Malignant Lymphomas

Atypical cytogenetic presentation of t(11;14) in mantle cell lymphoma

Eighteen cases of mantle cell lymphomas (MCL) with an atypical t(11;14) were studied using fluorescence *in situ* hybridization experiments (FISH). The atypical presentation was confirmed and unsuspected duplicated cases were identified in six patients. These data underline that FISH analysis must be be systematically performed in cases with an aberrant presentation to prevent a misdiagnosis.

haematologica 2005; 90:1708-1709
(*http://www.haematologica.org/journal/2005/12/1708.html*)

Conventional karyotypic analysis of patients with mantle cell lymphoma (MCCL) usually demonstrates the presence of the t(11;14) in 70 to 75% of cases. When FISH studies using specific probes are performed, the abnormality is identified in virtually all cases.[1] Up to now, rare cases of masked t(11;14) have been described.[2-4] The present data, based on conventional karyotypic analysis of 103 MCL patients with clonal abnormalities, reports 18 cases with an atypical pattern. Diagnoses were established according to the WHO classification. Cytogenetic studies, conducted at diagnosis and prior to therapy, were performed as previously reported and abnormalities were described according to the ISCN Nomenclature.[5] FISH experiments using the IgH/CCND1 dual color probe set (Vysis, Downer's Grove, IL, USA) were performed on fixed cells according to standard methods. This probe set is a mixture of IgH (14q32 - Spectrum Green) and CCND1 (11q13 - Spectrum Orange) probes. As a result of the translocation two fused orange-green signal are identified (der(11) and der(14)), in addition to one orange and one green signals (homologous chromosomes 11 and 14). According to the karyotypic presentation of the translocation, three groups of patients were defined (*Table 1, see online appendix*): group 1, demonstrating unidentifiable material on the long arm of the der(14); group 2, displaying additional material on the short arm of the der(14); and group 3 demonstrating insertion of the translocation within an extra chromosome. In all cases, the derivative chromosome 11 was identical to the der(11) observed in the classical presentation. Because of tetraploid metaphases, two der(14) were observed in two patients (nos.14 and 15). Metaphase FISH analysis, applied to an average of 10 to 15 metaphases per case, was performed in all but two patients (nos. 12 and 14) for whom no abnormal mitosis were available. Two fused signals were observed in 12 patients whereas one patient with tetraploid metaphases (no. 15) has four orange/green signals. In one case (no. 8) a large additional green signal corresponding to overrepresented IgH sequences was located on the der(14), confirming the der(14)t(11;14;14) (Figure 1A). In three patients (nos. 3, 7 and 18) a third CCND1/IgH fusion signal was identified. This additional signal was located on the der (14) in two patients (nos. 3 and 7) and on the normally looking homologous chromosome 14 in the third case (no. 18) (Figures 1 B,C). Four fused signals were observed in one patient (no. 11), located on the der(11), on the der(14) and on two marker chromosomes. Interphase FISH studies confirmed the results in all cases and identified five fused signals in one patient (no. 14). Additional FISH studies using the C-MYC probe (Vysis) confirmed the involvement of chromosome 8q24 on the der(14) in one patient (no. 7). While atypical interphase FISH patterns have

