Maximizing the clinical utility of descriptive lymphoid pathology reporting

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Abstract

Dermatopathology reporting can be both exact and inexact. Exact reporting represents the use of terminology that corresponds to a disease sui generis, such as discoid lupus erythematosus or disseminated superficial porokeratosis. Inexact reporting can vary greatly amongst various practitioners—both in terms of the exact semantics used and also stylistically—and can be used habitually by pathologists as a means to provide cover for diagnostic uncertainty or inexperience. This article explores the use of descriptive (inexact) reporting as it applies to cutaneous lymphoma and its differential diagnosis. A collection of practical descriptive diagnostic categories that will be of use to both dermatologists and dermatopathologists is included.

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In routine practice, the experienced clinician is accustomed to receiving pathology reports that include a provisional or nonexact diagnosis—or what can be referred to as a descriptive diagnosis—that refers to or describes a particular scenario or situation, at which point the dermatopathologist perceives herself/himself to be stuck and unable to render a fully exact or unequivocal diagnosis. By convention, a descriptive diagnosis should be accompanied by a differential diagnosis, which spells out what potential options the diagnostic menu might include. Simple and common examples of descriptive diagnoses from daily practice include a category such as lichenoid dermatitis—a broad diagnostic spectrum that includes narrow and exact disease types such as lichen planus, pityriasis lichenoides, or lupus erythematosus—as well as contrived but commonly utilized designations such as “atypical basaloid proliferation” (often applied in the situation of possible basal cell carcinoma) or “proliferation of atypical melanocytes” (applied similarly in the context of “is it melanoma or not?”). It is important for the clinician to realize that the language utilized in descriptive histopathologic diagnoses is invented and generally should not be taken as alluding to a specific narrow diagnostic entity, even though there may be linguistic similarities between a descriptive diagnosis and an exact diagnosis. If a descriptive microscopic diagnosis has been forwarded in the absence of a differential diagnosis, it is generally an indication of suboptimal or incomplete reporting, meaning that the diagnosis has been rendered in an inexact fashion without indicating what specific diagnostic possibilities remain in play. (As an aside, if a clinician is not routinely receiving a differential diagnosis in this context, then one should be requested from the pathologist.)

Arriving at a narrow clinicopathologic diagnosis constitutes a tight partnership between the clinician and the dermatopathologist, even if the two practitioners never interact interpersonally and simply communicate through requisition forms, pathology reports, phone or secure email messages, and/or shared clinical photographs. Of late, with prevalent usage of an advanced electronic health record (EHR) by most practitioners, a great deal of communication can be automated and digital in nature. Both the clinical office and the pathology laboratory need to recognize the importance of holding up their end of this communication relationship. On one side of the coin, the clinical team should optimally be providing (1) a description of the clinical morphology, distribution, clinical pictures, or all; (2) provisional thoughts regarding what narrow diagnosis seems likely or what needs to be excluded or both; and (3) any ancillary information (review of systems data, laboratory results, relevant history, or old pathology reports) that might be germane to the interpretation of the current histopathologic findings. Many EHR systems autofill a morphologic description and also autofill some of the potential considerations in the differential diagnosis, and the clinical team should exert care to be certain that “neoplasm of uncertain behavior” or “dermatitis unspecified” does not constitute the entirety of what is passed through to the interpreting dermatopathologist. If the full clinical setting is not conveyed, the descriptive histopathologic diagnosis received in return may have simply been triggered by the lack of clear clinical data. For example, because the clinical morphology associated with mycosis fungoides (MF) is diverse, rendering an unequivocal diagnosis in the absence of precise knowledge of the exact clinical circumstances can be irresponsible, as discovering that the clinical situation was incompatible might subsequently undermine the interpretation.

On the other side of the coin, the laboratory team should be receiving and archiving the clinical description, differential diagnostic impression, clinical pictures, and ancillary data and responding with a lucid, in-depth interpretation that integrates the clinical, histopathologic, and ancillary findings. If information is missing, timely attempts to retrieve key information are appropriate. If an exact diagnosis remains impossible based upon available information or based upon the limitations of the available tissue, then providing a descriptive diagnosis represents a necessary component of medical practice. The optimal descriptive diagnosis will include commentary that explains exactly what is missing—whether there is too little tissue, poorly preserved or artifactualy distorted tissue, inconclusive special stains, and/or nonrepresentative findings—to provide the clinician with a clear understanding as to why the di-
agnosis has been kept inexact. Additionally, a thoughtful differential diagnosis should be incorporated. In the clinical analysis of descriptive diagnoses from the dermatopathology laboratory, it is always appropriate to consider why the diagnosis was kept provisional. As has been partially alluded to above, some key possibilities include incompletely supplied data regarding the medical history or the clinical morphology, inadequate tissue because of inherent limitations or artefactual distortion, or a limitation in the diagnostic acumen and experience of the interpreting dermatopathologist. In the context of the latter situation, obtaining a second opinion regarding the histopathologic findings should be strongly considered.

