IgM myeloma: a rare entity characterized by a CD20−CD56−CD117− immunophenotype and the t(11;14)

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Summary
IgM myeloma is a very rare and poorly defined entity. In a detailed assessment of 10 cases, it was demonstrated that 70% had an aberrant phenotype based on the expression of CD19, CD45, CD27 and Cyclin D1 but all cases lacked CD56 and CD117. Interphase fluorescence in situ hybridization demonstrated deletion 13 in 50% while 5/8 cases assessed had a t(11;14). Despite the high incidence of the t(11;14), CD20 was only expressed in one of nine cases. We conclude that IgM myeloma is a distinctive subset characterized by a CD20−CD56−CD117− phenotype and the t(11;14).

Keywords: IgM, myeloma, immunophenotype, t(11;14), genotype.

Multiple myeloma (MM) is a mature B-cell malignancy characterized by the clonal proliferation of pathological plasma cells in the bone marrow. The majority of MM patients produce a paraprotein (PP) of IgG or IgA type. A PP of IgM type is most commonly associated with Waldenström macroglobulinaemia (WM) and other lymphoproliferative disorders (Kyle & Garton, 1987; Owen et al, 2000). True IgM myelomas are very rare and represent a poorly characterized entity which account for <0.5% of all myelomas (De Gramont et al, 1990) and <0.2% of patients with an IgM PP (Kyle & Garton, 1987; Owen et al, 2000). Only limited immunophenotypic and genotypic data are available for IgM myeloma and some reports have suggested that the clinical and laboratory features are intermediate between those of WM and MM (Haghigi et al, 1998). Therefore, laboratory diagnosis is challenging in such cases. It has been noted that typical clinical features, such as lytic bone lesions in myeloma or organomegaly in WM, are not always present to help with the distinction (Annibali et al, 2006) and therefore additional diagnostic tools are necessary for a definitive diagnosis of IgM MM. As the phenotypic and genotypic features of WM and MM have been better defined over recent years, the purpose of this study was to fully characterize the immunophenotype and genotype of IgM myeloma using flow cytometry, immunohistochemistry and fluorescence in situ hybridization (FISH).

Patients and Methods

Patient characteristics
We retrospectively evaluated the clinical and laboratory data from 10 patients presenting with IgM myeloma between 1997 and 2006. Limited data from three of these patients has been reported (Owen, 2003; Ackroyd et al, 2005). The median age at diagnosis was 71 years (range 54–83 years). A diagnosis of IgM myeloma was made on the basis of IgM paraproteinaemia, bone marrow infiltration by >10% plasma cells and the absence of a B-lymphoid component by morphology, flow cytometry and/or immunohistochemistry.
Flow cytometry

Plasma cell immunophenotyping was performed as previously reported (Rawstron et al., 2002), using CD38, CD138 and CD45 expression for primary gating with a minimum of CD19 and CD56 for characterization in accordance with the European Myeloma Network consensus (Rawstron et al., 2008). B cells were enumerated using Kappa/Lambda/CD19/CD5. Monoclonal antibodies were either purchased from BD Biosciences, Oxford, UK (CD3, CD5, CD19, CD45 and CD56), Serotec, Oxford, UK (CD138) or produced in house (Kappa, Lambda and CD38).

Immunohistochemistry

Expression of the following antigens was determined by using standard streptavidin-biotin techniques: CD20, CD117, IgG/A/M kappa and lambda (all Dako, Glostrup, Denmark), PAX5 (BD Bioscience, Oxford, UK), MUM1/IRF4 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), Cyclin D1 (Lab Vision Corporation, Fremont, CA, USA) and CD27 (Novocastra Laboratories, Newcastle upon Tyne, UK).

Fluorescence in situ hybridization

Cases with available material were initially screened for monosomy 13/13q deletions and IGH rearrangements using 13q14 spectrum red/13q34 spectrum green and LSI IGH dual colour breakapart probe sets (Abbott Molecular Diagnostics, Maidenhead, UK). Cases with an IGH rearrangement were further investigated with the following dual colour dual fusion probe sets: IGH/CCND1, IGH/FGFR3 and IGH/MAF (all Abbott Molecular Diagnostics).

