**Leukaemia Section**

**Review**

**del (13q)**

Edmond SK Ma, Thomas SK Wan

Hematology Division, Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong, P.R. China (ESKM, TSKW)

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### Identity

Partial karyotype in 2 cases of AML with del(13q): Left panel: Relapsed AML in a 17-year-old man; Right panel: Acute monoblastic leukaemia in a 31-year-old woman at diagnosis. G-banding with trypsin / Giemsa.

### Clinics and pathology

**Disease**

**Myeloid disorder**

Among myeloid malignancies, deletion 13q is encountered in myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and myeloproliferative disorders (MPD). The deletion is described as interstitial in most cases although a few cases of terminal deletion are reported.

A survey of 640 patients with primary MDS showed that del(13q) was rare, and existed as the sole abnormality in 2 cases of refractory anaemia. Besides de novo MDS and AML, del(13q) was also reported in therapy-related MDS. In a series of 137 cases of therapy-related MDS and AML, del(13q) was detected in 3 cases of the former group but not the latter. Moreover, del(13q) was detected in 2 out of 55 patients with unexplained cytopenia and clonal cytogenetic abnormalities in bone marrow cells but without definite morphological evidence of dysplasia, which might be a harbinger of MDS.

With respect to MPD, del(13q) appeared to be more common in chronic idiopathic myelofibrosis, and was also detected in post-polycythaemic myelo-fibrosis. A high prevalence of chromosome 13q deletion or translocation was reported as a second aberration in chronic myeloid leukaemia (CML) with persistent or relapsed disease after bone marrow transplantation. In 6 such CML patients, a common region of deletion at 13q12-14 was identified by fluorescence in-situ hybridization (FISH) with a panel of 13q YAC clones. Interestingly, del(13q) was detected in aplastic anaemia and these patients showed hypoplastic bone marrow without morphological dysplasia.

**Cytogenetics**

**Morphological Cytogenetics:** Characterization of del(13q) in 20 patients with myeloid malignancies, including MPD, AML and MDS patients, showed that the deletions consistently involved region 13q14 - 21 by conventional G-banding assessment.

Molecular alterations of 13q may be more common than is suggested by conventional cytogenetics. First, loss of heterozygosity (LOH) at the RB1 locus, which maps to 13q14, has been observed in 15 out of 39 patients with BCR-ABL negative MPD patients, with an over-representation in chronic idiopathic myelofibrosis.
in chronic idiopathic myelofibrosis and polycythaemia vera patients without 13q abnormality on conventional cytogenetics. These show that 13q deletions may occur as a sub-microscopic lesion only detectable with molecular techniques such as LOH study and FISH. Molecular Cytogenetics: In a series 20 patients with myeloid malignancies, FISH analysis with a panel of DNA probes for 13q13.1-14.3 delineated a common deleted region that was flanked by YAC 833A2 and YAC 854D4. Subsequent study on one case of 13q translocation with accompanying cryptic 13q deletion allowed the genomic segment to be narrowed down to around 4 cM that included YAC 937C7, RB1 and YAC 745E3. This overlaps with the critical deleted segment in CLL which is limited by RB1 and D13S25 markers. A number of genes lie within this region and include RB1, CHCIL and RFP2. Despite initial report of RB1 abnormality in MDS and AML, subsequent reports failed to shows RB1 rearrangement in myeloid malignancies. In one series involving 39 cases of BCR-ABL negative MPD, the RB1 gene displayed a germline configuration in all, suggesting that 13q deletions most probably affect a tumour suppressor locus distinct from RB1. No mutations in candidate genes have been identified in any of the lymphoid neoplasms as well. Prognosis Unlike the lymphoproliferative disorders in which del(13q) shows prognostic significance, for example associating with the longest survival in chronic lymphocytic leukaemia when compared with other chromosomal changes, no data are yet available for the prognostic outcome of del(13q) in the myeloid disorders. Aplastic anaemia with del(13q) appears to be clinically benign. In a series of 9 cases, 6 responded to immunosuppressive therapy while the other 3 improved with steroids. None of these patients developed acute leukaemia. These findings indicated that aplastic anaemia with del(13q) resembled bone marrow failure syndrome without cytogenetic abnormalities rather than preleukaemia. Concurrent with this notation was the report of spontaneous clinical and cytogenetic remission in an aplastic anaemia patient with del(13q).