A scenario worth watching for—by both dermatopathologists and clinicians—is the setting in which a descriptive diagnosis has been issued, yet only one differential diagnostic possibility remains under serious consideration. This can happen when the clinical findings seem compelling while the histopathologic findings are less convincing, and it can also occur when the histopathology seems persuasive while the clinical context seems odd or atypical. It is important that the use of descriptive diagnostic language—or what in some sense might also be termed “downgrading” the diagnosis—be habitual, as persistently understating the diagnosis can interfere with or delay appropriate clinical care. In this setting, pursuing a second opinion should be strongly considered.

Creating descriptive diagnoses with relevance
Dermatopathologists should aim to offer (and the clinical team should negotiate with their microscope-based colleagues to be certain they are receiving) descriptive diagnoses that hold the greatest possible bearing so that dermatologists can respond to a pathology report in a practical way in patient evaluation and management. The oft-used designation “atypical lymphocytic infiltrate” is far too vague and broad to provide any keen or clear insight to the clinician regarding what the underlying diagnosis might be. In terms of providing histopathologic categorization that correlates to various clinical realities, as a starting point it is of value for both the clinician and histopathologist to consider whether the process under evaluation is of B-cell or T-cell lineage, even though many biopsies contain mixed populations of both cell types, and thus a perfect discrimination cannot be made on any given specimen.

Within the spectrum of B-cell lymphoid proliferations, the differential diagnosis—stated broadly—includes both B-cell lymphoma and B-cell lymphoid hyperplasia, but a report carrying a diagnosis of “atypical B-cell infiltrate” appended with a comment that “the differential diagnosis is between B-cell lymphoma and lymphoid hyperplasia” does not really provide much in the way of diagnostic clarity or exactness. More relevant provisional or descriptive categorizations include terms such as “follicular B-lymphoid infiltrate,” “lymphoplasmacytic infiltrate,” or “small B-cell lymphoid infiltrate.” Additional detail regarding the underlying diagnostic possibilities will be included in the sections that follow.

In direct analogy to the content of the superjacent paragraph, a diagnosis of “atypical T-cell infiltrate,” accompanied by a comment indicating that the differential diagnosis is between T-cell lymphoma and T-cell lymphoid hyperplasia, holds little clinical relevance given the extreme breadth and diversity observed in association with T-cell lymphoid proliferations, which may be epidermotropic or nonepidermotropic; nodular or maculopapular; or epidermal, dermal, or subcutaneous in distribution. Provisional diagnostic categories of greater clinical relevance for an infiltrate of presumed T-cell lineage include the superficial (or perijunctional or partially epidermotropic) infiltrate, the CD30+ infiltrate, the nodular nonepidermotropic infiltrate, and the subcutaneous infiltrate.

Summing the approach espoused in the 2 preceding paragraphs, 5 clinically relevant categories of descriptive diagnosis—directly related to the diagnosis of lymphoma or considerations in the differential diagnosis of lymphoma—rise to the surface. Those include (1) the superficial (or partially epidermotropic) infiltrate; (2) the nodular nonepidermotropic infiltrate, with subcategories including the follicular B-cell lymphoid infiltrate and the partially plasmacytic infiltrate; (3) the CD30+ infiltrate; (4) the subcutaneous infiltrate; and (5) the small cell lymphoid infiltrate. These categories are not necessarily mutually exclusive but are largely nonoverlapping, and these categories are not comprehensive but cover most of the work that enters the dermatopathology laboratory. Additional detail regarding the differential diagnosis within these overarching categories will be included in the paragraphs that follow.

