Problematic "High Grade" Lesions in Lymphoproliferative Pathology

Snjezana Dotlic

Department of Pathology and Cytology
University Hospital Centre Zagreb, Croatia

High error rate in primary lymphoma diagnosis by generalist pathologists has imposed a requirement for a redesign of diagnostic services in this subspecialty. [1] In all developed countries and in most of the countries in transition, diagnosis of lymphoid proliferations has become centralised, relying on regional panels of experts and dedicated specialised laboratories. However, the initial steps in the management and subspecialist referral of patients with suspected lymphoma still rely on diagnostic skills of general histopathologists. Their detailed awareness of classification changes, diagnostic requirements and standards is essential for the success of the diagnostic pathway.

Here a range of scenarios are highlighted where the outcome of the initial pathological assessment, before any specialist investigations have been carried out, could "sidetrack" the referral process and adversely affect management. The term "High Grade" in this context is used for lesions histologically characterised by high pleomorphism and "blastic" appearance and also for processes with an aggressive clinical behaviour.

Over the past two decades the wealth of accumulated knowledge on the biology of lymphoid cells and lymphomas culminated in a series of classifications which emphasised the need for extensive immunophenotypic and genetic interrogation of lymphoid proliferation in the course of pathological diagnosis. [2] As a consequence gone past are the days when treatment of lymphomas could commence after morphological assessment alone. On morphological grounds so many different aggressive lymphomas may show striking similarity. Burkitt lymphoma (BL), blastoid variant of mantle cell lymphoma, lymphomas of the "grey zone" between BL and diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma, plasmacytoid dendritic cell neoplasm and many others may show very similar morphology. This morphological mimicry is further complicated by similarities aggressive lymphoid malignancies may in certain circumstances show with non-haematological malignancies and reactive, inflammatory conditions. Examples of this contentious spectrum are provided together with an update of the most recent classification changes and the impact this has made on the practicalities of pathological diagnosis and management.

Abundant reactive lymphoid infiltrate is seen in a range of different tumours: Follicular dendritic cell tumour / sarcoma is an example of this category. This is an uncommon entity displaying a spectrum of biological behaviour involving lymph nodes and a range of extranodal sites. The tumour cells amongst the abundant reactive lymphoid infiltrate could show spindle cell morphology, epithelioid or Reed-Sternberg-cell features. Accurate diagnosis relies on the recognition of the specific immunophenotype (CD21, CD23, CD35, clusterin). [2-4] This is of benefit only if this tumour is included in the initial differential diagnosis which should also consider tumours such as classical Hodgkin lymphoma, T-cell rich B-cell lymphoma, "lymphoepithelioma-like" carcinoma, inflammatory myofibroblastic tumour, metastatic germ cell tumour, medullary carcinoma of breast, "B-type" thymomas, inflammatory pleomorphic sarcoma or interdigitating dendritic cell sarcoma.

Aggressive lymphomas may be negative for commonly used lymphoid lineage markers: ALK positive large B-cell lymphoma is a rare entity characterised by a high degree of pleomorphism and epithelioid morphology. [5] This aggressive lymphoma in addition displays an aberrant phenotype, lacking expression of CD45 and other lineage markers. The initial use of broad immunocytochemical screens may classify this lymphoma as undifferentiated malignancy. A range of haematolymphoid neoplasms may display loss of expression or are by definition characterised by the absence of markers generally considered to be robust lineage discriminators. Such tumours are myeloma, plasmablastic lymphomas, anaplastic large cell lymphoma and classical Hodgkin lymphoma which may all pose a difficult differential diagnosis with non-haematological malignancies. Plasma cell myeloma as well as other haematological malignancies may also aberrantly express cytokeratins, which in the context of paucity of expression of other B-cell lineage markers could be highly confusing.[6] In addition, a common tumour such as small cell carcinoma of lung on occasions expresses

lymphoid lineage marker PAX5 and lacks most other lineage markers, thus morphologically and immunophenotypically closely resembling lymphoblastic lymphoma. [7]

Marked histiocytic infiltrate and granulomatous reaction may morphologically obscure aggressive lymphomas: Lymphoepithelioid (Lennert) lymphoma is a morphological variant of peripheral T-cell lymphoma of unspecified type. Due to its rich histiocytic infiltrate with formation of granulomas, Lennert lymphoma is frequently misinterpreted as an inflammatory process. [2;8] Granulomatous inflammation and rich histiocytic infiltrate could be diagnostically misleading in a range of lymphoma types such as BL lymphoma [9], classical Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, T-cell rich B-cell lymphoma, mediastinal large B-cell lymphoma and lymphomatoid granulomatosis.[10]

Classification changes and how they affect practice: The update of the WHO classification (2008) introduced several new entities.[2] It focused on resolving contentious differential diagnoses and providing pathologists and clinicians with therapeutically meaningful classification categories. To resolve sometimes difficult differential diagnosis between BL and DLBCL, a new category of "B-cell lymphoma, unclassifiable, with features intermediate between BL lymphoma and DLBCL" was introduced. This "grey zone" category encompasses lymphomas with atypical, BL-like morphological features but also with atypical immunophenotypes and genotypes, including the clinically aggressive "double hit" tumours. [11-13] The practical consequence of this attempt at more stringent classification is that pathological diagnosis of BL and the "grey zone" overlap with DLBCL requires mandatory genetic testing for MYC gene rearrangements but also for other most commonly encountered genetic abnormalities which include rearrangements of the BCL2 and BCL6 genes. In addition, patterns of MYC rearrangements in BL and those lymphomas which would fall into the "grey zone" category are different requiring specific testing for both immunoglobulin and non-immunoglobulin gene partners. The controversy of the differential diagnosis between BL and DLBCL has not been eliminated with the introduction of this category. The strongest criticism of this category is that it does not concern "typical" DLBCLs based on subjective assessment of morphology alone. There is accumulating evidence for the need of systematic genetic testing of morphologically typical DLBCLs which may also show a range of genotypes including those similar to BL and with much more diversity as seen in the "double hit" cases. This could only be resolved by a consensus on systematic genetic testing of all or most of DLBCLs and with additional clinical agreement how to treat this cases which are currently still being classified using diversely different approaches. [14] This will inevitably change practice of pathologists in the near future, requiring extensive routine genetic diagnosis in the context of highly specialised laboratories.

Key learning points:

Generalist pathologists play an essential initial role in the process of centralised, sub specialist diagnosis of lymphoid malignancies; Their awareness of non-haematological mimics of lymphoid tumours, and vice versa, is highly important for the process of case selection for the specialist referral pathway;

A range of lymphomas and non-haematological malignancies are characterised by a dense reactive lymphoid infiltrate. In the differential diagnosis even rare entities such as follicular dendritic cell sarcoma should be considered to enable specific immunocytochemical diagnosis;

A range of high grade lymphomas harbour abundant histiocytic infiltrate and granulomatous reaction which may obscure the underlying neoplastic process;

Lack of expression of lineage markers such as CD45, CD3 and CD20 does not exclude diagnosis of aggressive lymphomas; Other tumours may in addition mimic lymphomas, expressing markers conventionally associated to lymphoid lineage;

New classification changes introduced even more controversy and require further consensus amongst the experts regarding genetic classification of BL and DLBCL. Further consensus on specific treatments is also needed in this context;

Diagnosis of haematological malignancies has become dependant on systematic genetic interrogation of the biopsy materials; This is increasingly becoming mandatory for more and more entities and forms basis for entity specific therapies.

Literature

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