Disease Lymphoid disorder Del(13q) involving the band q14 occurs frequently in B-cell chronic lymphocytic leukaemia (CLL), being detectable in 8 - 10% of patients by conventional cytogenetics and up to 40 - 50% of patients by FISH. The deletion may occur in isolation or associated with other recurrent cytogenetics abnormalities including +12, del(11q), del(6q) and del(17p). In a large survey of 325 patients with CLL by FISH, del(13q) was the commonest genetic aberration, detected in 55% of cases, and correlated with the longest survival of 92 months. The subcategory of isolated del(13q) was also associated with the longest median survival time of 133 months. Subsequent investigations showed the presence of del(13q) in other non-Hodgkin's lymphoma (NHL), including both low grade and aggressive lymphoma. A preferential association with mantle cell lymphoma was suggested. It was also reported in 37 out of 74 cases (50%) of splenic lymphoma with villous lymphocytes in one study. More recently, del(13q) was recognized as a common genetic lesion in multiple myeloma. Cytogenetics and FISH studies detected the presence of del(13q) in 20 - 86% of myeloma, usually within the 13q14 region. The deletion may occur as an early event in the development of monoclonal gammapathies and possibly be involved in evolution of monoclonal gammapathy of uncertain significance (MGUS) into overt myeloma. A long-term follow up study on MGUS showed presence of deletion 13q14 as detected by FISH in 5 out of 18 cases, and all progressed to myeloma within 6 - 12 months after identification of the cytogenetics abnormality.

Cytogenetics Morphological Cytogenetics: The deletion in CLL, NHL and myeloma uniformly involves 13q14. Commonly used FISH probes to detect the deletion in the lymphoid disorders are chromosome 13q14 specific, including RB1, D13S319 and D13S25. Molecular Cytogenetics: The most commonly deleted marker in CLL and NHL initially reported was D13S319, between the retinoblastoma locus and D13S25 locus. The 13q14 deletions usually do not lead to inactivation of the RB1 gene, and del(13q) is associated with the presence of one intact RB1 gene on the homologous chromosome, implying the role of an adjacent locus that may harbour important tumour suppressor gene(s). However, the pathogenesis of splenic lymphoma with villous lymphocytes may be different. In one study, 13q14 deletion was identified in 50% of SLVL cases, in which 47% showed monosomatic loss of RB1, 12% showed hemizygous D13S25 deletion, and cases that displayed both RB1 and D13S25 deletion. It follows therefore that allelic loss of RB1 may indeed play a role in the patho-genesis of SLVL. A recent study on critically deleted region (CDR) at 13q14 in with three probes for 13q14 (RB1, D13S319, and D13S25) showed deletions in 29 out of 82 (35.4%) cases. Subsequently, contiguous YACs, PACs, and a BAC spanning the 13q14-q21 region were employed for deletion mapping in addition to a 13q telomere probe. Large deletions extending to the 13q34 region were found in 55% of the deleted cases, whereas an additional 13.8% showed loss of both 13q34 and 13q14 regions with retention of 13q21. A CDR of approximately 350 kb was identified at 13q14 with the proximal border approximately 120 kb centromeric
from D13S319, encompassing an area rich in expressed sequence tagged sites and containing DLEU1, DLEU2, and RFP2 genes. While direct sequencing of the RFP2 gene revealed no mutations in six patients and four myeloma cell lines harboring deletions of the CDR, a role for RFP2 in the pathogenesis of myeloma cannot yet be excluded.

**Prognosis**

Sole deletion of 13q14 is associated with a more favourable clinical outcome in CLL, with a reported median survival time of 133 months for this particular cytogenetics subgroup. However, among NHL in general, del(13q) is associated with presence of splenomegaly, peripheral blood dissemination, lower probability of attaining complete remission and a shorter survival. In myeloma, deletion of 13q14 also predicts an adverse prognosis. A recent FISH study on myeloma showed deletion of Rb gene in 48 out of 104 patients (46.2%), and deletion of D13S319 locus in 28 out of 72 patients (38.9%). Myeloma patients with 13q14 deletion were more likely to have stage III disease, high serum levels of b2-microglobulin, and a higher percentage of bone marrow plasma cells than patients with normal 13q14 status on FISH analysis. The presence of 13q14 deletion on FISH analysis was associated with a significantly lower rate of response to conventional-dose chemotherapy and a shorter overall survival than in patients without the deletion.

**References**


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