Selected relevant descriptive diagnostic categories

The superficial (or partially epidermotropic) lymphocytic infiltrate
In brief, a report carrying a diagnosis of “superficial lymphocytic infiltrate” implies a differential diagnosis including MF, maculopapular T-cell lymphoid hyperplasia, various forms of dermatitis, and lichen plaques—keratosis (LPLK). All of these processes are of T-cell lineage, and in most instances, they display a similar immunophenotype and exhibit partially overlapping histopathologic features (Figure 1). A large number of terms that are unique to various dermatopathologists—including but not limited to such designations as epidermotropic lymphoid infiltrate, lichenoid/pseudosarcoma lymphoid infiltrate, or suggestive of MF—are utilized in this context. These terms are deployed as a hedge when the diagnosis might be MF, while histopathologic uncertainty remains. The clinician should appreciate that diagnostic hesitation on the part of the dermatopathologist may be triggered by an incomplete understanding of the clinical context, by a paucity of cytologic atypia associated with intraepidermal lymphocytes, by an iffy degree of epidermotropism, or through inexperience.

It is a common clinical (and also dermatopathologic) misconception that immunophenotyping can be of value in substantiating the diagnosis of MF.1-3 This proves rarely to be the case, with the possible exception of a small subset of cases, such as hypopigmented MF in childhood or adolescence, in which a CD8+ immunophenotype may be identified. By and large, the immunophenotype of MF is the same or similar to that associated with T-cell lymphoid hyperplasia or dermatitis, and thus immunohistochemistry is unlikely to be diagnostically decisive. The additional steps that hold the greatest potential to be diagnostically momentous include careful clinicopathologic correlation, obtaining additional biopsies in the hope of identifying greater epidermotropism or cytologic atypism, or the completion of genotyping to screen for T-cell clonal-
ity. While the identification of clonality cannot be equated with a diagnosis of lymphoma, certainly the documentation of clonality provides significant momentum toward a diagnosis of lymphoma. There is preliminary evidence that this is particularly true if an identical T-cell clone is identified in more than one tissue biopsy.$^4$

It is important for the clinician to remember that an intense interface reaction not uncommonly triggers unwarranted concern for the possibility of a lymphoproliferative disorder or lymphoma by their microscopic colleagues (Figure 2). This can be seen with both LPLK and discoid lupus erythematosus (DLE). A biopsy that enters the dermatopathology laboratory with a clinical impression of “rule out BCC” may catch the clinician off guard when it eventuates with a pathology report delineating the results of numerous immunostains and expressing concern for the possibility of cutaneous lymphoma. Strategies that can be useful for avoiding confusion in this context include careful clinicopathologic correlation, recognition of the fact that the infiltrate associated with an LPLK can be heterogeneous, and targeted immunostaining to shift the diagnosis away from lymphoma, such as the application of CD123 immunostaining to support interpretation as DLE.$^5$

The nodular nonepidermotropic lymphoid infiltrate
Nonepidermotropic and nonmacular lymphoid involvement of the skin (Figure 3) constitutes a broad and heterogeneous diagnostic category that includes as its most common considerations low-grade B-cell lymphoma, B-cell and T-cell lymphoid hyperplasia, and small/medium pleomorphic T-cell lymphoma (SMPTCL). Because of indolence, the latter entity is also referred to as small/medium pleomorphic T-cell lymphoproliferative disorder (SMPTCLPD). Key subcategories in this spectrum include the follicular B-cell infiltrate (a B-cell infiltrate with germinal center formation) and the lymphoplasmacytic infiltrate, with B-cell lymphoid hyperplasia, T-cell lymphoid hyperplasia, and SMPTCLPD representing most of the remainder.

The key considerations in the differential diagnosis of the lymphoplasmacytic infiltrate include marginal zone lymphoma (MZL), lymphoplasmacytic plaque, and cutaneous plasmacytosis. Lymphoid hyperplasia (with admixed plasma cells) and syphilis can occasionally enter into this differential as well. When plasma cells are abundant in a given infiltrate, the key next step in evaluation is the completion of kappa/lambda light chain assessment to evaluate light chain restriction. In the modern era, light chain restriction assessment can be extremely valuable in confirming the presence of plasma cells.
Chain evaluation should be completed by in situ hybridization (ISH) and not by immunohistochemistry, as the latter technique is handicapped by its proclivity toward high background labeling that impedes interpretation. If ISH confirms light chain restriction, the diagnosis becomes, for all practical purposes, MZL. If instead ISH demonstrates polyclonal/polytypic reactivity, then clinicopathologic correlation can be employed to further subclassify the plasmacyte-rich infiltrate under evaluation. Presentation in solitary fashion in a child or adolescent is typical of lymphoplasmacytic plaque. Multipapular truncal involvement in a patient of Asian ethnicity represents the stereotypical presentation linked to cutaneous plasmacytosis, although the full breadth of this clinicopathologic spectrum is still being defined. If a nodular presentation of syphilis represents a plausible consideration, then the possibility of infection can also be assessed through the use of immunostaining for *Treponema pallidum*. In one memorable case from this author’s practice, a nodular plasma cell-rich infiltrate evaluated in the absence of an accompanying clinical history was misinterpreted as possible lymphoma during an initial pathology evaluation. Consultative evaluation included *T. pallidum* immunohistochemistry, which highlighted tremendous numbers of coiled spirochetes. The clinicopathologic denouement was nodular primary syphilis induced by a human bite during a brawl.

