

Large B cell diffuse lymphoma

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Abstract

Primary diffuse large B-cell lymphomas (DLB-CL) are aggressive tumors accounting for approximately 40% of the B-cell malignancies. DLB-CL are commonly composed of a mixture of centroblast-like and immunoblast-like cells. These cells express typically the B-cell markers CD19, CD20, and CD22 and the surface immunoglobulin (slg). DLB-CL are clinically and genetically heterogeneous tumors. The frequently recurring chromosomal translocations t(3;14), t(8;14) and t(14;18) have been shown to characterize genetic subsets, which together constitute approximately 50% of DLB-CL. However, the genetic basis of the clinical heterogeneity of DLB-CL remains poorly understood. The median age of presentation is in the sixth decade, but the age range is broad, and these tumors may be seen in children. Patients often present with single or multiple rapidly enlarging, symptomatic masses in nodal or extranodal sites; up to 40% of these masses are extranodal. The most common extranodal site is the stomach, although most primary lymphomas of the central nervous system, bone, kidneys and testes are also DLB-CL. Approximately 40% of DLB-CL can be cured with standard therapy. However, 50% of patients relapse after treatment and die of recurrent lymphoma.

Keywords

B-cells, non-Hodgkin lymphomas, diffuse large B-cells lymphomas, BCL2, REL, MYC, survivin, apoptosis, chemotherapy

Disease name and synonyms

Diffuse large-B cell lymphoma (DLB-CL)
 Rappaport: Diffuse histiocytic, occasionally diffuse mixed lymphocytic-histiocytic.
 Kiel: Centroblastic, B- immunoblastic, large-cell anaplastic (B cell).

Lukes-Collins: Large cleaved or large non-cleaved FCC, B-immunoblastic.
 Working-Formulation: Large-cell cleaved, noncleaved or immunoblastic; occasionally diffuse mixed small and large cell.

Differential diagnosis

The differential diagnosis of large B-cell lymphoma includes nonlymphoid tumors such as poorly differentiated carcinoma, germ cell tumor, glioma, melanoma and sarcoma. Lymphoma is often suspected in the differential diagnosis when patients present with lymphadenopathy; however, the disease may not be suspected when patient present with extranodal involvement.

Clinical features that support the diagnosis of lymphoma include:

- presence of multiple, noncontiguous lesions.
- characteristic radiographic findings (permeative lesions in bone, ring-enhancing lesions in the central nervous system).
- additional involvement of lymphoid organs.
- systemic symptoms such as fever and weight loss.

Frequency

DLB-CL is one of the most common lymphoid malignancy in adults, representing about 30-40 % of adult [non-Hodgkin's lymphoma \(NHL\)](#) diagnosed *de novo* on basis of morphology and immunophenotype.

Large cell lymphomas in children are relatively rare as they represent less than 5% of NHL in childhood.

Definition

NHL constitute an heterogeneous group of neoplasms and among high-grade malignant NHL, the updated Kiel classification (Engelhard *et al.*, 1997) identifies three major B-cell entities: centroblastic (CB), B-immunoblastic (B-IB), and B-large cell anaplastic (Ki-1+), now termed anaplastic large cell [CD30+], [B-ALC]. The revised European-American Lymphoma (REAL) classification proposed in 1994 by the International Lymphoma Study Group unified these lymphomas in the single category of diffuse large-B cell lymphomas, as there are no major differences in the clinical behavior or approach to therapy of these three entities.

Diffuse large-B cell lymphomas were previously thought to represent malignant counterparts of germinal center B-cells. However recent analysis using microarrays suggested that there are at least two subsets, with gene expression patterns similar either to germinal center B-cells or to activated B-cells.

Clinical description

The median age of presentation is in the sixth decade, but the age range at onset is broad, and these tumors may be seen in children.

Patients often present with single or multiple rapidly enlarging, symptomatic masses in nodal or extranodal sites; up to 40% of these masses are extranodal.

