Unusual Variants Of Diffuse Large B-Cell Lymphoma At Extranodal Sites: - Are These Distinct Diagnostic Entities?

Dr. Hansh Woen Akye

Submitted Monday, October 07, 2013
Accepted Wednesday, November 20, 2013
Published Wednesday, November 27, 2013

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Context
Diffuse Large B-Cell Lymphoma (DLBCL) is a heterogeneous category of Malignant B-Cell Neoplasms in the updated 2008 WHO Classification. We present here the more uncommon variants in extranodal locations that have unique clinicopathologic features and which the authors believe are possibly distinct biologic entities in our experience.

Objective
We highlight here the clinicopathologic and immunohistochemical features of a few of the more uncommon variants and also discuss clinicopathologic and practical difficulties encountered in cases presenting to our institution.

Data sources
Material from the author’s institution, CAP PathNet for the examination of specimens from patients with Non-Hodgkin Lymphomas (NHL) extranodal neoplasms. Literature from PubMed and the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues 2008.

Conclusions
While WHO recognizes several morphologic and clinical subtypes of DLBCL, their distinction and categorization as specific entities remain difficult to reproduce, lack of consensus among reporting pathologists further hampering accurate diagnosis. Many variants described, distinct under the rubric of DLBCL. NOS probably are distinct biologic entities, which need to be recognized as such.

Key words
diffuse large B-cell lymphoma, extranodal sites, distinct diagnostic entities

Background
Diffuse Large B-Cell Lymphoma is an aggressive non-Hodgkin lymphoid cell type, which follows the 2001 World Health Organization (WHO) classification. In the revised European American classification of lymphoid neoplasms (REAL 2008), maintaining the recognition of lymphoid and plasma cell neoplasms as distinct entities, leaving the bulk of DLBCL as a unique entity. The 2008 REAL classification recognizes primary extranodal (PLEN) extracellular and primary large B-cell lymphoma arising in the CNS, primary DLBCL, and others. The classification also addresses differences in organ-specific presentations e.g. primary extranodal involvement by DLBCL and other large B-cell lymphomas.
Variants of Diffuse Large B-Cell Lymphoma at Extranol Sites. - Are These ...

Inflammatory mediators e.g. cytokines associated with large B-cell lymphomas. There are also a chaotic number of morphologic subtypes like DLBCL with plasmablastic, angioimmunoblastic, and immunoblastic features. DLBCL with pseudolymphoma, the biologic and prognostic significance of which are being assessed. Though the 2008 WHO classification still mention some rare morphologic variants.

Immunohistology and Gene Expression Profiles of DLBCL. NOS DLBCL express variable number of B-lineage markers (CD10, CD20, CD32, CD79a and PAX5) some studies suggesting that lack of expression of CD20 or CD32 correlates with a poorer outcome [4]. The lymphomas often express surface Ig and or immunoglobulin (Ig), but loss of surface Ig may be seen even in the absence of plasmacytoid differentiation [9]. CD10 is positive in 40% cases and bcl-6 in 60% cases indicating a germinal centre phenotype. Cases positive for MUM1 or BCL6 or C-MYC indicate an Activated B-Cell phenotype [1].

CD30 expression is often associated with sarcomatous morphology and the authors believe represents a distinct entity with a sarcomatoid pattern [6] and negativity for CD15. Gene expression profiling [11] has identified 5 major subgroups of DLBCL - DLBCL, Germinal Centre B-Cell-like (GCB), Activated B-Cell-like (ABC) and primary Mediastinal DLBCL (PMBCL). ABC-DLBCL has frequent copy number gains of 3q and 1q in 63-94% cases and losses of 11q in 75-87% cases while GCB-DLBCL has increased copy number gains of 11q and PMBCL has gain of 6p and 2p16 in 5-15% cases [7]. Immunophenotypically these are characterized by CD10+ and/or bcl-6+ and/or MUM1+ and/or FISH. Several studies random translocations have been reported in DLBCL involving bcl-2 and bcl-6 (more common in extranodal lymphomas) [11].

Unusual and Site Specific Variants of Dlbclprimary Mediastinal Large B-Cell Lymphoma (PMBCL)

A large B-Cell lymphoma of lymphoid origin arising in the anterior Mediastinum. These represent about 6% of all lymphomas, [11] in adults and 20% of childhood NHLs. It occurs in adolescents and young adults, women being affected twice as often as men.

