Cutaneous nonmycotic T- and natural killer/T-cell lymphomas: Diagnostic challenges and dilemmas

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Mycosis fungoides is the prototype of primary cutaneous T-cell lymphoma and is more common in the West than in the East, whereas nonmycotic primary cutaneous T-cell lymphoma is more frequent than mycosis fungoides among Asians. Nonmycotic primary cutaneous T-cell lymphomas comprise several categories of neoplasms and might pose diagnostic challenges because of the rarity of these lesions and overlapping features among certain entities. The authors recommend diagnostic approaches including histopathological evaluation, immunohistochemical markers, and ancillary studies. Diagnostic dilemma in certain entities and cases with atypical clinicopathological features are discussed. (J Am Acad Dermatol 2014;70:724-35.)

Key words: $CD30^+$ lymphoproliferative disorder; cutaneous T-cell lymphoma; extranodal natural killer/T-cell lymphoma, nasal type; hydroa vacciniforme–like lymphoma; peripheral T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma.

T-cell lymphomas (TCLs) involve the skin either as primary lesions or secondary manifestations of systemic diseases. Mycosis fungoides (MF) is the prototype of primary cutaneous TCL (CTCL) and accounts for nearly half of the CTCL cases in the West.[1] MF is more common in the West than in the East, whereas nonmycotic CTCL is more frequent among Asians.[2-6] The prognosis of nonmycotic CTCL is generally poorer than MF. Table I summarizes the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification of cutaneous nonmycotic T- and natural killer (NK)/T-cell neoplasms.[1,7,8] These tumors often pose significant diagnostic challenges to (dermato)pathologists. The authors discuss the diagnostic approaches and the overlapping features between certain entities.

GENERAL DIAGNOSTIC APPROACH

Growth patterns and levels of involvement

The levels/sites of involvement by cutaneous T- and NK/T-cell lymphoproliferative disorders (LPDs) may be broadly separated into predominantly epidermal, dermal, or subcutaneous involvement, and might have various combinations in certain tumor types. Patch lesions of MF show superficial bandlike lesions involving basal epidermis with expanded papillary dermis. Plaque and tumor stage always involve the dermis and the tumor stage lesions may involve the subcutis. Under low-power examination, nonmycotic lesions essentially present as a diffuse pattern with a possible exception of a vaguely nodular pattern in primary cutaneous $CD4^+$ small/medium pleomorphic TCL (CD4TCL).[9,10] Morphologically, the atypical lymphocytes may range from small, medium, to large and anaplastic with Reed-Sternberg–like cells. The location and depth of lymphomatous infiltration may offer initial clues to differential diagnosis. In lymphomatoid papulosis (LyP), the benign end of primary cutaneous $CD30^+$ T-LPD, the lesion is predominantly, if not exclusively, dermal. However, in primary cutaneous anaplastic large-cell lymphoma (PC-ALCL), the tumor cells show extensive dermal infiltration and the deeper part usually extends into the subcutaneous fat. Primary cutaneous $CD8^+$

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aggressive epidermotropic cytotoxic TCL (CD8TCL) is also predominantly epidermal with some dermal involvement. The major entities of T-cell and NK/TCL with subcutaneous involvement and features of panniculitis include subcutaneous panniculitis-like TCL (SPTCL), $\gamma\delta$ TCL, and extranodal NK/TCL (ENKTL), nasal type.[11] For differential diagnosis among these entities, the most useful markers are CD4, CD8, CD56, βF1, T-cell receptor (TCR)γ, and/or TCRδ, and in situ hybridization for Epstein-Barr virus (EBV)-encoded messenger RNA (EBER). According to the current WHO classification, SPTCL is a neoplasm of $\alpha\beta$ T-cell origin, whereas cases with a $\gamma\delta$ phenotype are now classified as $\gamma\delta$ TCL. In SPTCL and CD4TCL, the epidermis is spared in the great majority of cases.

