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Leukaemia Section

Mini Review

Mucosa-associated lymphoid tissue (MALT) lymphoma

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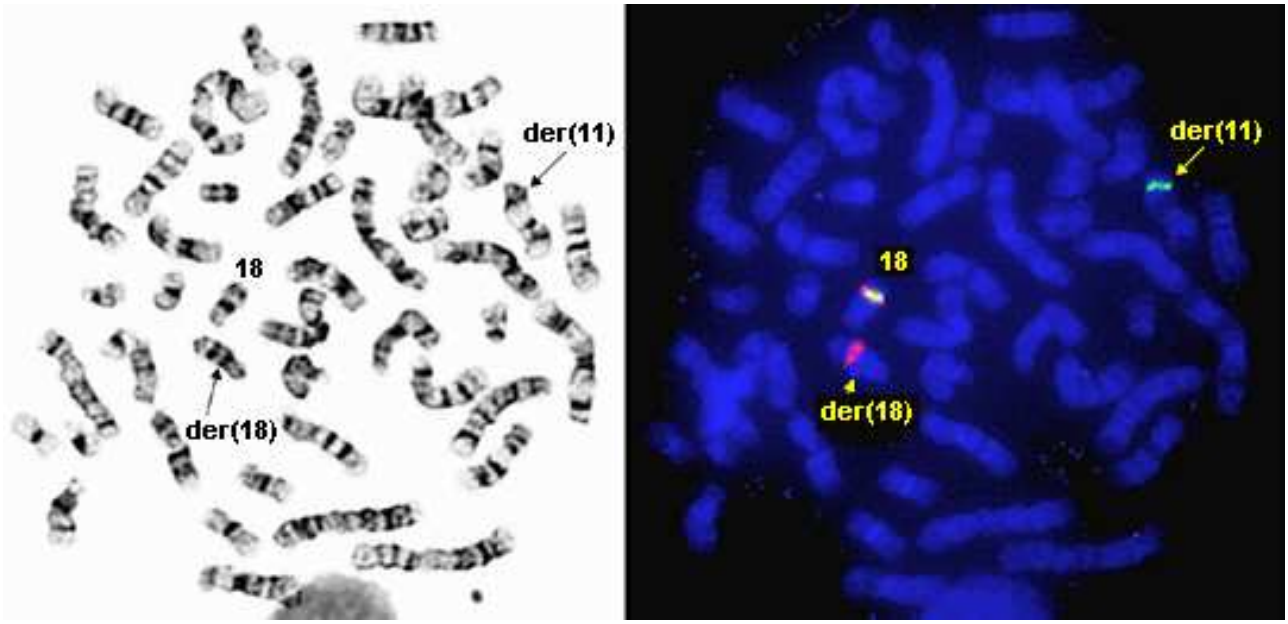

t(11;18)(q21;q21) FISH - Courtesy Charles Bangs, Ilana Galperin.

Clinics and pathology

Disease

MALT lymphoma is the extra-nodal presentation of marginal zone B-cell lymphomas (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 incidence of extra-nodal MZBCL of MALT type in western countries is approximately 7% of all NHL diagnosed by histologic examination.

Clinics

Extra-nodal MZBCL of MALT type 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 and in the orbit, where an association was documented with Chlamydia Psittaci infection.

AS with other clinicopathological forms of MZBCL (i.e. splenic MZBCL and nodal MZBCL) transformation into high grade lymphoma may occur.

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. Typically, lymphoepithelial lesions are seen in the stomach.

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. Rituximab (anti-CD20 monoclonal antibody) is an effective treatment. Gastrectomy is indicated in non-responding patients.

Prognosis

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

Cytogenetics

Cytogenetics molecular

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 associated with low-grade MALT lymphoma of the stomach, and of the lung. Importantly, this translocation was associated with increased rates of persistent disease or recurrence after HP eradication therapy.

The translocation t(14;18)(q32;q21)/IgH -MLT1 fusion, leading to enhanced MLT1 expression may occur in 10-20% of all MALT lymphomas. It is associated with MALT lymphoma of the liver, skin, ocular adnexa, lung and salivary gland. It was not found in MALT lymphomas of the stomach, intestine, thyroid, or breast.

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.

The t(3;14)/IgH- FOXP1 fusion may occur in 10% of all MALT lymphomas. It is associated with MALT lymphoma of the orbit, of the thyroid and skin, whereas it was not found in MALT lymphoma of the stomach, of the salivary gland and in other forms of MZBCL.

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.

BCL6 rearrangements were documented to occur in a minority of cases, especially in the presence of a high-grade component.

Probes

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

IgH-FOXP1 and IgH-MLT1 fusions can be studied by FISH.

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.

Results of the chromosomal anomaly

Fusion protein

Oncogenesis

MALT1 overexpression and API2-MALT fusion confer constitutional NFkB activity. This, in turn, leads to enhanced proliferation and resistance to apoptosis by B lymphocytes.

BCL10 functions in conjunction with intracellular proteins (Carma1 and MALT1), producing the ubiquitination of NFkB inhibitor, leading to NFkB activation. These findings, along with the documented role of BCL10 in promoting survival of antigen-stimulated lymphocytes, suggest the IgH/BCL10 translocation may contribute to lymphomagenesis by enhancing BCL10 function.

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