Biopsy interpretation can be challenging because of the often abundant eosinophils that compartmentalizes the tumor into nests of large centroblastic cells. Sometimes with clearing Mediastinal large B-Cell lymphoma expresses a B-Cell phenotype (CD30+, CD20+, CD79a+) with CD30 co-expression leading to confusion with a Nodular Sclerosis Hodgkin’s which resembles in many ways than one. However diffuse strong CD30 positivity with CD15 negativity and CD45 (LCAM positivity is sufficient for diagnoses in most cases. Expression of MAC, or T-Cell restricted markers in 70% cases and CD3 are additional findings.

Gene array studies have shown characteristic molecular abnormalities distinct from DLBCL - NQO1 including amplification of 6q, 8q and deletion or frequent bcl-2 & bcl-6. These tumors also frequently over express the MALT gene with striking similarities to Nodular Sclerosis Hodgkin’s Lymphomas.

Primary Large B-Cell Lymphoma of Bone

Primary lymphoma of bone is defined as a lymphoma that is confined to the bones or bone marrow. We consider primary DLBCL of bone to be a distinct entity accounting for 2% to 3% of all extranodal NHLs, though not singled out in the 2008 WHO classification, with absence of BCL-6 and increased incidence of BCL-2 and C-MYC rearrangements compared to other extranodal sites [12, 13]. Most cases are CD10+ and CD20+ and commonly have CD10 expression.

There are also indicators that pediatric and adult DLBCL are distinct entities [14].

Primary NHL of bone can be difficult to diagnose with a high level of suspicion [15]. It occurs most often in the knee bones. In adults with the tumor being one of the most common sites, DLBCL of bone typically shows polymorphic lymphoid cells with prominent large centroblastic cells and a monomorphic T-Cell / lymphocyte rich or anaplastic morphology [15, 16, 17].

According to the WHO classification, lymphomas involving bone can be classified into 4 groups - Group 1 lymphoma with a single bone site with or without regional lymph node involvement.

Group 2 - Lymphoma with multiple bones involved but no visceral or lymph node involvement.

Group 3 - Bone tumour with involvement of other skeletal sites or lymph nodes at multiple sites and Group 4 - Lymphoma involving other sites and found by bone biopsy for staging.

Plasmablastic Lymphoma

The current WHO classification recognizes Plasmablastic lymphoma (PBL), as a distinct subtype of DLBCL, with morphologic and immunophenotypic features of terminal B-Cell differentiation and involving the skin and oral mucosa of HIV positive patients. [16] as described originally. It is now recognized that the clinical spectrum is much broader and the entity is heterogeneous in terms of clinical presentation and morphology with occurrence in immunocompetent patients as well [19]. Also described as arising in multi-focal cardiac disease, the entity is now recognized to involve lymph nodes and extranodal sites (GIT, upper respiratory tract, bones and soft tissues).

Variants of Diffuse Large B-Cell Lymphoma at Extranodal Sites: Are These...

Morphologically, the cells are large with prominent nucleoli and Plasmablastic/Immunoblastic features. The tumor cells are CD30 negative, CD10 positive, CD56 negative, and MUM-1 positive. Staining for EBV is negative. CD45RB is often but not always negative and EMA is variably positive (19, 20). We have reported a Plasmablastic lymphoma in the transverse colon of an immunocompromised HIV negative 45F who presented with a necrotic ulcer in a previously resected mass and underwent an extended Right Hemicolectomy. The tumor was negative for all epithelial and lymphoid markers including CK, CD30, CD5 andALK-1. There was focal positivity for CD3 and strong EMA staining in tumor cells with subsequent diffuse CD15 positivity and Light chains restriction. The Myelomaワーク was positive. The staining for EMA with often weak to negative CD45RB may lead to a mistaken diagnosis of carcinoma.

The clinical course of PEL is aggressive with frequent treatment resistance and often rapidly fatal (20). PEL usually expresses CD138 only if it is associated with Castleman disease (21).

Plasmablastic lymphoma shares many morphologic and immunophenotypic features with Plasmablastic transformation of plasma cell Myeloma. (22) MYC translocation has been associated with tumor progression in myeloma and in some studies in Plasmablastic lymphoma which also showed clinical overlap with Myeloma.

Several cases have now been described in extra-oral and extranodal sites like the auricular and Parotid since (23).

**Primary Extranodal DLBCL**

Studies in the pre-Rituximab era have identified important differences between nodal and primary extranodal DLBCL. The most commonly involved extranodal sites include bone (33.1%), Soft tissue (26.9%), Stomach (15%), Intestine (12.2%) and paranasal sinuses (10.5%) (24).

Molecular studies have indicated significant differences between nodal and extranodal DLBCL, suggesting that both have different genetic origins and could be regarded as separate entities (25) an issue that is not addressed in the current WHO classification.

