

Brief report

Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants

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In an attempt to address the issue of cytogenetic features of multiple myeloma (MM) variants, we have analyzed a series of 8 IgM, 9 IgD, 2 IgE, and 14 nonsecretory (NS) MM cases using fluorescence in situ hybridization. A very high incidence (83%) of t(11;14)(q13;q32) was detected in the IgM (7 of 8), IgE (2 of 2), and NS (11 of 14) MM cases, but not in the IgD cases (2 of

9). Of note, no t(4;14) was observed in this cohort of patients. This increased incidence of t(11;14) was associated with 2 dominant features in these variants, namely, a "lymphoplasmacytic" presentation mainly in IgM MM and a lower secretory capacity in the others, 2 features previously associated with t(11;14). Of major interest, t(11;14) was never ob-

served in Waldenström macroglobulinemia or in IgG/IgA "lymphoplasmacytic" lymphomas. Thus, for unknown reasons, t(11;14) is the hallmark of IgM, IgE, and NS MM, (but not IgD MM), with a 5-fold increase of its incidence compared to that of IgG and IgA MM. (Blood. 2003;101:1570-1571)

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Introduction

Most multiple myelomas (MMs) and primary plasma cell leukemias (PCLs) are characterized by the secretion of a monoclonal component, mainly of IgG and IgA types, and less frequently of Bence Jones, that is, light-chains only type. However, in rare cases of MM/primary PCL, other monoclonal components are found in the serum of patients, that is, IgD (1%-2% of the cases), IgM (0.2% of the cases), or IgE (even less frequent).¹ Finally, some patients are characterized by the absence of any detectable monoclonal component, either in the serum or in the urine, and are described as having nonsecretory (NS) MM. To further characterize these MM variants, we have analyzed the chromosomal abnormalities of 8 patients with IgM MM, 9 patients with IgD MM, 2 patients with IgE MM, and 14 patients with NS MM. We report a very high incidence (83%) of t(11;14) in IgM, IgE, and NS MM, but not in IgD MM, in which t(11;14) has the same incidence as that of IgG and IgA MM (16%).²

Study design

Patients with variant isotypes

We analyzed 8 patients with IgM MM, 9 with IgD MM, 2 with IgE MM, and 14 with NS MM. Three patients with IgM MM had hypercalcemia, whereas one patient presented "lymphoma-type" symptoms with liver and spleen enlargement. None of them presented disseminated osteolytic lesions (only one patient displayed 2 osteolytic lesions, whereas 2 others showed only one or no lesion). Apart from the IgM isotype, the cellular features were typically those of myeloma cells, as previously reported.^{3,4} The 9 patients with IgD MM all had typical MM and did not present significant differences with classical MM. The 2 patients with IgE MM had lytic bone lesions. Patients with NS MM (defined by the absence of an M component on serum and urine electrophoreses) did not present any specific feature; 9 of them displayed extensive bone lesions, including 3 patients with

symptomatic hypercalcemia. Approval was obtained from the ethical committees of the University Hospital of Lille and Toulouse institutional review boards for these studies. Informed consent was provided according to the Declaration of Helsinki.

Control population

The results obtained in these MM variants were then compared to those of a control population. This population included 679 patients with IgG, IgA, or light-chains only MM (some have been previously reported),² 16 patients with lymphoplasmacytoid lymphoma (LPL) and IgG or IgM (or both) secretion,^{5,6} and 13 patients with typical Waldenström macroglobulinemia (WM). Samples from all the MM patients were analyzed under similar conditions, including plasma cell separation. Patients with LPL and WM were selected on the basis of availability of frozen bone marrow specimens. After thawing, cells were fixed in methanol/acetic acid (3:1 vol/vol) and dropped on slides.

