The Pathology of Cutaneous T-Cell Lymphoma

The diagnosis of cutaneous T-cell lymphoma (CTCL) requires accurate histopathology, including immunocytochemistry, as well as careful clinical appraisal and analysis for T-cell clonality. This paper reviews the key histologic features of mycosis fungoides (MF) and its variants, and of lymphomatoid papulosis (LyP). Mycosis fungoides is an epidermotropic CTCL that evolves through distinct disease stages of patch, plaque, and tumor, often leading to transformation in the final stages. Disease staging is made clinically, and diagnosis may be difficult during the early stages because several common dermatologic conditions share features with MF. Therefore, clinical appraisal plus the presence of characteristic histopathologic features are needed to ensure accurate diagnosis. Clinical information is particularly important in the diagnosis of LyP, as the disease appears malignant histologically, but has a benign clinical course. Several other T-cell lymphomas were defined in a recent classification of these cutaneous lymphomas, and some key features of these disorders are also briefly reviewed.

There is a tendency in medicine for practitioners to consider histopathologic evidence as definitive. However, in cutaneous T-cell lymphoma (CTCL), successful diagnosis requires not only accurate histopathology, including immunocytochemistry, but also good clinical appraisal and analysis for T-cell clonality. Without due attention to each of these three parameters, there is a real danger of misdiagnosis and, therefore, inappropriate treatment of patients. This brief review will outline the principal histologic features of mycosis fungoides (MF), the most common CTCL, and lymphomatoid papulosis (LyP), with a few select comments on some lesser known T-cell lymphomas on which data are beginning to emerge.

Classification of T-Cell Lymphomas
In 2005, an updated World Health Organization/European Organisation for Research and Treatment of Cancer classification of cutaneous lymphomas was published, which aimed to resolve some of the shortcomings of earlier classifications (Table 1).[1] Mycosis fungoides is the most common of the T-cell lymphomas, and folliculotropic MF (formerly follicular mucinosis), pagetoid reticulosis (the solitary form-Woringer-Kolopp), and granulomatous slack skin (GSS) are regarded as variants of MF. Sézary syndrome and adult T-cell leukemia/lymphoma are also included in this classification, but will not be discussed further in this review.
There is then the umbrella term primary cutaneous CD30+ lymphoproliferative disorders, which includes primary cutaneous anaplastic large-cell lymphoma (ALCL) and LyP. The classification also includes subcutaneous panniculitis-like T-cell lymphoma (SPTCL), for which there has been emerging evidence that the αβ variant has a better prognosis and is distinct from the γδ form. The latter is now included within the provisional category of cutaneous γδT-cell lymphoma, whereas SPTCL is
reserved for the αβ variant. Three provisional groups are included in the updated classification: primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (Berti's lymphoma), cutaneous γδT-cell lymphoma, and primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma. The provisional status of these entities reflects the paucity of data on their clinical, pathologic and prognostic importance.

There remains a heterogeneous group of T-cell lymphomas that do not fit into any of the previous categories; for these, the term "peripheral T-cell lymphoma, unspecified," is reserved.

Mycosis Fungoides
Mycosis fungoides, which accounts for almost 50% of all primary cutaneous lymphomas, is an epidermotropic CTCL that is characterized by a proliferation of small- to medium-sized T lymphocytes with cerebriform nuclei.[1] The disease evolves through well-defined stages of patch, plaque, and tumor, often culminating in "transformation" in the final stages of the disease. Staging is a clinical judgement and should not be guessed histopathologically, although undoubtedly the histopathology does broadly reflect the disease stage.

Patch Mycosis Fungoides
Patch MF is difficult to diagnose because it has several differential diagnoses, most of which are more common, and the histopathologic differences are subtle. The differential diagnoses may include spongiotic dermatitis (most commonly eczema), lichenoid dermatitis, chronic superficial scaly dermatitis and pigmented purpuric dermatoses. Moreover, pigmented purpuric dermatosis can evolve into MF over some years, and longitudinal biopsy data have demonstrated the same clones in biopsies of the pigmented purpuric dermatosis and subsequent MF; thus, there is an uncertain relationship between these two conditions. Another differential diagnosis is that of isolated regressing lesions, which can mimic MF. This is not usually significant in practice, however, as the presence of only a single lesion seldom favors a diagnosis of MF.