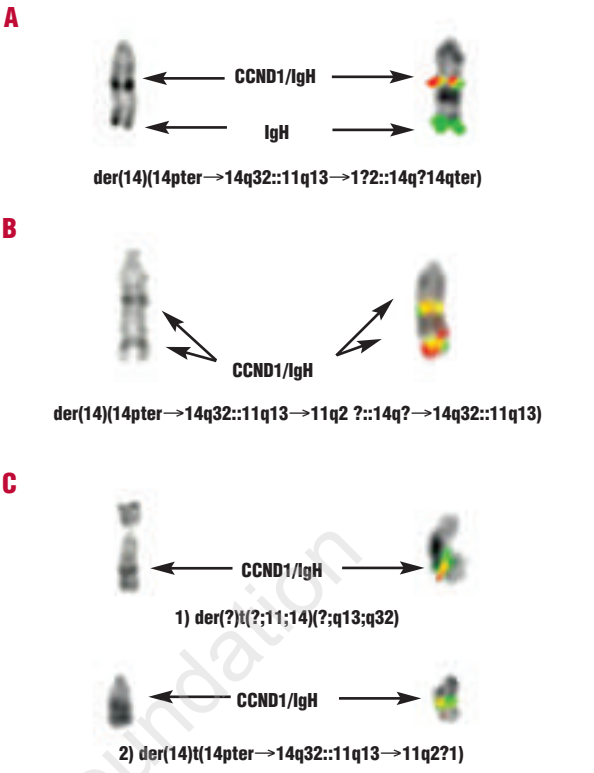

Figure 1. Karyotypic and FISH presentation of three patients with atypical t(11;14). **A.** Patient no. 8 presenting one fused red-orange signal corresponding to the presence of the t(11;14) [small arrow] and a second green signal corresponding to overrepresented IgH sequences [large arrow]; **B.** Patient no. 3 presenting a duplication of the CCND1/IgH sequences (arrows); **C.** patient no. 18, presenting an (1) insertion of the t(11;14) within an extra chromosome and (2) a duplication of the translocation within the apparently normal homologous chromosome 14.

been previously described in MCL, rare cases of complex rearrangements have been documented based on conventional karyotypic analysis.[2,3,4,6] Here we show that atypical t(11;14) presentations are not such infrequent events, occurring in about 17% of MCL patients. This therefore confirms that FISH experiments such be systematically performed in cases with an aberrant karyotype determined conventionally. Among the atypical reported cases, two described the cryptic insertion of CCND1 sequences into the 14q32 region on an apparently normal chromosome 14.[2,3] More recently, a duplication of the CCND1/IgH region was reported in one patient.[4] We observed the same presentations in six patients of the present series. This therefore suggests that unsuspected sub-microscopic or duplicated cases can occur in at least 5% of patients. The small proportion of such presentations in single center series makes it difficult to analyze their prognostic significance. Although the median survival of MCL patients is close to 3 to 4 years, it has been suggested that the presence of three or more chromosomal aberrations in addition to the specific t(11;14) may have a negative impact on survival rate.[7,8] Thus, further multi-center cytogenetic studies are required to ascertain whether patients with an atypical karyotype, determined conventionally, and particularly duplicated cases, experience a more aggressive clinical course, as occurs in chroni0c myeloid leukemias displaying duplications of the Philadelphia chromosome. This approach may facilitate the molecular identification of critical genetic

events associated with disease development and allow a more accurate stratification of patients into prognostic categories.

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Key words: MCL, atypical t(11;14), FISH.

Fundings: this study was supported by grants from la Ligue Nationale contre le Cancer (Comité de la Loire).

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References

1. Li JY, Gaillard F, Moreau A, Harousseau JL, Laboisse C, Milpied N, et al. Detection of the translocation t(11;14)(q13;q32) in mantle cell lymphoma by fluorescence in situ hybridization. Am J Pathol 1999;154: 1449-52.
2. Mohamed AN, Ali W, Kopptich F, Al Katib A. Banded chromosomes versus fluorescence in situ hybridisation in the diagnosis of mantle cell lymphoma: a lesson from three cases. Cancer Genet Cytogenet 2002;136:108-12.
3. Aventin A, Nomdedeu J, Briones J, Espinosa I, Bordes R, Sierra J. Insertion of the CCND1 gene into the IgH locus in a case of leukaemic small cell mantle lymphoma with normal chromosomes 11 and 14. J Clin Pathol 2003;56:798-800.
4. Gruska-Westwood AM, Atkinson S, Summersgill BM, Shipley J, Elnenaei MO, Jain P, et al. Unusual case of mantle cell lymphoma with amplified CCND1/IgH F fusion gene. Genes Chrom Cancer 2002;33:206-12.
5. Callet-Bauchu E, Salles G, Gazzo S, Poncet C, Morel D, Pages J, et al. Translocations involving the short arm of chromosome 17 in chronic B-lymphoid disorders: frequent occurrence of dicentric rearrangements and possible association with adverse outcome. Leukemia 1999;13:460-8.
6. Kodet R, Mrhalova M, Krskova L, Soukup J, Campr V, Neskudla T, et al. Mantle cell lymphoma: improved diagnostics using a combined approach of immunochemistry and identification of t(11;14)(q13;q32) by polymerase chain reaction and fluorescence in situ hybridization. Virchows Arch 2003;442:538-47.
7. Campo E, Raffeld M, Jaffe ES. Mantle cell lymphoma. Semin Hematol 1999;36:115-27.
8. Cuneo A, Bigoni R, Rigolin GM, Roberti MG, Bardi A, Piva N, et al. Cytogenetic profile of lymphoma of follicular mantle lineage: correlation with clinicobiologic features. Blood 1999;93:1372-80.