Results and discussion

Morphology and immunophenotype

Myeloma plasma cells are phenotypically distinct from normal plasma cells in their expression of CD19, CD20, CD27, CD45, CD56 and CD117 (Rawstron et al., 2008) but there are very few data in the literature relating specifically to the phenotype of IgM myeloma (Haghighi et al., 1998). Flow cytometric studies were performed in all 10 cases and supplemented by immunohistochemistry in nine. The results are detailed in Table I and Fig 1. All cases were characterized by a morphologically pure plasma cell population on both aspirate smears and trephine biopsies. In those with cellular representative smears, plasma cells comprised a median of 49% (range 14–70%) of bone marrow cells. There was universal expression of the plasma cell markers CD38, CD138 and MUM1/IRF4 and all cases assessed expressed light chain restricted cytoplasmic IgM. There was no evidence of a definable B-cell component either by morphology or CD20/ PAX5 immunohistochemistry. Similarly, B cells identified by

<table>
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<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>PP type</th>
<th>PP level (g/l)</th>
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<th>CD38</th>
<th>CD19</th>
<th>CD56</th>
<th>CD45</th>
<th>CD20</th>
<th>CD27</th>
<th>PAX5</th>
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<th>Cyclin D1</th>
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<td>M</td>
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<td>Normal</td>
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<td>+</td>
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Table I. Clinicopathological features of 10 cases with IgM myeloma.

PP, paraprotein.
flow cytometry on the basis of scatter characteristics and CD19 expression were present in very low numbers (median 2.8%) and were polyclonal with respect to surface light chain expression. An aberrant plasma cell phenotype was demonstrated in seven of 10 cases based on the expression of CD19 (6/10 cases negative), CD45 (4/10 cases negative), CD20 (1/9 cases positive), CD27 (2/6 cases negative), PAX5 (2/8 cases positive) and Cyclin D1 (6/8 cases positive). It was, however, interesting to note that none of the cases assessed expressed either CD56 (n = 10) or CD117 (n = 6). These

Fig 1. Representative immunohistochemistry and FISH images in IgM multiple myeloma (MM) (patient 1 in Table 1). In this example the plasma cell infiltrate is clearly defined by morphology (A), expression of CD138, MUM1 and cytoplasmic IgM (images B, C and D respectively) and absence of PAX5, CD20 and CD117 (images E–G). There is clear expression of Cyclin D1 protein (H) and the t(11;14) is confirmed by FISH (I). In this instance, there was no evidence of deletion 13 (J). Magnifications ×600 (A–H) and ×1000 (I and G).
specific clinicopathological characteristics, in particular the neutral effect on outcome but appears to be associated with a translocation.

While PAX5 expression was noted in two of eight cases (2/5 (R. G. Owen, unpublished data). In this analysis of IgM MM, 53% of standard class switched myeloma with a t(11;14) (2003). In our experience, CD20 and/or PAX5 is expressed in these two studies, the incidence of the t(11;14) appears significantly higher in IgM myeloma compared with standard class switched myeloma. The published incidence of the latter was 7.8–15% (Avet-Loiseau et al, 2003; Dewald et al, 2005) and 6.8% and 15% in our experience (Avet-Loiseau et al, 2006; O’Connor et al, 2007). The t(11;14) has been reported to have a neutral effect on outcome but appears to be associated with specific clinicopathological characteristics, in particular the expression of B-cell antigens CD20 and PAX5 (Robillard et al, 2003). In our experience, CD20 and/or PAX5 is expressed in 53% of standard class switched myeloma with a t(11;14) (R. G. Owen, unpublished data). In this analysis of IgM MM, CD20 was expressed in one of nine cases [1/5 with a t(11;14)] while PAX5 expression was noted in two of eight cases (2/5 with a translocation).

Clinical features and outcome

The median PP concentration in this cohort of patients was 19.4 g/l (range 5.2–87.3 g/l). Four patients had immunoparesis and four patients had monoclonal light chains detectable in their urine. Radiological evidence of bone disease was present in four patients while renal impairment was detected in three but lymphadenopathy and splenomegaly was not documented. Follow-up data were only available in six patients with a median duration of follow-up of 14 months (range 2.4–46 months). However, four patients died at 2.4, 2.9, 4.4 and 45 months after diagnosis. The cause of death in all cases was sepsis. The overall outcome in IgM myeloma remains to be established. Annibali et al (2006) reported four cases of IgM myeloma and reviewed a further nine cases published in the form of case reports since 1998. In all but one case the reported survival was <36 months, suggesting that IgM myeloma may be associated with an inferior outcome compared with IgG/IgA MM.

Conclusions

This study determined a detailed clinicopathological assessment of 10 patients with IgM myeloma. They were characterized by an aberrant plasma cell immunophenotype and a high incidence of genetic changes associated with standard class switched myeloma. The application of plasma cell phenotyping and FISH enabled a clear distinction between IgM MM and WM. However, IgM myeloma appears to form a distinctive subset characterized by a CD20+CD56-CD117- immunophenotype and the t(11;14). The overall outcome of patients with IgM myeloma appears to be poor with a high rate of early death because of sepsis, and this requires further study.

References


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