

**Society for Hematopathology  
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**“Unusual Types of Cutaneous T-cell, NK-cell, and Precursor Lymphomas and their Relationship to the Innate Immune System”**

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This lecture covers several rare types of lymphoma that present in skin, including T-cell lymphomas of gamma-delta origin, natural killer (NK) cell lymphomas and blastic tumors of putative plasmacytoid dendritic cell lineage. The histogenetic relationship of these tumors to the cell types of the innate immune system is emphasized.

**Historical Perspectives and Current Classification**

Table 1 summarizes the current EORTC/WHO classification of cutaneous T-cell and NK malignancies. The recognition and classification of the rarer types of cutaneous lymphomas (indicated, in bold) has been a slow process. Most were recognized as more clinically aggressive than mycosis fungoides (MF) before their exact lineage was delineated.<sup>1</sup>

**Table I. WHO-EORTC 2005 Classification of Cutaneous Lymphomas.<sup>2,3</sup>**

**Cutaneous T-cell and NK-cell lymphomas**

Mycosis fungoides

MF variants and subtypes

Folliculotropic MF

Pagetoid reticulosis

Granulomatous slack skin

Sézary syndrome

Adult T-cell leukemia/lymphoma

Primary cutaneous CD30<sup>+</sup> lymphoproliferative disorders

Primary cutaneous anaplastic large cell lymphoma

Lymphomatoid papulosis

**Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)**

**Extranodal NK/T-cell lymphoma, nasal type (NK/T-L)**

**Primary cutaneous peripheral T-cell lymphoma, unspecified**

**Primary cutaneous aggressive epidermotropic CD8<sup>+</sup> T-cell lymphoma (provisional)**

**Cutaneous gamma/delta T-cell lymphoma (provisional) (g/d TCL)**

**Primary cutaneous CD4<sup>+</sup> small/medium-sized pleomorphic T-cell lymphoma (provisional)**

**Precursor hematologic neoplasm (BT)**

**CD4<sup>+</sup>/CD56<sup>+</sup> hematodermic neoplasm (blastic NK-cell lymphoma)**

**Summary of helpful pathological and immunophenotypic features**

### ***Cutaneous gamma/delta T-cell lymphoma***

Cutaneous  $\gamma\delta$ TCL was often grouped in the past with SPTCL prior to its recognition as a highly aggressive tumor, with distinct pathological features.<sup>4</sup>

Clinical appearance of lesions: Multiple, rapidly appearing nodules on extremities, often up to 10 cm in size, frequently with fungation/ulceration.<sup>5</sup>

Pattern of infiltration: Early stage: Mid-dermal, periadnexal and perivascular. Later stage: Dense infiltrates centered in mid-dermis, with variable extension into epidermis and into subcutaneous tissue.<sup>5,6</sup>

Cytomorphology: Often deceptively small size, but with blastoid nuclear features.

Immunophenotype: See Table II. Absence of CD4, CD8 and TCR-beta expression can be used in paraffin-fixed material as putative evidence of gamma-delta origin, although transformed MF can also be negative for all 3 markers.<sup>6</sup> With subcutaneous infiltration,  $\gamma\delta$ TCL may show large numbers of admixed reactive lymphocytes and monodendritic cells.

Clinical behavior: Multiple cutaneous recurrences, with minimal spread outside skin until late in disease course. Hemophagocytic syndrome (HPS) seen in up to 75%.<sup>7</sup> Poor response to conventional chemotherapy, some are radiosensitive, transplantation may be an option.

Differential diagnosis: Dermatoses (early stage lesions), SPTCL and transformed MF.

### ***Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)***

The distinction of cutaneous  $\gamma\delta$ TCL from SPTCL has highlighted the indolent behavior of a subset of these tumors.<sup>7,8</sup>

Clinical appearance of lesions: Slowly spreading subcutaneous masses or non-specific-appearing rash that may wax and wane. May show association with connective tissue diseases.

