Problematic "Low Grade" Lesions in Lymphoproliferative Pathology

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Abstract

Pathological diagnosis of lymphoproliferative processes has been associated with a high error rate of 17-35%, compared to a low diagnostic error incidence of 1-3% in general histopathology. In lymphoma diagnosis, one half of the diagnostic errors result in significant clinical consequences such as delayed or inappropriate therapy, unnecessary treatment, avoidable morbidity and compromised survival.[1] Inherent pathological ambiguity of lymphoproliferative processes, interpretational subjectivity, unfamiliarity with diagnostic criteria and novel entities, lack of expert opinion, inappropriate laboratory support and poor clinico-pathological correlation are the main reasons behind most pitfalls in this subspecialty.

Over the past 20 years, advances in classification have aided pathologists to better characterise lymphoid proliferation. The WHO lymphoma classification has imposed additional requirements for genetic and molecular interrogations. As a result, it has now been widely advocated that diagnosis of lymphoproliferative processes is centralised and conducted in dedicated, highly specialised laboratories.[2]

However, even in the context of central pathology review of lymphoid proliferations, the initial steps in selecting cases for referral depend on the diagnostic skills of generalist pathologists. Their familiarity with reactive conditions many of which closely mimic neoplasms, is essential. Reactive lymphoproliferations represent 10-20% of the cases referred to subspecialist diagnostic services. This high referral rate outlines the pathological ambiguity of these conditions and their difficult differential diagnosis with lymphoma. In many instances, this is complicated by a dramatic clinical presentation resulting in high concern and "pressure" from clinicians, which may further compromise diagnostic confidence. Such conditions comprise a variety of morphological patterns including follicular proliferations, paracortical expansions, intrasinusoidal and necrotizing processes. In the recent update of the WHO lymphoma classification there is a "plethora" of new entities which further widen the differential diagnosis of reactive lesions and "low grade" lymphomas. This particularly refers to a spectrum of early lesions which sit at the interface between the reactive and neoplastic.

In the context of this review, "low grade" lesions are not considered to represent a homogeneous group of entities. This colloquial term is here used for diverse both reactive and neoplastic processes the clinical course of which is mostly non-aggressive, even though the morphological features may sometimes imply otherwise. Examples of difficult differential diagnoses and newly recognised entities with their clinical implications are discussed with emphasis on the importance of clinico-pathological correlation.

Reactive lymphoproliferations with nodular architecture may mimic lymphoma (and vice versa): Progressive transformation of germinal centres is a rare reactive process of uncertain aetiology which may result in bulky lymphadenopathy. The morphological features mimic nodular lymphocyte predominant Hodgkin lymphoma or follicular lymphoma. Diagnosis relies on the identification of disrupted but retained components of the lymphoid follicles, without L&H cells. Other nodular/follicular proliferations including florid non-specific follicular hyperplasia and hyaline vascular variant of Castleman's disease pose a differential diagnosis with lymphomas exerting a nodular growth pattern. This relates primarily to variants of follicular lymphoma (FL)(Grade 3A/B, "floral variant", FL with hyaline vascular changes). Appreciation of retained lymph node architecture is essential for diagnosis. Difficult cases may need clonality and genetic studies.[3]

"In situ" and early neoplastic lesions in lymphoproliferative pathology do exist: Follicular lymphoma in situ is a recently recognised entity representing an early phase of neoplastic transformation with uncertain

potential for progression.[4,5] The typical morphological and immunophenotypic features distinguish it from partial involvement of lymph nodes by systemic lymphoma. Recognition of this condition prevents unnecessary treatment and patient anxiety. Early and "in situ" forms of other lymphomas include monoclonal B-cell lymphocytosis [6, 7], "in situ" mantle cell lymphoma[8], intestinal FL[9], intraepithelial monoclonal T-cell lymphoproliferation associated with refractory celiac disease[10] and early lesions of EBV positive age related lymphoproliferations.[11, 12] Accurate recognition of these entities has important clinical implications.

Lymphomas may display "reactive" architectural and immunocytochemical patterns; "Aggressive" looking morphology does not always indicate an aggressive clinical course: Follicular lymphoma grade 3B is part of the morphological spectrum of FL but appears to be different from grades 1, 2 and 3A. The genetic makeup of grade 3B is closer to the clinically aggressive diffuse large B-cell lymphoma.[13, 14] Due to high proliferation, abundance of tingible body macrophages and immunohistochemical negativity for Bcl2 FL grade 3B could be misinterpreted as reactive follicular hyperplasia. This is particularly problematic in cases of paediatric FL.[15] In adults, grade 3B is currently managed as most other aggressive large B-cell lymphoma, so accurate diagnosis of this subgroup is of high clinical relevance. However, childhood cases pursue an indolent course, despite grade 3 morphology.

