Small cell B-cell lymphoma

Michiel van den Brand

J Han JM van Krieken

Abstract

The group of small cell B-cell lymphomas accounts for approximately half of all B-cell lymphomas. Although most of the small cell B-cell lymphomas can be classified reliably, difficult differential diagnoses remain. This review discusses the pathological diagnosis of the most common small B-cell lymphomas in the lymph node. Remaining differential diagnostic difficulties are discussed in relation to recent research efforts that are or might become helpful to resolve these remaining difficulties. Particular attention is paid to large-scale sequencing efforts and their effect on our understanding of disease pathogenesis and their value for both diagnosis and prognosis.

Keywords B-cell chronic lymphocytic leukaemia; B-cell lymphoma; classification; follicular lymphoma; histopathology; mantle cell lymphoma; marginal zone B-cell lymphoma

Introduction

The group of small cell B-cell lymphomas accounts for approximately half of all B-cell lymphomas. In contrast to aggressive B-cell lymphomas that typically present with a rapidly growing mass and B symptoms, most patients with small cell B-cell lymphomas present with painless lymphadenopathy without B symptoms. The indolent behaviour of the small cell B-cell lymphomas is reflected by a clinical course that is usually protracted. Because these lymphomas are slowly proliferating, they also tend to respond poorly to treatment and are generally considered incurable. Mantle cell lymphoma (MCL) has been considered the odd one out in the group of small cell B-cell lymphomas with a more aggressive clinical course and incurability. However, also for MCL, indolent subgroups are now emerging (discussed below).

This review discusses the pathological diagnosis of small cell B-cell lymphomas in the lymph node, with particular attention to recent insights from large-scale sequencing efforts.

B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma

Definition

B-cell chronic lymphocytic leukaemia and small lymphocytic lymphoma (B-CLL/SLL) represent different manifestations of the same disease entity, but with a different anatomical distribution. B-SLL is diagnosed in the presence of lymphadenopathy and/or splenomegaly, and with $<5 \times 10^9$ lymphocytes per litre in the peripheral blood. A diagnosis of B-CLL is made if the peripheral blood contains $\geq 5 \times 10^9$ lymphocytes per litre.[1]

Morphology

In the lymph node, B-CLL/SLL typically grows in a diffuse pattern with scattered poorly defined lighter areas, referred to as proliferation centres or pseudofollicles. Rarely, B-CLL/SLL shows a perifollicular, interfollicular or marginal zone growth pattern.[2] At high power in the typical growth pattern, the darker areas contain a monotonous infiltrate of small B-cells with round nuclei with a coarse chromatin structure. The proliferation centres contain additional medium-sized cells with nucleoli (prolymphocytes) and large cells with prominent central nucleoli (paraimmunoblasts). It is in these proliferation centres that the majority of cell divisions take place. The percentage of prolymphocytes and paraimmunoblasts is variable and high numbers of prolymphocytes in the peripheral blood ($>15 \times 10^9$/litre) are associated with a worse outcome. An 'atypical variant' of CLL/SLL is recognised as well, in which typical tumour cells are admixed with cells showing plasmacytoid features or cells with cleaved nuclei. This atypical variant also carries a worse prognosis. The presence of cells with the morphology of Hodgkin and Reed–Sternberg cells is a rare but well recognised phenomenon in B-CLL/SLL. A diagnosis of progression to Hodgkin lymphoma or of composite Hodgkin lymphoma and B-CLL/SLL should only be made if the typical inflammatory background of Hodgkin lymphoma is present.

Immunophenotype

The typical immunophenotype of B-CLL/SLL is that of a mature B-cell with expression of pan B-cell markers. CD20 typically shows dim expression. The large majority of B-CLL/SLLs are positive for CD5; most studies report a small subset of CD5-negative B-CLL/SLL, but a study on CD5-negative B-cell lymphomas showed that these can only rarely be classified as B-CLL/SLL.[3] CD23 is positive in approximately 90% of CLL/SLL, but flow cytometry is more sensitive for CD23 expression than immunohistochemistry. CD10 is only rarely expressed; cyclin D1 is virtually always negative. Positivity for lymphoid-enhancer-binding factor 1 (LEF1) has recently been reported to be both highly sensitive and specific for B-CLL/SLL in the differential diagnosis with other low-grade B-cell lymphomas.[4]

Cell of origin

The cell of origin has been the subject of considerable debate. Historically, B-CLL/SLL was thought to derive from naive B-cells, but the fact that B-CLL/SLL carries signs of antigen exposure does not fit with this hypothesis. The subsequent hypothesis that B-CLL/SLL derives from memory B-cells was recently challenged by a study that showed a CD5+ B-cell subset in the peripheral blood of human adults with an expression pattern resembling B-CLL/SLL.[5] Moreover, they detected subsets of CD5+ B-cells with both mutated and unmutated IGHV regions, corresponding to the mutated and unmutated subsets of B-CLL/SLL discussed below.