The most common extranodal site is the stomach, although most primary lymphomas of the central nervous system, bone, kidneys and testes are also DLB-CL.

Rare cases present with predominantly intravascular involvement -the so-called intravascular lymphoma, angiotropic lymphoma, or malignant angioendotheliomatosis- producing ischemic changes in a variety of organs, particularly in the central nervous system, kidneys and skin.

The large cell lymphomas of childhood are clinically, histologically and immunologically more heterogeneous than the other subtypes of NHL. Because of the relative rarity of large cell lymphomas in children, most of the available data derive from studies in adult patients.

The onset of the clinical manifestations may be sudden, and the duration of symptoms is characteristically short. Initial symptoms (including cough, sore throat, abdominal pain, vomiting, and adenopathies) are nonspecific and may be indistinguishable from those of a variety of common childhood illnesses. Constitutional symptoms such as fever, night sweats, and weight loss are more common in patients with high-grade lymphomas. Rarely, children present with widely disseminated disease in which the site of origin cannot be determined. Clinical manifestations in children with DLB-CL are less predictable, and these tumors tend to arise in lymph nodes and in the lymphoid tissue of the gastrointestinal tract, bone, mediastinum, and skin.

Mediastinal large B-cell lymphoma (MLB-CL) has been recently identified as a subgroup of DLB-CL that affects especially young female patients. The molecular characteristics of MLB-CL differ from these of classical DLB-CL and share features with classical [Hodgkin lymphoma](#).

Tumor morphology and immunophenotype

DLB-CL are composed of layers of large cells that resemble centroblasts or immunoblasts, the most common finding being a mixture of centroblast-like and immunoblast-like cells. Other cells types include large cleaved or multilobated cells and anaplastic cells identical to those of T- or null cell-anaplastic large cell lymphoma. Some large B-cell lymphoma may be rich in small T lymphocytes or histiocytes, thereby resembling either T-cell lymphoma or Hodgkin's disease (lymphocyte predominance type).

Diffuse large B-cells typically express the B-cell markers CD19, CD20, and CD22 and the surface immunoglobulin (slg). The tumor cells are larger and more irregular than immunoblasts and the cytoplasm is less basophilic. An additional characteristic feature is the cohesive growth pattern of the blasts, which can

frequently only be recognized in the well-fixed areas of the slides.

Etiology

The extent to which malignant B-cell migration mimics that of its normal putative counterpart, the mature B-cells, remains to be defined. Mature B-cells migrate to secondary lymphoid organs, where they encounter antigens, engage their B-cell receptors, and subsequently move to the germinal center where they undergo hypermutation and affinity maturation.

Events in DLB-CL indicate that the tumor cell population is arrested at a stage where both somatic mutations and isotype switch can continue after malignant transformation. Most of the mutational activity appears to be finished by the IgMD+ stage, although there may be few further mutations following the isotype switch.

The IgG isotype variants probably reflect an influence of Th1 cells. These variants appear functional at the RNA level, and protein expression is seen at least for some of the transcripts. Mutational patterns are consistent with the existence of subpopulations within the tumor and with parallel switch events to either IgG3 or IgG1, which can then switch to IgA (Ottensmeier *et al.*, 2000). These findings do not necessarily reflect deregulation, but rather indicate that the tumor cells respond to normal signals without being able to achieve a fully differentiated state.

A subset of DLB-CLs is thought to derive from mature effector cells that left the germinal center and re-entered the circulation. The mechanisms that govern the migration of normal antigen-activated B-cells and their malignant counterparts are currently under intense investigation.

Genetic features

Although most DLB-CL arise *de novo*, a subset of them may result from the transformation of indolent lymphomas, including immunocytoma, follicular lymphoma, and marginal zone lymphoma; these transformed lymphomas often have a prognosis worse than that associated with *de novo* large B-cell lymphomas.

In DLB-CL the Ig variable region genes commonly undergo somatic mutations (Taniguchi *et al.*, 1998; Lossos *et al.*, 2000), and this applies also to the morphologically different subsets of DLB-CL that are located in the central nervous system or the skin, and to the T-cell-rich B-cell lymphoma.