If the infiltrate includes germinal centers, MZL constitutes one possibility in the differential diagnosis, as colonizing follicles are common in association with this entity. The differential also includes B-cell lymphoid hyperplasia with germinal center formation and primary cutaneous follicular (follicle center) lymphoma. If the follicles present are reactive in nature and if ISH demonstrates light chain restriction, then the diagnosis becomes MZL. If the follicles present are reactive in nature and a significant plasmacytic component is not present, then the diagnosis becomes B-cell lymphoid hyperplasia. If the follicles present are neoplastic in nature, then the diagnosis becomes follicular lymphoma. Distinguishing neoplastic from reactive follicles can be challenging, and thus in some instances pursuing genotyping to screen for underlying B-cell clonality may be diagnostically expeditious. In the absence of genotyping, identifying many intrafollicular tingible body macrophages in routine sections favors interpretation as reactive follicles (indicating a diagnosis of lymphoid hyperplasia), while in contrast the identification of extrafollicular clusters of follicular center cells that express bcl-6, or, alternatively, the identification of irregular follicles with a low Ki-67 cell proliferation index, suggests that the follicles may be neoplastic (favoring a diagnosis of follicular lymphoma).

Once the plasmacyte-rich or follicular lymphoid infiltrate has been excluded, the remaining examples of a nodular nonepidermotropic lymphoid infiltrate include a mix of lymphoid hyperplasia of B-cell or T-cell lineage as well as SMPTCL. The case can be made that this residual differential diagnosis is trivial, given the indolence of SMPTCL and the recent momentum to increasingly utilize the alternative designation SMPTCLPD. All of the considerations mentioned in the first sentence of this paragraph share in common the presence of a mixed infiltrate that includes significant numbers of both B-cells expressing CD20 or PAX-5 and T-cells expressing CD3 and CD4. SMPTCLPD can be identified on immunoperoxidase grounds through the use of PD-1 staining, which highlights enlarged lymphocytes arranged in cords, nests, and rosettes. In contrast, PD-1 staining of lymphoid hyperplasia typically demonstrates prominent positivity limited to small lymphocytes.

### The CD30+ lymphoid infiltrate

A pathology report carrying diagnostic language along the lines of “atypical CD30+ lymphoid infiltrate,” “CD30+ lymphoproliferative disorder,” or “CD30+ lymphoma” should immediately trigger consideration of a clinical differential diagnosis including the spectrum of lymphomatoid papulosis (LyP), anaplastic large T-cell lymphoma (ALCL), and a CD30-positive tumor of MF (Figure 4). On occasion, CD30 expression can be prominent in conjunction with lymphoid hyperplasia as well.

This diagnostic setting can be readily sorted out by comprehensively evaluating the clinical context. If the patient has an existing diagnosis of MF or if total skin examination reveals a chronic/persistent eruption that might represent MF, then the possibility of a CD30-positive tumor of MF remains clinically realistic (it goes without saying that biopsy evaluation of any chronic/persistent eruption discovered via clinical examination is indicated). If the circumstances described in the preceding sentence are not met, then the diagnosis of MF has been effectively excluded. If the patient has fixed nodules and if the vast majority of the infiltrate expresses CD30, then ALCL remains as a potential consideration. If the clinical eruption is papulonodular with many or few papules or nodules, and particularly if involution of papules or nodules has been noted, then LyP (of classic “type A” or of “type C”) becomes the leading consideration.

### The subcutaneous lymphoid infiltrate

Although many types of leukemia or lymphoma can present on occasion as a subcutaneous nodule, the primary considerations in the differential diagnosis in this context include subcutaneous...
panniculitic T-cell lymphoma and primary cutaneous gamma/delta lymphoma (PCGDTCL) with subcutaneous involvement (Figure 5). As an important historical note, these two entities were lumped together in the original or early descriptions of subcutaneous T-cell lymphoma, and thus early reports regarding panniculitic lymphoma may be diagnostically misleading. The differential diagnosis of the subcutaneous nodular infiltrate also includes lymphoid hyperplasia and lupus erythematous panniculitis.