Useful diagnostic features for MF include the following: the perinuclear halo, which is a clear space around the nuclei of lymphocytes and, while not absolutely pathognomonic, is a useful characteristic feature of early MF; Indian filing, or lining up of lymphocytes, in the basal epidermal layer; and a relative lack of spongiosis for the amount of infiltrate present. In lichenoid examples of MF, the lymphocytes produce little or no basal epidermal damage but appear simply to colonize the epidermis. This is in contrast to autoimmune lichenoid dermatoses, in which there is destruction of the stratum basalis and often colloid body formation. In addition, in the early stages of disease the lymphocytes are generally not very atypical; cytologic pleomorphism develops pari passu disease progression. Pautrier's microabscesses may be seen in patch MF, but are a more characteristic feature of plaque-stage disease.

Plaque Mycosis Fungoides
Essentially, this stage of MF tends to display the epidermal features of patch-stage disease, but simply in more florid form. Pautrier's microabscesses are, however, more numerous; these denote the presence of collections of neoplastic lymphocytes within a nonspongiotic epidermis. The dermal infiltrate is also more pronounced, and cytologic atypia of the lymphocytes more readily appreciated.

Tumor Mycosis Fungoides
In tumor MF, the epidermal component of the earlier disease stages is lost. Most of the disease is centered in the dermis, although there is often some residual epidermal disease. This stage is characterized by a large population of lymphocytes, usually markedly atypical, in the dermis. A diagnosis of tumor MF requires clinical evidence of patch- and plaque-stage disease, otherwise a different type of lymphoma is most likely. Although there are reports in the literature of MF tumor d'emblée, or de novo onset of tumor-stage MF, many of these cases were described before the availability of immunocytochemistry so they may well represent unidentified CD30+ anaplastic lymphoma. If MF tumor d'emblée occurs at all, it is exceptionally rare.

Transformed Mycosis Fungoides
In transformed MF, the infiltrating cells appear very high grade cytologically, are atypical, and constitute at least 25% of the population in cohesive expansile clusters. Formerly the diagnosis required that these cells express the CD30 surface antigen, but it is now predicated on high-grade cytology alone. The differential diagnosis at this stage includes other lymphomas, LyP (which may show some similar histologic features), and some infections such as herpesvirus, which can give a very florid inflammatory response with atypia. As ever, good clinical appraisal is required for diagnostic accuracy.

Immunophenotype of Mycosis Fungoides
In the early stages of MF, immunophenotyping does not usually show features that differentiate the disease from eczema or other non-neoplastic infiltrates. At this point in the disease, the infiltrating anti-CD30
lymphocytes in the epidermis represent "well-differentiated" T-cell lymphoma and usually express the normal complement of T-cell antigens. As the disease progresses, some of these, in particular CD7, may be lost. Although the T cells in MF are far more commonly CD4+ than CD8+ (T-helper rather than T-suppressor/cytotoxic cell types), this is also the case in most inflammatory dermatoses, and therefore CD4+ dominance alone does not differentiate between neoplasia and "reactive" infiltrates. In tumor MF, there may be expression of cytotoxic granules and, with high-grade transformation, expression of CD30 protein. Tumor cells are never anaplastic lymphoma kinase-1 (ALK-1)-positive. There are rare cases of abnormal immunophenotypes (eg, CD8+). In such instances, a reliable clinical diagnosis is not ruled out by an unusual immunophenotype.

Variants of Mycosis Fungoides
Folliculotropic Mycosis Fungoides
A characteristic feature of folliculotropic MF is the presence of mucin accumulation in hair follicles (follicular mucinosis), although this is not pathognomonic for this condition. Furthermore, MF that involves the hair follicles is not necessarily associated with mucin accumulation. The condition generally involves the head or neck, and there may be conventional MF in other parts of the body. As in classical MF, in the early stages atypia is not marked. This disorder has implications for skin-directed treatment; the extension of neoplasia into the hair follicles means that there is deeper penetration into the tissues, so skin-directed therapy may not be as effective as in conventional MF.

Pagetoid Reticulosis
In pagetoid reticulosis there is localized disease in the form of a solitary lesion, which histologically is characterized by striking, if not exclusive, epidermotropism. Examples of the disseminated form of pagetoid reticulosis—so-called Ketron-Goodman disease—are likely to represent either Berti's lymphoma or cutaneous γδT-cell lymphoma. It is therefore unclear whether disseminated pagetoid reticulosis exists. There is some evidence that pagetoid reticulosis is more likely to display a CD8+ than CD4+ immunophenotype.

Granulomatous Slack Skin
Patients with GSS have pendulous skin folds, particularly in flexural areas. These folds correspond to the pathologic process in which elastic tissue in the skin is engulfed by elastocytic granulomas with multinucleated giant cells; between these are the atypical neoplastic T cells. The current inclusion of GSS as a variant of MF reflects the recognition that there is an overlap between MF and GSS-patients with MF may have features of GSS and those with GSS can develop more obvious MF over time. In addition, patients with classical MF may have interstitial granulomas and atypical lymphocytes without the clinical features of GSS, a feature of no prognostic import.