The frequently recurring chromosomal translocations, t(3;14)(q27;q32), t(8;14)(q24;q32) and t(14;18)(q32;q21), have been shown to characterize genetic subsets, which together correspond to approximately 50% of DLB-CL. The most common cytogenetic abnormality in patients diagnosed with diffuse large cell

lymphomas is the t(14;18)(q32;q21), which appears in about 25-30% of patients.

These translocations deregulate the expression of *BCL6* (3q27), *MYC* (8q24), and *bcl-2*(18q21) genes, as a result of their juxtaposition to the Ig genes.

However, the genetic basis underlying the clinical heterogeneity of DLB-CL remains poorly understood.

Gene amplification is a genetic lesion frequently associated with progression of the tumor (Rao *et al.*, 1998). The commonly recurring Ig gene site-associated translocations leading to deregulation of specific genes occurs only in a proportion of cases.

Recent studies suggest that *REL*, *MYC*, and *bcl-2* genes may be more frequently involved in DLB-CL than the frequency of their disruption by chromosomal rearrangement seems to indicate. The role of aberrant expression of these genes (due to cytogenetic translocations or DNA rearrangements) in lymphomatogenesis is important.

BCL6

BCL6 is one of the three genes deregulated by such translocations, plays an important role in the genesis of DLB-CL. In addition, *BCL6* undergoes mutations (hypermutations) in the 5' regulatory region in more than 70% of the cases of DLB-CL, providing another possible mechanism for the gene deregulation.

MYC

MYC deregulation has been suggested to compromise a second and contributing event in the progression of *bcl-2*-deregulated follicular center cell lymphoma into DLB-CL.

bcl-2

bcl-2(18q21) overexpression itself has been associated with adverse clinical outcome.

REL

REL amplification may be associated with extranodal presentation.

Diagnostic methods

Overcoming the difficulties in distinguishing the three main types of large B-cell lymphomas requires experience and sensitive histological techniques.

Histopathologic diagnosis should always be based on microscopic examination of appropriated selected tissue sections obtained by biopsy, fine-needle aspiration or cytologic examination of appropriate body fluids.

The diagnostic slides are prepared for optimal Giemsa staining and the procedure is supplemented by immunohistochemistry and molecular genetic methods, to study the patterns

of immunoglobulin and receptor genes rearrangements.

The most important factors in establishing the diagnosis are a high index of suspicion and a recognition of the morphologic spectrum of diffuse large B-cell lymphoma.

In most cases, immunoperoxidase stains on paraffin sections enable definitive diagnosis; however, a panel of several antibodies may be required (cytokeratin, EMA, CD45, pan-B and pan-T antigens, Ig light chains, and if relevant, S-100 and HMB-45).

Staging

Recommended staging studies include careful physical examination with attention to all sites of palpable disease, a complete blood cell count including platelets and differential, bone marrow aspiration, and lumbar puncture with cytocentrifuge examination of the cerebrospinal fluid and measurement of serum lactic dehydrogenase.

Clinical studies include computed tomography (TC), magnetic resonance imaging (MRI) and radionuclide bone scans for unsuspected bony lesions.

The most commonly used staging system for childhood NHL is the St Jude staging system (Shad *et al.* 1997). In general the prognosis worsens with increasing stage of the tumor.

Prognostic parameters

Although combination chemotherapy has improved the disease outcome, many patients do not achieve complete remission and they ultimately relapse, prompting the search for parameters that enable the identification of patients at risk of recurrent disease.

The formulation of an International Prognostic Index (IPI) has provided a widely accepted set of criteria to predict the evolution of aggressive lymphomas and thus to design appropriate therapies (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993).

IPI delineates DLB-CL patients with low (L), low-intermediate (LI), high-intermediate (HI), and high (H) risk disease, and associated differences in overall survival.

IPI takes into account factors that are mostly linked to the patient's characteristics or to the disease extension and growth, including age, lactate dehydrogenase level, performance status, clinical stage, and number of extranodal sites.