Pattern of infiltration: Largely confined to subcutis, with rimming of fat, necrosis, karyorrhexis and lymphohistiophagocytosis.

Cytomorphology: Variable size, often prominent nuclear irregularities in a subset of tumor.

Immunophenotype: See Table II. Mixed infiltrates are common, but CD8 expression in tumor cells is usually apparent.<sup>9</sup> CD4+ tumors with otherwise typical SPTCL features are reported.

Clinical behavior: Local, expansile growth until time of transformation when extensive extracutaneous dissemination may occur.

Differential diagnosis: Panniculitis (focus on atypia and diffuse growth), systemic PTCL, NOS

### ***Extranodal NK/T-cell lymphoma, nasal type***

The boundaries of this entity are still being established, with both highly aggressive and more indolent variants seen. Whether EBV-negative cases should be separately classified is unclear.

Clinical appearance of lesions: Multiple, ulcerating nodules, may mimic MF plaques.

Pattern of infiltration: Dermis, often extending to subcutis.

Cytomorphology: Highly variable from small cells with minimal cytologic atypia to large cell morphology.<sup>10</sup>

Immunophenotype: See Table II. EBV+ positivity is most helpful since it is extremely rare in other cutaneous lymphomas.<sup>10</sup> Strong CD30 expression may be seen in transformed cases.<sup>11</sup>

Clinical behavior: Highly variable, some cases may be largely restricted to skin for years;<sup>12</sup> others may show frequent metastases to oropharynx, testes, GI tract, and lung.<sup>13</sup> A subset of tumors will overlap with aggressive NK-cell leukemia, with extensive marrow infiltration and rapidly fatal course.<sup>14</sup> Many tumors are radiosensitive.

Differential diagnosis: Cutaneous anaplastic large cell lymphoma and cutaneous presentations of peripheral T-cell lymphoma, especially CD8+ tumors expressing cytotoxic markers,<sup>15,16</sup> including aggressive epidermotropic CD8+ T-cell lymphoma.<sup>17</sup>

### ***CD4<sup>+</sup>/CD56<sup>+</sup> hematodermic blastic tumor (BT)***

This CD4+CD56+ agranular hematodermic neoplasm was classified provisionally as blastic NK lymphoma in the 2001 WHO scheme. Most recent evidence has suggested that it is related to plasmacytoid dendritic cells (DC2)<sup>18-20</sup> or to immature hematopoietic precursors with multilineage potential.<sup>21</sup> Cytogenetic changes are similar to acute leukemias.<sup>22</sup> This tumor is awaiting a definitive name due to uncertainties about its histogenesis.

Clinical appearance of lesions: Solitary nodules, to rapidly progressing tumors.

Pattern of infiltration: Dermis and subcutis, perivascular aggregates or single-file infiltration in early stages.

Cytomorphology: Medium-sized, with blastoid chromatin. Some cases have abundant cytoplasm. Nucleoli are variably prominent.

Immunophenotype: Positive for CD56, CD4 (can be weak) as well as CD43, CD45RA (4KB5), CD123 (IL3R-alpha) and TCL1.<sup>23</sup> The DC2 marker BDCA-2<sup>24</sup> is positive in subset, as is TdT.<sup>21,25</sup> Negative for CD3, CD20, and most T-cell markers.<sup>26</sup> Variable CD2, CD10, and CD33 expression seen.<sup>20</sup>

Clinical behavior: Highly aggressive, with marrow and peripheral blood dissemination within 12-18 months. A small number of indolent cases have now been described. Myeloid or myelomonocytic recurrences following chemotherapy are well-documented.<sup>21</sup>

Differential diagnosis: Myeloid leukemia (if MPO+), monocytic leukemia (if lysozyme or butyrate esterase+), lymphoblastic leukemia.