Subcutaneous lymphoma of alpha/beta T-cell lineage constitutes a low-grade malignancy and represents—per the nosology of the World Health Organization—what should be properly referred to as panniculitic T-cell lymphoma. Subcutaneous panniculitic T-cell lymphoma commonly expresses CD8 and beta-F1 and lacks expression of GM3. Periadipocytic “rimming” of CD8-positive T-cells represents a key diagnostic finding. The CD8-positive cells distributed in “rimming” fashion may also exhibit an elevated Ki-67 cell proliferation index, and this immunostaining result can serve as an additional diagnostic clue.

PCGDTCL is of gamma/delta rather than alpha/beta T-cell lineage. It also commonly presents with subcutaneous involvement, although a diverse histopathologic spectrum including vacuolar change, vasculitis-like change, and secondary granulomas can also be seen. Although PCGDTCL was initially believed to hold a universally ominous prognosis, it has since been recognized that the entity occasionally follows a low-grade clinical course. Immunophenotypically, PCGDTCL differs from panniculitic T-cell lymphoma in that it expresses GM3 and generally lacks expression of CD8 and beta-F1. Expression of CD56 can also be seen, and thus the immunophenotype overlaps with that of NK-cell or NK/T-cell lymphoma.

There are no specific criteria to recognize subcutaneous involvement by lymphoid hyperplasia. Rather, this can be viewed as a diagnosis of exclusion: if a subcutaneous infiltrate does not represent a specific infiltrate of panniculitic T-cell lymphoma, PCGDTCL, or lupus panniculitis, then classification as a subcutaneous manifestation of lymphoid hyperplasia becomes diagnostically plausible. Lupus erythematous panniculitis can be recognized on the basis of specific conventional histopathologic features, including hyalinization of fatty lobules, the presence of many plasmacytes, and increased mucopolysaccharide. Immunohistochemically, a substantial increase in subcutaneous CD123-positive plasmacytoid dendritic cells can also be utilized as a diagnostic tool.

When evaluating a subcutaneous infiltrate utilizing ancillary studies, it is important to keep in mind that the identification of clonal rearrangement is not the sine qua non of subcutaneous lymphoma, as T-cell clonality has also been observed in conjunction with lupus panniculitis.

The small cell lymphocytic infiltrate

The prototype of a diffuse infiltrate of small lymphocytes is chronic lymphocytic leukemia (CLL). Its “solid” counterpart, small lymphocytic lymphoma (SLL), is immunophenotypically similar and sits in the differential diagnosis, by definition, as well. Other entities that can present with a diffuse infiltrate of small lymphocytes include mantle cell lymphoma, a specific infiltrate of hairy cell leukemia, and a diffuse presentation of lymphoid hyperplasia or a diffuse dermatitis (Figure 6).

In the evaluation of a diffuse small lymphocytic infiltrate, a key step in evaluation is an assessment of T-cell versus B-cell lineage. If the infiltrate is diffusely of T-cell lineage, then for all practical purposes CLL or SLL has been excluded, as CLL represents a lymphoid proliferation of B-cell lineage. In the context of a diffuse T-cell infiltrate, the primary diagnostic consideration shifts to lymphoid hyperplasia or nodular dermatitis.

Once a diffuse small cell lymphoid infiltrate is confirmed to be of B-cell lineage, immunophenotyping, clinicopathologic correlation, and correlation with the patient’s underlying complete blood count can be utilized to provide the best overall diagnostic fit. With respect to immunophenotype, CD43, CD5, CD11c, and bcl-1 immunostaining can be utilized. Aberrant expression of CD43 and/or CD5 by CD20-positive lymphocytes is typically taken as being supportive of the diagnosis of CLL/SLL. Expression of CD11c is prototypical of hairy cell leukemia but can also be seen, occasionally, in conjunction with CLL/SLL and mantle cell lymphoma. Analogously, expression of bcl-1 favors subclassification as mantle cell lymphoma and is rare in conjunction with CLL/SLL or hairy cell leukemia.
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Conclusion

In summary, clinicians and microscopists should jointly recognize that there is little to be gained in utilizing diagnostic vagueness in the form of unintelligibly nonspecific terms such as “atypical lymphocytic infiltrate.” It is clear that descriptive diagnostic language remains an ongoing necessity, but by incorporating strategies similar to those discussed herein, dermatopathologists can keep their clinical colleagues informed regarding the key or realistic considerations in the differential diagnosis at times when a fully explicit diagnosis must be suppressed because of limitations in the clinical and/or histopathologic assessment.

References