CAPSULE SUMMARY

- Nonmycotic primary cutaneous T-cell lymphomas are rare, diagnostically challenging, and more common in Asia.
- We propose a practical diagnostic algorithm for these rare tumors.
- Rare examples with overlapping features or atypical clinical and/or pathological findings are emerging and they may lead to a more precise definition of these rare tumors in the future.

Immunohistochemistry

Table II summarizes the pertinent clinicopathological features of these nonmycotic tumors and the diagnostic algorithm depicted in Fig 1. The immunohistochemical panel recommended as initial screening includes CD3, CD20, CD30, and Ki67 with CD21 as optional only if a follicular/nodular pattern is observed/suspected. The rationale of including CD30 in the initial screening panel is that CD30$^+$ T-LPD is commonly CD3$^-$. This screening panel may be different in geographic regions. In Asia where ENKTL is more prevalent, EBER should be added, whereas it is not recommended at initial screening in the West. When a T-lineage tumor is confirmed, a subsequent panel including CD4, CD8, and CD56 is mandatory for further stratification. In cases of small lymphocytes with minimal cellular atypia, aberrant T-cell antigen expression might be needed for establishing the neoplastic nature, and immunostaining for CD2, CD5, and CD7 is recommended.[12-14] However, it is important to note that loss of CD7 is relatively common in reactive conditions, therefore CD7 loss alone is not helpful in making a diagnosis of TCL.[15,16] Of particular note is that although CD20 is the most commonly used B-cell marker, it is aberrantly expressed in very rare examples of T-cell and NK/TCL.[17,18] Additional markers such as CD25 and cytotoxic molecules (CMs) might be needed for differential diagnoses. In human T-cell lymphotropic virus (HTLV)-I-endemic areas, serum assay for anti-HTLV is mandatory to rule out adult T-cell leukemia/lymphoma (ATLL) with cutaneous involvement. Even in some nonendemic countries such as Taiwan where sporadic ATLL cases have been reported, this serum assay is recommended as ATLL might present with atypical morphologic and/or clinicopathological features.[19,20] For T-lineage tumors, $\alpha\beta$ versus $\gamma\delta$ T-cell origin could be determined by immunostaining with βF1 and TCRγ, respectively (Fig 2).[21,22]

Molecular assays

EBER and clonality study for TCR gene rearrangement are the most common molecular techniques used. Molecular diagnostic methods for nonmycotic cutaneous lesions have been reviewed elsewhere.[23]

Primary cutaneous CD30$^+$ T-LPD

CD30$^+$ T-LPDs include LyP, PC-ALCL, and borderline lesions.[1,24-26] These diseases form a continuous spectrum with LyP at the benign end characterized by multiple recurrent, often centrally necrotic, self-healing, papulonodular skin eruptions smaller than 2 cm in diameter. On the other end, PC-ALCLs present as solitary or multiple skin nodules larger than 2 cm, often with ulceration but without the waxing and waning feature of LyP.[26] CD30$^+$ T-LPDs should be restricted to those without extracutaneous manifestation for at least 6 months to exclude secondary cutaneous involvement by systemic lymphomas.[26]

Lymphomatoid papulosis

Three histologic subtypes (A, B, and C) of LyP have been described and they represent a continuum with overlapping features.[24-28] In type-A (conventional or histiocytoid) lesions, scattered or small clusters of CD30$^+$ large Reed-Sternberg–like giant cells are admixed with numerous inflammatory cells (Fig 3). Type-B (MF-like) lesions are uncommon (<10% of cases), and are characterized by epidermotropic infiltration of small atypical CD30$^-$ cells with cerebriform nuclei similar to MF. This is probably the only subtype of primary cutaneous CD30$^+$ T-LPD with a significant epidermotropism. Type-C (anaplastic large-cell lymphoma [ALCL]-like) lesions comprise monotonous or large sheets of CD30$^+$ large cells with relatively few inflammatory cells. Very rare cases of LyP may express CD56,