## Cutaneous immune surveillance and the innate immune system

The skin and mucous membranes are a major portal of entry for infectious organisms and have therefore developed a highly effective but non-specific immune surveillance program that complements the specific immunity provided by antibody-expressing B-cells and TCR- $\alpha/\beta$ -expressing helper and cytotoxic T-cells.<sup>27</sup>

This “innate” portion of the immune system, in contrast to adaptive acquired immunity, is focused on immediate (minutes to hours) detection and control of pathogens based on non-specific features. These immune targets include non-human glycolipids, glycoproteins and genomic material complexed with novel antigen presenting molecules.<sup>28</sup>

Key cellular players in the innate immune response are *dendritic cells* (particularly the DC2 subset which produces interferon-alpha), *NK cells* and *gamma-delta T-cells*.

Antigen receptors on  $\gamma\delta$  T-cells<sup>29</sup> and cognate receptors on NK cells<sup>30</sup> have relatively limited diversity consistent with their role in recognizing common microbial antigens. Dendritic cell maturation mediated by group of Toll-like receptors is also tuned to recognize broad antigenic patterns.<sup>31</sup> This generalized microbial recognition system is in contrast to the high level of specificity encoded by the TCR- $\alpha/\beta$ , which recognizes predominantly protein antigens with high affinity in the context of the highly polymorphic HLA class I and class II molecules.

## Differences between MF and cutaneous tumors of the innate immune system

Most of the cutaneous tumors discussed here have putative histogenetic origin from cell types of the innate immune system. The remarkable tropism of these tumors for adnexal structures and dermal vascular beds mimics the normal sites of innate immune surveillance.

The aggressive clinical behavior of these tumors may be partly related to their retained functional capacity to participate in uncontrolled cytokine-mediated innate responses. Such sequelae would include hemophagocytic syndromes, cytokine release syndromes and tissue necrosis/angiodestruction. The demonstrable immunophenotypic plasticity of the CD4+CD56+ BT may also be evidence of retained functional differentiation capacity.<sup>32,33</sup>

The majority of patients with mycosis fungoides have long precedent histories of chronic dermatitis, and their tumors develop out of oligoclonal phases in many cases. This suggests that MF (and perhaps lymphomatoid papulosis) can be regarded as T-cell “MALT”-like tumors, with specific antigens driving early stages of proliferation. Long-term control of early MF might thus be achieved by identifying and treating specific inciting agents.

In contrast, the factors driving expansions in the early stages of the innate-immunity group of cutaneous tumors is unknown but would likely be distinct. Given the highly dynamic nature of innate responses, immunotherapy may prove useful in treatment of these aggressive neoplasms.

**Table II. Immunophenotypic features of dermal and subcutaneous NK, T-cell and blastoid malignancies.**

	surface CD3	CD4	CD8	CD5	CD56	CD30	Cytotoxic proteins	EBV	TCR usage	TCR genes
<b>SPTCL</b>	+	-/+ (10%)	+	+	-/+ (20%)	-	+	rare	$\alpha\beta$	Rearranged
<b><math>\gamma\delta</math>-TCL</b>	+	-	-	-/+	+ (>90%)	-	+	-	$\gamma\delta$	R
<b>NK/T nasal</b>	-	-	-	-	+ (90%)	-/+ (15%)	+	+ (90%)	NKR	- /+ (20%)
<b>MFt</b>	+/-	+	-	+	-/+ (5%)	-/+ (35%)	+/- (50%)	-	$\alpha\beta >> \gamma\delta$	R
<b>ALCL</b>	-/+ (30%)	+/-	-	+/-	-/+ (10%)	++	+	-	- (50%)	R
<b>BT</b>	-	+	-	-	+	-	-	-	-	- /+ (10%, pre-TCR)

Marker expression frequencies are those seen in archival tumors from M. D. Anderson Cancer Center, and will vary widely in different geographical areas due to differences in EBV infection patterns and other etiologic causes.<sup>33-35</sup>



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