycosis fungoides defined case 4. There were 7 patients with $CD123^+$ $CD4^+$ $CD56^+$ hematodermic neoplasm, 4 dying within 18 months of presentation with peripheral blood/marrow involvement in 6 of the 7 cases. Two patients with granulocytic sarcoma dying within 100 days of presentation defined the last two cases.

Limitations: There were relatively small numbers in each of the categories and the follow-up was limited in those cases where death was not reported.

Conclusion: Cutaneous malignancies composed of $CD4^+$ $CD56^+$ hematopoietic cells define a varied group and oftentimes have an aggressive clinical course although not in every case. (J Am Acad Dermatol 2010;63:292-308.)

Key words: cutaneous; hematologic; malignancy.

Natural killer (NK) and NK-like T-cell lymphomas are aggressive hematologic malignancies that frequently have an extranodal presentation. The main affected organ sites include the gastrointestinal tract, skin, and nasal cavities. These neoplasms have been broadly categorized as nasal versus nonnasal in type.[1-3] All of these neoplasms can present initially in the skin and/or involve the skin as part of a multiorgan disseminated lymphoma, developing concurrently and/or after presentation at other sites.

In both NK and NK-like T-cell lymphomas, the neoplastic cells express CD2 and CD56; true NK lymphomas are $CD4^-$ and $CD8^-$ (ie, null phenotype). NK-like T-cell lymphomas are characteristically of the null or CD8 phenotype.[1-3] The distinction of NK versus NK-like T-cell lymphoma is based on

Abbreviations used:

AML:	acute myelogenous leukemia
EBV:	Epstein-Barr virus
IL:	interleukin
MDS:	myelodysplastic syndrome
MF:	mycosis fungoides
MxA:	myxovirus protein
NK:	natural killer
TCL1:	T-cell leukemia 1 oncogene
TCR:	T-cell receptor
UV:	ultraviolet

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Funding sources: None.

Conflicts of interest: None declared.

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Published online June 11, 2010.
0190-9622/$36.00

doi:10.1016/j.jaad.2009.08.044

the T-cell receptor (TCR)β and/or gamma (γ) gene rearrangement and surface CD3 expression; those that lack these features are categorized as NK lymphomas; those that manifest surface CD3 expression and exhibit a TCR rearrangement are considered NK-like T-cell lymphomas.[1-3]

In the original classification scheme there was a distinctive NK neoplasm phenotypically different from the other reported NK and NK-like T-cell lymphomas, as it manifested CD4 positivity. This tumor fell under the designation of blastic NK-like T-cell lymphoma. In the revised World Health Organization-European Organization for Research and Treatment of Cancer classification, blastic NK-cell lymphoma was considered a clinically aggressive T-cell neoplasm with a high incidence of skin involvement and a significant risk of leukemic dissemination.[1-3] A blastic cytomorphology and expression of CD56 were held to be evidence of an NK-precursor cell origin. More recently, however, it has been established that the cell of origin is a plasmacytoid dendritic cell.[4-6] Consequently the term "blastic NK-like T-cell lymphoma" has been supplanted by the term "$CD4^+$ $CD56^+$ hematodermic neoplasm" (HD) and most recently "blastic plasmacytoid dendritic cell neoplasm."[4-6] In those neoplasms categorized as true NK lymphomas, there is a frequent association with Epstein-Barr virus (EBV), especially in Asian patients with nasopharyngeal involvement[7,8]; EBV has not been pathogenetically implicated in $CD4^+$ $CD56^+$. $CD4^+$ $CD56^+$ hematodermic neoplasms (HD) are aggressive tumors that typically lead to patient demise within 12 months of presentation.[4-6]

Although the dominant literature addressing $CD4^+$ $CD56^+$ malignancies is in the context of $CD4^+$ $CD56^+$ hematodermic neoplasm, there are other hematologic malignancies that may express this particular phenotypic profile. We present a spectrum of $CD4^+$ $CD56^+$ cutaneous malignancies comprising agranular $CD4^+$ $CD56^+$ T-cell lymphoma, classic cutaneous T-cell lymphoma, $CD4^+$ $CD56^+$ hematodermic neoplasm, and cutaneous granulocytic sarcoma.

CAPSULE SUMMARY

- $CD4^+$ $CDD56^+$ malignancies are most frequently observed in the context of the $CD4^+$ $CD56^+$ hematodermic neoplasm.
- Thirteen cases of cutaneous malignancies exhibiting this distinctive phenotypic profile were examined.
- $CD4^+$ $CD56^+$ malignancies are a heterogeneous group including the $CD4^+$ $CD56^+$ hematodermic neoplasm, granulocytic sarcoma, and conventional cutaneous T-cell lymphoma.
- Although the course can be aggressive, other common forms of cutaneous T-cell lymphoma with this phenotypic profile may be indolent. A broader array of immunohistochemical studies in concert with molecular studies enables correct categorization.

METHODS

All cases were encountered in the consultative and routine dermatopathology files at the Weill Medical College, New York Presbyterian Hospital. In all cases paraffin-embedded formalin-fixed tissue was available for routine light microscopy and immunohistochemistry. On all cases a comprehensive battery of phenotypic markers was conducted including CD2, CD3, CD4, CD8, CD62L, CD7 EBV-encoding small nonpolyadenylated RNA, CD56, granzyme, FoxP3, cutaneous lymphocyte antigen, CD123 myxovirus protein (MxA), CD83, CD123, and T-cell leukemia 1 oncogene (TCL1). The procedures for MxA, CD83, and TCL1 will be described in greater detail. The study received institutional review board approval in August 2007. One of the cases has been previously published.[9]

Immunophenotyping

Sections (5 μm) of formalin-fixed paraffin-embedded tissues were cut on to plus slides (Fisher Inc, Pittsburgh, PA). Routine deparaffinization from xylene to 95% alcohol and rehydration before patented microwave antigen recovery were carried out. The detection of the antigens was performed using a two-step immunohistochemistry procedure. After a 30-minute incubation with the primary antibodies, staining was performed using the commercially available Vision BioSystems Define Kit (Norwell, MA) adhering to the protocol. Incubation with the primary antibodies was conducted using the following dilutions: CD83 1:80 (Novocastra, part number NCL CD83, Bannockburn, IL), MxA 1:1600 (Dr Otto Haller, Freiburg, Germany), TCL1 1:50 (Cell Signalling, Danvers, MA).

$CD4^+$ $CD56^+$ MALIGNANCY ASSOCIATED WITH T-CELL CLONALITY (NK T-CELL LYMPHOMA, ANAPLASTIC LARGE CELL LYMPHOMA, AND MYCOSIS FUNGOIDES)

NK T-cell lymphoma (cases 1 and 2)

The two patients were both men, ages 62 and 76 years. One patient presented initially with a sudden onset of ulcerative skin tumors whereas the other