Lymphomatoid Papulosis
Lymphomatoid papulosis falls under the umbrella of primary cutaneous CD30+ lymphoproliferative disorders. It appears malignant histologically, but is benign clinically. Clinical information is essential to make the diagnosis. Histologically, the disorder has three subclassifications: in type A, there are many Reed-Sternberg cells—large cells with prominent nucleoli, which are immunopositive for CD30. In type B, the cells are similar to those found in MF (cerebriform atypical lymphocytes) and are often CD30-. Type C, of uncertain nosologic status, is characterized by sheets of very atypical cells indistinguishable from ALCL histologically and which are CD30+; clinically, however, these lesions wax and wane, thereby following the natural course of LyP. Histologically, LyP often shows ulceration, which mimics the clinical scenario of papules or nodules growing, ulcerating, and regressing. As with MF, LyP is primarily a CD4+ disease, though CD8+ examples do occur. The large atypical CD30+ cells are always ALK-1-. Clonality is detected in about 50% of cases.

The main differential diagnoses of LyP are lymphoma, including the exceptionally rare cutaneous Hodgkin's disease (in type A lesions), MF, and pityriasis lichenoides—an inflammatory dermatosis (in type B lesions). Histopathologically, some lesions from LyP are very similar to those in pityriasis lichenoides. However, pityriasis lichenoides is characteristically a CD8+ T-cell lymphoproliferation, whereas LyP is CD4+. The differential diagnosis from ALCL is difficult because in type C lesions the histologic appearance is similar, and in both conditions there may be regression. Clinical information is needed to make the diagnosis.

The Significance of CD30 Expression
CD30 Antigen
Expression of the CD30 antigen is seen in a variety of lymphomas: primary cutaneous ALCL, systemic (lymph node origin) ALCL that involves the skin, transformed MF, and LyP. CD30+ T cells are also seen in inflammatory dermatoses and a variety of other inflammatory conditions, including herpesvirus infection. Thus, while it is important in several diagnoses, the significance of CD30
expression is highly dependent on the particular diagnosis in question.

Cutaneous Aggressive Epidermotropic CD8+ CTCL (Berti's Lymphoma)

Cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma constitutes a provisional category in the recently revised classification. It is an aggressive lymphoma that presents as papules/nodules, ulceration, and necrosis de novo, without a long history of patches or plaques. Lesions are often hemorrhagic. It is likely that some cases of the Ketron-Goodman type of pagetoid reticulosis represent examples of this lymphoma. There is a characteristic histopathology with striking epidermotropism of large atypical cells, which immunocytochemically express CD8+ and CD45 RA+.

Cutaneous γδ+ T-Cell Lymphoma

Cutaneous γδ+ T-cell lymphoma also represents a provisional category in the recent joint classification. It is aggressive, presenting as disseminated plaques, ulceronecrotic nodules, and tumors, and appears without a history of patches or plaques. There is often marked epidermotropism but subcutaneous involvement is not uncommon. Indeed, examples of subcutaneous T-cell lymphoma of the γδ+ class are now included within this category rather than alongside the subcutaneous T-cell lymphoma αβ variant (vide infra).

Subcutaneous Panniculitis-Like T-Cell Lymphoma

In SPTCL patients present with multiple subcutaneous nodules, usually in the extremities or trunk, together with often rather nonspecific features of weight loss and malaise. It is proposed that this category be restricted to αβ variants of subcutaneous lymphoma. This distinction is based on the increasing notion that the αβ and γδ subtypes are different diseases, and portend quite different prognoses; the αβ form of the disease appears relatively indolent in comparison with the γδ form. Furthermore, the αβ lymphoma is usually restricted to the subcutis, while γδ cases often show epidermal or dermal involvement histologically.

Initially, the fat involvement is mainly lobular with fat necrosis, and karyorrhexis with nuclear debris; however, as the disease progresses the septae often become involved too. The cells vary from small lymphocyte-like cells to large, very atypical blast cells. A characteristic feature of the disease is rimming of adipocytes—the lining of atypical cells around the periphery of adipocytes. With immunocytochemistry, the neoplastic cells are usually CD8+ and express cytotoxic granules. In the γδ form of the disease, the cells are more likely to be CD4-, CD8-, and CD56+.

Conclusions

Cutaneous T-cell lymphoma is not a single disease but a group of very different conditions. An accurate diagnosis is of paramount importance not only to distinguish between neoplastic and inflammatory processes, but also to determine the precise type of lymphoma. These judgements require careful attention to the clinical presentation, critical histopathologic/immunocytochemical appraisal, and use of molecular data.

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References:

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