FISH experiments

All the MM samples have been purified using the Miltenyi technology (anti-CD138-coated magnetic beads; Paris, France), as previously reported.² After purification, plasma cells were fixed, and fluorescence in situ hybridization (FISH) experiments, using probes specific for the chromosome 14q32 rearrangements, that is, t(14q32) and the t(4;14) and t(11;14) translocations were performed. The technique and the probes have been previously published.³

Results and discussion

A high incidence of t(11;14) was observed in IgM, IgE, and NS MM, but not in IgD MM. Indeed, whereas t(11;14) is observed in 16% of all MM and in 2 of 9 (22%) IgD MM cases, FISH analysis of IgM MM revealed *IGH-CCND1* fusion(s) in 7 of 8 cases

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Table 1. Incidence of t(11;14) and t(4;14) within each MM type

Ig type	t(11;14)	t(4;14)
IgG*	15%*	8%*
IgA*	10%*	19%*
Light chains only*	31%*	4%*
IgD (n = 9)	22%	0%
NS, IgM, IgE (n = 24)	83%	0%

*As reported in Avet-Loiseau et al.²

(88%; Table 1). A similar high incidence was observed in IgE MM (2 of 2) and in NS MM (11 of 14; 79%). Overall, t(11;14) was observed in 83% of IgM, IgE, and NS MM cases, a 5-fold increase as compared to IgD and IgG/IgA MM. Of note, none of these patients presented t(4;14): 0 of 33 versus 66 of 679 (10%; $P = .14$). Thus, IgM, IgE, and NS MM present a strikingly higher incidence of t(11;14) than IgD or other classical MM, all these variants lacking t(4;14). A literature survey did not reveal any cytogenetic analysis in variant MM cases, but showed a cryptic t(11;14) in the unique IgE myeloma cell line.⁷ In the control MM population, ie, IgG, IgA, and light-chains only MM, the incidence of *IGH-CCND1* fusions was 15%, 10%, and 31%, respectively. Even though light-chains only MM differ from IgG and IgA MM by a higher incidence of t(11;14), this incidence is incomparable to that observed in the current MM variants.

A “lymphoplasmacytic” morphology and a lower secreting capacity have been recently reported as the only correlations between presenting features and t(11;14) in a large cohort of individuals with MM.⁸ It was of interest to see if such correlations were observed in our current study. As previously emphasized,^{3,4} all IgM MM had a “lymphoplasmacytic” presentation. No slide was available for the 2 IgE MM cases. Bone marrow smears of 8 of the 14 patients with NS MM were available. Interestingly, a “lymphoplasmacytic” morphology was observed in 4 of 8 cases, and especially in 4 of 6 of the t(11;14)⁺ cases. Thus, a “lymphoplasmacytic” morphology is the hallmark of IgM and NS MM at least, but not of IgD MM. Of note, whereas in LPL and WM, malignant cells are essentially lymphoid cells with a plasmacytic inflection, in MM variants, the cells resemble essentially small mature plasma cells, rather than “lymphoplasmacytic” cells, and correspond to the “small cell type” of the Bartl classification.⁹ Finally, the analysis of 16 LPL and 13 WM cases failed to identify any *IGH-CCND1* fusion.

What about the correlation with a lower secreting capacity? Fourteen of these 22 variants were NS MM, thus directly involved in this correlation. On the other hand, in comparison with classical IgG and IgA MM, IgM cases were not low-secreting MM (median serum M component = 64 g/L; range = 14-95 g/L). NS MM presents a special form of sterile plasma cells, characterized by an incapacity to assemble Ig chains.¹⁰ However, from an immunologic viewpoint, they have to be considered as postswitch MM. Of note, an abnormally high (but to a much lesser extent) incidence of t(11;14) is also observed in light-chains only MM.³ A likely hypothesis would be to consider that this MM subclass would be heterogeneous, some of them corresponding to NS (or low-secreting) MM. Careful prospective analyses of light-chains only MM would enable us to answer this question. Interestingly, a high incidence (55%) of t(11;14) has also been reported in systemic amyloidosis, another form of plasma cell dyscrasia characterized by a low but amyloidogenic light-chain production.¹¹ Overall, a plausible hypothesis would be to consider that t(11;14) is mainly observed in clones with small mature cell type or low-secreting features or both.

Until now, the reasons for the specific selection of the 11q13 chromosomal region in the MM variants remain unknown, as it remains unknown in mantle cell lymphoma (MCL), the only B-cell malignancy with 100% of such translocations. Furthermore, the molecular consequences of the up-regulation of the cyclin D1 are totally obscure because patients with t(11;14) do not display a higher proliferative index (personal data and Fonseca et al⁸) and have a better prognosis.¹² This is compatible with the well-documented better prognosis of NS MM,¹³ knowing that the prognosis of IgM and IgE MM is not evaluable (not > 0.2% of the cases). Further experiments, especially using the microarray technology, should enable us to decrypt the molecular changes associated with this specific translocation.

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