

Leukaemia Section

Mini Review

Marginal Zone B-cell lymphoma

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Clinics and pathology

Disease

Marginal zone B-cell lymphoma (MZBCL), including three distinct clinicopathological forms (Harris et al., 1999), namely:

- 1- extra-nodal MZBCL of mucosa-associated lymphoid tissue (MALT) type;
- 2- splenic MZBCL, corresponding to splenic lymphoma with villous lymphocytes (SLVL);
- 3- nodal MZBCL.

Phenotype/cell stem origin

The morphologic and phenotypic characteristics of malignant cells correspond to those of lymphocytes belonging to the marginal zone, harbouring hypermutated IgV genes with the following immunophenotype:

Pan-B+; CD5-/+; CD10-; CD23-; CD11c+/-; cyIg+(40% of the cells), sIgM+ bright; sIgD-.

Epidemiology

The global incidence of MZBCL in western countries is approximately 10% of all non Hodgkin lymphomas (NHL) diagnosed by histologic examination.

Clinics

Extra-nodal MZBCL of MALT type (7% of all NHL) is an indolent disease involving most often the stomach, where it usually follows chronic gastritis due to *Helicobacter pylori* (HP) infection. The disease may also localize in the lung, the thyroid, the salivary gland, the orbit.

Splenic MZBCL (1% of all NHL on histologic samples) usually, though not invariably, presents splenomegaly associated circulating villous lymphocytes and BM involvement. It runs an indolent course.

Nodal MZBCL (2% of all NHL) is a low-grade lymphoma, frequently presenting with advanced-stage disease, but not with large masses. Early relapse after chemotherapy may be observed in some patients and survival is shorter than in MZBCL of MALT type. All subsets may transform into a high grade lymphoma.

Pathology

The tumour consists of a cytologically heterogeneous infiltrate including centrocyte-like cells, monocytoid B-cells small lymphocytes and plasma cells. Large cells and/or blast-like cells may be present. In epithelial tissues (i.e. stomach) typical lymphoepithelial lesions are characteristically seen. In the spleen, involvement of the mantle zone and marginal zone of the white pulp occur, usually centered around a residual germinal centre. The red pulp is usually involved.

Treatment

Low grade MALT with limited disease involving the stomach is usually HP+ and respond to eradication of the HP infection. Cases presenting at a more advanced stage or with transformation into high grade lymphoma require single-agent or multi-agent chemotherapy. Splenic MZBCL and nodal MZBCL are treated using various forms of chemotherapy depending on the disease stage and patient's conditions. Splenectomy is an option for splenic MZBCL.

Prognosis

The patients usually have prolonged survival, as in other indolent lymphomas, but some cases may feature an aggressive disease.

Cytogenetics

Cytogenetics morphological

The most common anomalies in extra-nodal MZBCL of MALT type include:

The t(11;18)(q21;q21) / API2 - MLT fusion, having a 20-50% incidence. The translocation is an almost specific finding for low-grade MALT lymphoma. Importantly, this translocation was associated with resistance to HP eradication therapy.

The translocation t(1;14)(p22;q32) and/or the corresponding deregulation or rearrangement of BCL10 at 1p22 is another recurrent chromosome aberration in a minority of cases (6% by molecular genetics, including cases with BCL10 mutations and small deletions not detectable by cytogenetics) and it appears to be more frequent in high grade-MALT than in low grade MALT lymphoma.

Trisomy 3 and trisomy 18 were reported in low-grade as well as high-grade MALT lymphoma. FISH studies found a 20-60% incidence for +3, the difference being possibly accounted for by the variable sensitivity of methods adopted in different studies and by heterogeneity of patient populations. At the present time, there is no evidence that +3 plays an important role in disease progression. Trisomy 18 was observed more frequently in high grade MALT than in low grade MALT lymphomas.

The most common anomalies in splenic MZBCL include:

7q deletions or unbalanced 7q translocations, usually involving a relatively large segment, centred around the 7q22-q32 region. The incidence is 10-30%, but as many as 40% of the cases may harbour a sub-microscopic deletion of this region,

Total or partial trisomy 3, involving the 3q21-23 and 3q25-29 chromosome regions. The incidence of +3q falls in the 30-50% range,

Total or partial trisomy 12, found in 20-30% of the cases,

17p- involving the p53 gene, found in 10-30% of the cases. This aberration is associated with a more aggressive clinical course,

A recurrent translocation t(11;14)(p11;q32) is found in a minority of cases featuring a relatively aggressive disease with PB involvement by a blast-like cell component,

The classical t(11;14)(q13;q32) was found in some cases of splenic lymphoma with villous lymphocytes (Oscier et al., 1993), but more recent studies did not detect this translocation in histologically documented splenic MZBCL,

Nodal MZBCL

At the present time there is insufficient data to establish whether nodal MZBCL has a distinct cytogenetic profile. Trisomy 12 may be more frequent in nodal MZBCL, but there is evidence that this disease subset may share clinicopathologic and cytogenetic features with other forms of MZBCL.

In the 3 principal clinicopathological subsets of MZBCL, BCL6 rearrangements were documented to occur in a minority of cases, especially in the presence of a high-grade component.

Probes

The most frequently occurring DNA gains or losses which can be studied by interphase/metaphase fluorescence in situ hybridisation (FISH) are the following:

Deletions: a 5cM segment at 7q31, defined by the D7S685 and D7S514 markers; 17p/p53.

Total/partial trisomies: 3q21-23; 3q25-29; 5q13-15; 12q15-21.

BCL6 rearrangements and the API2-MLT fusion, encoded on the derivative chromosome 11 resulting from the t(11;18)(q21;q21), can be studied by FISH as well as by molecular genetic methods.

BCL10 rearrangements associated with the t(1;14) can be detected by Southern blotting, whereas mutations or small deletion not associated with the t(1;14) can be studied by PCR-SSCP analysis and gene sequencing.

Genes involved and proteins

Note

Oncogenesis:

API2 is an inhibitor of apoptosis, but the role in lymphomagenesis of API2-MLT fusion is unknown.

The physiologic role of MLT is unknown;

BCL10 is a pro-apoptotic gene and the different forms of rearrangements demonstrated in lymphomas may act through a loss-of-function mechanism;

P53 is a key tumour suppressor gene having an established role in disease progression in a number of hematologic and extra-hematologic neoplasias.

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