Extranodal DLBCL is usually associated with older age and adverse performance and lower incidence of DLH reactions. There is compelling evidence that extranodal lymphomas at some sites have rather specific biology that are cell specific such as: HL pulse in gastric lymphomas and extracranial thymomas in thyroid lymphomas. Moreover, at least some extranodal (DLBCL) represent exclusively transformed MALT lymphomas. (26) of gastric and extranasal origin Extravascular (DLBCL) appearing as part of the spectrum of post transplant lymphoproliferative disorder (PTLD) represents the most common type of monomorphic B-PTLD (27) and may represent further variation in the theme of extranodal (DLBCL).

Significantly different chromosomal aberrations exemplified by gains of 1q, 7p, 12q, 13q, 21, 22q, 3q, 17p, 20, 9, and loss of chromosomes 4, 5q, 6q, 11, 12, 13, 17q, 20, and 9 in chromosome 4. 5q, and 17p, 22q, 3q, 20 have been demonstrated in extranodal vs nodal DLBCL. (24) IHC-based algorithms have shown that extranodal (DLBCL) are more often associated with GCB. We have observed differences in nodal and extranodal DLBCL with a higher incidence of CD10 and Bcl-2 immunostaining in extranodal (DLBCL) particularly in DCLBCLs of the GIT at variance with some of the literature (31).

**Primary Splenic DLBCL**

Feasibly the unusual form of DLBCL with red pulp involvement of the spleen and an aggressive clinical course. (31) is discussed. This is also considered by several authors to be a distinct Clinicopathological entity with some overlap with the CD20+ large B-Cell lymphomas and extravascular (DLBCL). (32). Three groups have now been identified:

Group 1 with diffuse splenic involvement no other clinical evidence of mass disease and microscopic disseminated disease on further workup.

Group 2 with an immunophenotype resembling Mantle cell lymphoma and

Group 3 with a Miscellaneous phenotypes.

We have reported splenic (DLBCL) some with no evidence of nodal or extranodal involvement of any other sites presenting with enlarged, splenomegaly and a well-defined hypercellular mass on USG, (33) with no necrosis involvement at diagnosis and no evidence for cytoplasms. The tumor cells were large and nucleolated with a large hamor/macromonomer involvement of the spleen and an admixture of smaller and medium sized cells with focally located nuclei.

The cell-expressed diffuse strong CD20 and CD45 RB.

Large B-Cell Lymphoma presenting initially in bone marrow, spleen and liver, is associated with cytogenetic changes in loci 14q12 and 14q24 as well as del (3) (q27), del (7) (q22), del (13), del (16) (p26), +16 and add (16) (q21)(q22). Clinical behaviour is usually aggressive with a 2yr survival rate of 18%. Most cases of primary splenic DLBCL are treated with splenectomy. If the malignancy is confined to the spleen, (34) the differential diagnosis includes reduplication low grade B-Cell lymphoproliferative disorders like hairy cell leukemia (35). A recent report of 25 spleen-DLBCLs described 5 patterns of lymphomatous infiltration.

Maceronuclear or turalar, macromonomer (or mixture) and diffuse (34, 77). The diffuse pattern was the local common with involvement of red pulp cords and sinuses.

http://www.npplweb.com/wjsmro/fulltext/2/13

28/04/2014
Primary systemic DLBCL may therefore constitute a heterogeneous entity with variable prognosis and may need further evaluation for definite categorization.

References


(2) de Jesus ES, Harila NL, Stein H, Vardimon JA. Pathology and Genetics of tumors of hematopoietic and lymphoid tissues, in World Health Organization Classification of Tumors Lymphoma. IARC Press Lyon, France 2001.


(19) Fehmke S, Reul RV. Dept of pathology, Stanford university school of Medicine, Radiology, pathology, Pathology, Pathology, 2008 May; 1.

(20) Fehmke S, Reul RV. Dept of pathology, Stanford university school of Medicine, Radiology, pathology, Pathology, Pathology, 2008 May; 1.

(21) Fehmke S, Reul RV. Dept of pathology, Stanford university school of Medicine, Radiology, pathology, Pathology, Pathology, 2008 May; 1.

(22) Fehmke S, Reul RV. Dept of pathology, Stanford university school of Medicine, Radiology, pathology, Pathology, Pathology, 2008 May; 1.

(23) Fehmke S, Reul RV. Dept of pathology, Stanford university school of Medicine, Radiology, pathology, Pathology, Pathology, 2008 May; 1.