However one limitation of this prediction strategy is that IPI does not encompass molecular abnormalities of tumor cells, which can lead to different clinical outcomes in patients within the same group defined by IPI.

Molecular abnormalities of the cell death-cell viability balance, as reflected in *bcl-2*

overexpression or *p53* mutation, have emerged as important prognostic indicators of DLB-CL.

Survivin, a member of the inhibitor of apoptosis gene family has been recently identified as a candidate molecule involved in the apoptotic balance (Ambrosini *et al.* 1997). Recent studies demonstrate that survivin expression influenced unfavorably overall survival, but had no effect on the response to treatment, being a new independent prognostic factor of poor outcome in DLB-CL (Adida *et al.*, 2000).

The newly identified B-aggressive lymphoma (BAL) gene encodes a protein that is significantly more abundant in high-risk DLB-CLs than in low-risk tumors (Aguiar *et al.*, 2000). BAL overexpression increases the rate of migration of B-cell lymphoma transfectants, suggesting that the risk-related protein may promote the dissemination of high risk DLB-CL.

Treatment

Although approximately 40% of DLB-CL can be cured with standard therapy, the majority of adult patients will ultimately die of their disease. Approximately 50% of patients relapse after treatment and succumb to recurrent lymphoma.

A comprehensive experience in the management of clinically aggressive NHL has been accumulated internationally, and a multitude of treatment protocols have been developed and successfully applied. The different treatment approaches include:

Chemotherapy with or without radiation therapy for stage I disease.

Multiagent doxorubicin-containing chemotherapy regimen for stages II through IV:

- MBACOD (doxorubicin, cyclophosphamide, bleomycin, methotrexate, Deadron).
- ACVB (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone).

In pediatric patients large B-cell diffuse lymphomas are treated with the same regimes used for treatment of the other B NHL (Burkitt type). The most extended therapeutic regimes in pediatrics are:

- Total B (St. Jude Children's Research Hospital)
- BFM 86
- LMB 89 (SFOP)

Overall survival with these regimes is over 60-70%, depending on the initial stage of the disease. The reported event free survival (EFS) of patients treated by the Spanish Cooperative Group (SHOP), using de LMB89 protocol is 0.77 ± 0.12 .

For second-line therapies, a variety of combination regimes such as ifosfamide, methotrexate, and etoposide or dexamethasone, cytarabine, and cisplatin can induce second remissions.

- VIM3 (mitoxantrone, ifosfamide, methyl-GAG, Vehem, prednisone, methrotexate)
- VIM (mitoxantrone, vepesid, methrotexate)

Autologous bone marrow transplantation in chemotherapy-sensitive relapsed disease.

Chemotherapy administered at the standard doses is rarely effective to cure patients with relapsed or refractory diffuse LDB-CL. High-dose chemotherapy or radiation therapy followed by autologous or allogeneic bone marrow transplantation can cure some patients.

Further candidate gene and/or positional cloning approaches should help identifying additional genes mapping to the amplified chromosomal regions identified, thereby providing new clues to the genetic basis of progression and clinical behavior of DLB-CL.

Molecular targeting of *bcl-2* and survivin improved disease *in vivo* and caused spontaneous apoptosis *in vitro*, thus suggesting that manipulation of this antiapoptotic pathway may offer a potential therapeutic strategy to achieve stable remission in lymphoma (Li *et al.* 1998, 1999).

Survival

The survival of patients with DLB-CL is both age- and stage- dependent. Even in patients with advanced disease, about 30% to 60% may have prolonged survival with effective combination chemotherapy regimens.

Up to 80% of patients who present with minimal disease at diagnosis can be long-term disease free survivors.

After patients achieve complete remission with an aggressive combination of chemotherapy regimens, 30-50% eventually suffer a relapse. Most relapses occur within the first 2 years after therapy has been finished.

Patients who remain in complete remission for more than 2 years have 70% to 90% probability of being cured.

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