Prognosis

Although B-CLL/SLL represents a single disease entity, it shows a very heterogeneous disease course, varying from a nearly normal

Michiel van den Brand *MD Pathology Resident, Radboud University Medical Center, Nijmegen, The Netherlands. Conflicts of interest: none declared.*

J Han J M van Krieken *MD PhD Pathologist and Head, Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands. Conflicts of interest: none declared.*

life expectancy to an aggressive disease course. A myriad of prognostic markers has been proposed and only the most significant ones will be discussed here. Clinical staging according to Rai and/or Binet is widely used to stratify patients into prognostic groups, based on the presence of lymphadenopathy, splenomegaly, anaemia, and thrombocytopenia. Although the clinical relevance of these staging systems has been shown repeatedly, significant heterogeneity remains within groups, particularly for the early stages. Therefore, to further refine prediction of the disease course, multiple tumour characteristics have been studied for their prognostic value. An unmutated status of the variable region of the immunoglobulin heavy chain locus (IGH), defined as >98% resemblance to the closest germline sequence, is associated with a shorter survival time. Expression of zeta chain-associated protein kinase 70 (ZAP-70) was initially identified as a surrogate marker for an unmutated IGH status, but subsequent studies showed that its expression also has prognostic value independent of IGH mutational status. Expression of CD38 was also shown to be associated with a worse prognosis. Cytogenetic features also correlate with prognosis; deletions of 13q14 are associated with low-risk disease, while deletions of 11q22-23 and 17p13 are associated with high-risk disease. More recently, whole genome and whole exome sequencing efforts have identified recurrent mutations in B-CLL/SLL. Although few recurrent mutations were recognised, these do appear to have an impact on prognosis. *NOTCH1*, *SF3B1*, *BIRC3* and *TP53* are among the most frequently mutated genes in B-CLL/SLL and are associated with a worse prognosis compared to wildtype.[6] Also, mutations in these genes are associated with resistance to fludarabine-based chemotherapy regimens.

Considering the multitude of prognostic markers proposed, the challenge will now be to translate this into a comprehensive prognostic model. Rossi and colleagues made a first step to this end by constructing and validating a prognostic model based on mutations and cytogenetics, which separated patients into four prognostic groups.[7] Clonal evolution from lower to higher risk groups was associated with the emergence of mutations in *NOTCH1*, *SF3B1* or *BIRC3*.

Follicular lymphoma

Follicular lymphoma (FL) is the most common type of small cell B-cell lymphoma, accounting for approximately 30% of all B-cell lymphomas. It is considered the prototype of indolent B-cell lymphomas, being generally incurable and characterised by waxing and waning disease with slow progression. Despite this generally indolent behaviour, approximately 3% of patients per year show progression to more aggressive disease, which is associated with a median survival of less than 2 years.

Clinically, patients typically present with widespread lymphadenopathy. The median age at presentation is 60 years, but patients can present at a wide age range. The follicular lymphoma international prognostic index (FLIPI) was developed to predict patient outcome by looking at age, stage, haemoglobin, LDH, and the number of nodal sites involved. Although in recent years significant advances have been made in understanding the pathogenesis of FL, clinical decision-making is still largely based on clinical features. The coming years will teach us if the increased knowledge on FL pathogenesis will be translated to improvements in patient care.

Morphology

Follicular lymphoma resembles the normal germinal centre both morphologically and immunohistochemically. Most cases show a follicular growth pattern, at least in part of the tumour. A predominantly diffuse growth pattern is rare and does not seem to affect prognosis. A subset of FLs shows a marginal zone growth pattern with follicles surrounded by marginal zones. These marginal zones are composed of tumour cells with a monocytoid appearance. Other morphologic variants include a floral, signet ring, and epithelioid variant. Hodgkin and Reed–Sternberg (HRS) cells are sometimes encountered, but a diagnosis of composite FL and Hodgkin lymphoma should only be made if the HRS cells are present in the mixed inflammatory background typical of Hodgkin lymphoma.

The neoplastic follicles of FL can be distinguished from their normal counterparts by their lack of polarization, tingible body macrophages, and mantle zones. Whereas normal germinal centres are highly organised structures, this organization is lacking in FL where the random admixture of centrocytes and centroblasts imparts an unstructured appearance. Although tingible body macrophages are almost always absent in FL, follicular dendritic cells and follicular T-helper cells typically remain in follicular lymphomas. Also, more inconspicuous macrophages are present. This microenvironment of FL is thought to be of major importance for the growth and survival of FL cells, and for suppression of the antitumour immune response.[8]

Grading

Follicular lymphomas are graded according to the average number of centroblasts present per high power field (hpf defined as 0.159 mm^2). This should be the average of at least 10 follicles that are representative of the tumour (i.e. not selected for the highest number of centroblasts). Low-grade FL on average contains 15 or fewer centroblasts per hpf. Low-grade FL is further subdivided into grade 1 (0–5 centroblasts/hpf) and grade 2 (6–15 centroblasts per hpf), but these two grades are generally taken together as low-grade FL as no important clinical differences exist between grade 1 and grade 2 FL. Grade 3 FL contains more than 15 centroblasts per HPF and is further subdivided in grade 3A, in which centrocytes are still present, and grade 3B, in which the neoplastic follicles are made up of solid sheets of centroblasts (Figure 1). Note that only low-grade FLs are allowed to have a diffuse growth pattern; areas of diffuse growth in a grade 3 FL are classified as diffuse large B-cell lymphoma.

Proliferative activity as indicated by the percentage of Ki67 positive cells correlates strongly with FL grade. However, some low-grade tumours show high proliferative activity (≥30%) and this is associated with more aggressive behaviour. It is advisable to mention this high proliferative activity in the report (e.g. low-grade (grade 1–2) FL with high proliferative activity).

Differentiation between grade 1–2 and 3A is controversial. The largest study to date showed no significant differences in clinical course between grade 1–2 and grade 3A FLs.[9] In the same study, FL grade 3B showed a behaviour similar to DLBCL with aggressive, but curable disease.