Florid, atypical blastic lymphoproliferations could be reactive: Infectious mononucleosis affects young individuals often presenting as an alarming, rapidly developing lymphadenopathy with a worrying histological appearance which may suggest lymphoma. Diagnosis relies on the identification of the polymorphous nature of the infiltrate, retention of lymph node architecture and EBV positivity. The differential diagnosis usually includes classical Hodgkin lymphoma or T-cell rich B-cell lymphoma. In very young patients a consideration should also be given to EBV positive T-cell lymphoproliferation of childhood. Similar problems may be seen with Kikuchi lymphadenitis, drug induced or post-vaccinal reactions further expanding the differential diagnosis. Clinico-pathological correlation is essential but early laboratory investigations ("monospot") may be misleading.[16, 17]

Dramatic clinical presentation with massive or generalised lymphadenopathy is not always due to lymphoma: Rosai – Dorfman disease (sinus histiocytosis with massive lymphadenopathy) presents with massive localised or generalised lymph node enlargement, occasionally with extranodal involvement. Severe constitutional symptoms are common. Diagnosis relies on the identification of an intrasinusoidal proliferation of histiocytes with a specific S100/CD68 positive immunophenotype. The course is self limiting but administration of steroids may be beneficial.[16] The differential diagnosis includes non-specific sinus histiocytosis and infection but also a sinusoidal spread of tumours such as carcinoma, melanoma, angiosarcoma, anaplastic large cell lymphoma or "villous/sinusoidal" large B-cell lymphoma. Examples of other reactive conditions resulting in a dramatic clinical presentation where the pathological diagnosis may be problematic include plasma cell variant of Castleman's disease[18] and infectious mononucleosis.

Clinical history and correlation are essential for accurate diagnosis, prognostication and choice of management: EBV positive mucocutaneous ulcer (EBVMCU) is a localised immunosuppression associated B-cell lymphoproliferation involving skin and a range of mucosal sites, most commonly oropharynx. It displays Hodgkin-like morphological features and is frequently misdiagnosed as such. Despite its aggressive appearance, EBVMCU is an "early lesion" and follows an indolent course upon reduction of immunosuppression. However, with sustained iatrogenic immunosuppression this process is locally destructive and patients may receive unnecessary aggressive treatment.[11, 12] This new entity is used to highlight a range of lymphoproliferations associated with various immunosuppressive aetiologies.[11, 12, 14] History of immunosuppression is often omitted from the information available to the pathologist and some clinicians may not be aware of its importance in the context of B-cell lymphoproliferations.[14, 16, 17]

Formalised communication between pathologists and clinicians in the form of Multidisciplinary Meetings (MDM) would prevent most misdiagnosis due to lack of relevant clinical information. It hugely aids diagnosis and management and has become essential. Professional regulatory and advisory bodies highlight the mandatory requirement for MDMs as part of the patient management pathway.[19]

Key learning points:

All the common patterns of reactive lymphoid hyperplasias morphologically overlap with a range of lymphomas. Recognition of architecture retention by simple stains such as CD20, CD3 and bcl2 is often very helpful. Difficult cases may require additional clonality or cytogenetic studies;

"In situ" and early lymphoms are being increasingly characterised. Awareness of these conditions is needed to prevent unnecessary treatment and to distinguish them from partial involvement by systemic disease;

Reactive lymphoproliferations may result in a worrying histological picture as seen in infectious mononucleosis. This is one of the most misdiagnosed reactive lymphadenitidies with potentially catastrophic clinical consequences. Clinicopathological correlation is essential but laboratory tests may be misleading;

Other reactive lymphadenitidies may have dramatic clinical presentation as seen in Rosai-Dorfman disease, Kikuchi disease and plasma cell variant of Castleman's disease. In all these conditions conservative therapy is beneficial. While the clinical context is always important, the alarming clinical presentation and increased pressure from clinicians should not impact upon the pathological diagnosis;

Immunosuppression associated B-cell lymphoproliferations represent a wide biological and pathological spectrum including the new entity of EBV positive mucocutaneous ulcer. Information on immunosuppressive management is frequently lacking from pathology requests. Information on immunosuppression should be specifically sought;

Referral of reactive conditions to specialist diagnostic services is not unjustified as their precise characterisation may require complex ancillary studies which are routinely unavailable;

MDM has become an essential and mandatory principle in the management of patients.

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