Multiple myeloma

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Clinics and pathology

Disease

Multiple myeloma (MM) is a malignant monoclonal plasma cell proliferation. Monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma (SMM) are premalignant states susceptible to transform in MM.

Phenotype/cell stem origin

Phenotype of mature terminally differentiated B-cell, but also with CD56 expression, which is not found in normal plasma cells; CD138+ CD38+ CD40+.

Epidemiology

Multiple myeloma’s annual incidence: 30/10^6; i.e. around 1% of malignancies in adults and 10% of hematologic malignancies; mean age: 62 years.

Clinics

Patients may be asymptomatic at the time of diagnosis; bone pain; susceptibility to infections; renal failure; neurologic dysfunctions.

Pathology

MM staging: stage I: tumour cell mass < 0.6 x 10^12/m2; Hb> 10 g/dl; serum calcium ¾ 120 mg/l; no bone lesion; low monoclonal Ig rate (IgG < 50 g/l, IgA < 30 g/l, BJ urine < 4 g/day); stage II: fitting neither stage I nor stage II; stage III: tumour cell mass > 1.2 x 10^12/m2; Hb < 8.5 g/dl and/or serum calcium > 120 mg/l and/or advanced lytic bone lesions and/or high monoclonal Ig rate (IgG > 70 g/l, IgA > 50 g/l, BJ urine > 12 g/day).

Treatment

None before onset of symptoms; chemotherapy or BMT afterwards. Various new therapies, mainly acting by apoptosis induction in MM cells, are or will be involved in clinical trials (thalidomide, proteasome inhibitor PS-341, 2 methoxy estradiol, arsenic trioxide, TNF alpha).

Prognosis

Evolution: multiple myeloma can evolve towards plasma cell leukemia, where plasma cell count is greater than 2000/ mm^3; survival is highly variable (median is around 3 years); prognosis is according to the staging and other parameters (such as age, serum albumin, b2 microglobulin, C-reactive protein, and plasma cell labeling index); the karyotype is emerging as an important prognostic factor: median survival in case of a normal karyotype could be 4 years vs 1 year in case of -13/del(13q) and/or 11q rearrangements (the chromosome anomalies with the worst prognostic impact).

Cytogenetics

Cytogenetics morphological

Cytogenetic information is limited, as the malignant cells have a low spontaneous proliferative activity; abnormal karyotypes are found in 30-50% of cases, more often in advanced stages than in newly diagnosed patients (is this because chromosome abnormalities are secondary events, or because malignant cells have an increased proliferative activity in advanced stages: see below);
karyotypes are complex; hyperploidy is found in 2/3 of cases; karyotypes may evolve from normal to abnormal during course of the disease; structural (and variable) abnormalities of chromosome 1 are found in 30-40% of cases, 14q rearrangements in 25% of cases, 11q abnormalities in 20%, t(11;14)(q13;q32) representing 10%; 6q anomalies represent 15% of cases; FISH is indicated, as metaphases are arduous to obtain in such a disease implicating mature cells, and tend to show that most cases bear chromosome anomalies, irrespective of the disease staging.

**Cytogenetics molecular**

All MM cells should express chromosome abnormalities, as strongly suggested by interphase FISH and CGH. Aneuploidy is detected in 67-90% of cases, allowing to define 2 prognosis entities:

1) hyperdiploid sub-group with a significantly better overall survival, gains involving primarily +3, +5, +7, +9, +11, +15, +19, +21 and infrequent structural abnormalities.

2) hypodiploid group (+hypotetraploid cases by endoreduplication of a prior hypodiploid karyotype) strongly correlated with complex structural rearrangements, 14q32 translocations, del(13q)/-13 and a more aggressive evolution. IG rearrangements: translocations involving 14q32 are found in at least 65-70% of patients, most of them result from short segments exchange and are detected quite exclusively by FISH. Five translocations involving IGH locus are particularly relevant and considered as very early primary events: t(4;14)(p16;q32), t(6;14)(p21;q32), t(11;14)(q13;q32), t(14;16)(q32;q23), t(14;20)(q32;q11). Other translocations involving IGH are rare or sporadic; they should be secondary and not mediated by specific recombination mechanisms.

**Genes involved and proteins**

**FGFR3**

**Location** 4p16

**Note** Involved in t(4;14)(p16;q32), approximately 15% of MM cases. FGFR3 (tyrosine kinase receptor) and MMSET (novel gene homologous to a Drosophila dysmorph gene, see below) are in opposite transcriptional orientation at 4p16. Both are involved in t(4;14). The translocation generates 2 fusion genes, IGH-MMSET on der(4) and FGFR3-IGH on der(14).

**WHSC1 (MMSET)**

**Location** 4p16

**Note** Involved in t(4;14)(p16;q32) (see above).

**CCND3 (Cyclin D3)**

**Location** 6p21

**Note** Involved in t(6;14)(p21;q32) (3-5% of MM cases). Detected quasi exclusively by FISH.

**BCL1**

**Location** 11q13

**Note** BCL1 (also called Cyclin D1 or CCND1) is involved in t(11;14)(q13;q32) cases. Approximately 15-20% of cases. Same translocation as mantle cell lymphoma but IGH breakpoint different (IGHS vs IGHJ).

**MAF**

**Location** 16q23

**Note** Basic zipper transcription factor, involved in t(14;16)(q32;q23) (5% of MM cases). Detected quasi exclusively by FISH.

**MAFB**

**Location** 20q11

**Note** MAF family basic region / leucine zipper transcription factor, involved in t(14;20)(q32;q11) (2% of MM cases).

**C-MYC**

**Location** 8q24

**Note** Overexpression (mainly without rearrangement or amplification) correlated with increased tumour cell burden. RAS mutations (found in 20% of cases) and P53 mutations are associated with advanced disease.

**RB1**

**Location** 13q14

**Note** RB1is deleted in more than 1/3 of cases. 13q14.3 deletions have been observed without RB1 loss, which should mean that RB1 is not the only critical locus of 13q14.3 sub-band. D13S25 and D13S319 appear as the more commonly deleted loci.
References


This article should be referenced as such: