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New complex chromosome abnormalities in multiple myeloma associated with a poor prognosis: A case report

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1. Introduction

Multiple myeloma (MM) is a malignant proliferation of monoclonal plasma cells characterized by its accumulation in the bone marrow, production of excessive monoclonal immunoglobulin (M protein) in serum or urine, and osteolytic bone lesions. These features lead to a wide range of common manifestations that include pathological bone fragility, nephropathy, immunodeficiency and hematopoietic disorders. Non-specific clinical manifestations of MM are challenges for accurate diagnosis [1].

On a worldwide scale, incidence of MM is estimated as 86,000 new cases annually, accounting for about 0.8% of all new cancer cases and affecting both sexes equally. About 63,000 MM deaths are reported each year, accounting for 0.9% of all cancer deaths. Geographically, there is an uneven distribution in the world, with highest incidence in the industrialized regions of Australia/New Zealand, Europe and North America [2].

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Conflict of interest statement

All authors have no conflict of interest to report.

Contributions. ACFC designed the study, checked the karyotypic analysis, oversaw the whole study and critically reviewed the manuscript. ABCS carried out the karyotypic analysis and photographed the slides. CBV carried out karyotypic analysis and co-wrote the original manuscript. PP followed up the patient and carried out the clinical data collection. PCF carried out karyotypic analysis and co-wrote the original manuscript. MVG carried out the SKY karyotypic analysis and critically reviewed the manuscript. All authors read and approved the final draft.

The MM clinical course is highly variable, and the heterogeneity largely reflects different genetic abnormalities; therapy is not optimized and despite recent progress, the disease remains incurable [3].

The MM genome is very unstable, typically aneuploid and with a complex combination of abnormalities, but the molecular basis of the disease is still unclear. Genetic and molecular subtypes of the disease have been identified in association with unique clinic pathological features and dissimilar outcome. Numerous and complex chromosome aberrations (8–10 changes at diagnosis) represent a hallmark of MM [4]. The majority of hyperdiploid type MM (50–60%) have chromosomal content including trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19 and 21, deletions on chromosomes 13 and 17, and deletion and amplification of chromosome 1. The non-hyperdiploid MM includes several types of immunoglobulin heavy chain (Ig) translocations [t(11;14)(q13;q32), t(4;14)(p16;q32) and t(14;16)(q32;q23)]. The chromosome ploidy status and Ig gene rearrangements are two genetic criteria that are used to help stratify patients into prognostic groups based on the findings of conventional cytogenetics and fluorescence in situ hybridization (FISH). In general, the hypodiploid group is considered a high-risk group, while the hyperdiploid patients are considered a better prognostic group [4–6].

In this report, we describe an adult male patient diagnosed with MM who presented a complex hyperdiploid karyotype with aberrations not previously described and showed poor clinical course.

2. Case report

In November 2008, a 54-year-old man was seen in the ambulatory clinic with complaint of significant weight loss (16 kg in about 3 months), difficulty in walking, and pale skin and mucosa. He revealed that since July 2007 was suffering of weakness and mild pain in the lumbar spine that has not responded to anti-inflammatory drugs and painkillers. His hemogram showed 10 g/dL of hemoglobin, a hematocrit of 29% and a white blood cell count of 4700 (54% neutrophils, 30% lymphocytes, 3% eosinophils, 10% monocytes). A bone marrow aspirate showed 39.2% of plasmocytes, many with bilobed nuclei. The radiological investigation showed lytic lesions in long bones, spine and pelvis, and fractures of ribs and vertebral bodies. Serum protein electrophoresis showed increased levels of M protein, observed as a narrow peak in the fraction of gamma globulins, and the diagnosis of MM was concluded.

Bone marrow aspirate withdrawn at disease diagnosis was used for classical and molecular cytogenetic analysis after a 24-h non-stimulated culture in RPMI1640 medium with 20% fetal calf serum. GTG-banding (30 cells) and spectral karyotyping (SKY) analyses (10 cells) were performed as described in Vendrame-Goloni et al. [7]. The karyotype by GTG-banding was normal in 14 cells and 16 cells showed clonal alterations defined as: 50,XY,der(1),+5,del(7)(q32),der(10),+4mar. SKY analysis was more informative in the identification of abnormalities and detected the der(1) as a rea(1) with longer p-arm, the der(10) as der(19)t(10;19), and the 4 markers as der(2)t(2;21), der(6)t(X;6), der(8)t(3;8), and del(19). Moreover, SKY also identified a small insertion in 3p and additional material in one 13p, which appeared more stained than just extended satellites but that could not be resolved by SKY due to its limitation with acrocentric p-arms. In summary, the karyotype of the abnormal clone was designated as: 50,XY,rea(1),der(2)t(2;21)(q27;q11),ins(3;?8or1)(p21;?),+5, der(6)t(X;6)(?q24;q27),del(7)(q32),der(8)t(3;8)(q12;p11.2),+9,-10,add(13)(p11),del(19)(?p11.2),+der(19)t(10;19)(q11.2;p13.3) (Fig. 1). Metaphase fluorescence in situ hybridization (FISH) analyses performed according to a standard protocol using the LSI13

(RB1) SpectrumOrange (Abbott Molecular) probe showed that the *RB1* gene was not deleted.

The patient was submitted to remission-induction with thalidomide and dexamethasone and achieved complete remission. In 2009, he was submitted to transplantation of autologous peripheral hematopoietic stem cells and at 304 days post-transplant relapsed with plasma cell leukemia. He received a 4-dose treatment cycle with Bortezomib with no response, and then progressed to death in April 2010, 17 months after the diagnosis.

3. Discussion

The genetic profile of MM is determinant of patient survival and response to treatment. The disease has 3-year median survival, and a 10-year survival rate of only 10%. Abnormal karyotypes are found in 30–50% of cases, more often in advanced stages than in newly diagnosed patients [1]. Although any cytogenetic abnormality is considered a high-risk factor, the worse risk is associated with deletions in 13 or 13q and 17p, and with t(4;14) and t(14;16) [8,9].

As the disease progresses, it can become more proliferative and develop a number of secondary chromosome aberrations. Progressive disease is then correlated with an increased complexity of chromosomal abnormalities, mostly structural aberrations. The reported patient presented a complex karyotype, which shows that the disease compatible with advanced stage. The malignant cells had no deletion of chromosome 13, suggesting a good prognosis, but there were other reported and novel alterations, whose prognostic significance is unknown. It is difficult to conclude that all abnormalities seen in the karyotype are intimately related to the myeloma process or whether some are randomly due to an underlying instability process.

The hyperdiploid karyotype is common in MM. In a series of 120 multiple myelomas with abnormal karyotypes described by Mohamed et al. [1] it was found in 64% cases, while hypodiploidy was detected in 25%, and the remaining 11% cases had a pseudodiploid karyotype. Gain of chromosomes 5 and 9, and loss of chromosome 8 are common [10]. *MYC* gene activation by gene fusion or amplification was found in up to 45% of patient with advanced MM. Translocations involving *MYC* and the Ig locus are known to be late events in tumor progression, when tumors are becoming more proliferative and less stromal dependent. Rearrangements in chromosome 1 have long been known to be highly prevalent and associated with shorter survival [5,4]. However, it has been difficult to identify potential genomic targets associated with the poor prognosis. No previous descriptions of t(2;21), der(3)t(3;8), t(6;X), del(19)(p11.2), or der(19)t(10;19) were found in MM, suggesting a new combination of alterations. In all chromosomal breakpoints identified in our patient's karyotype there are tumorigenesis-related genes mapped, but their participation in the pathogenesis and evolution of this case was not investigated.

There is an expectative that the risk features change in the future, when treatment with new agents or possibly new regimen combinations are implemented. Nevertheless, it is critical to identify the actual gamma of molecular changes that may occur in MM thus the relevance of this case report. This patient's tumor cells exhibited a hyperdiploid chromosome content including abnormalities associated with good prognosis and a set of novel anomalies, which by themselves or by contributing to the chromosomal complexity may be related to his aggressive disease course.

Acknowledgments

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Fig. 1.

(a) Partial karyotype by GTG-band showing del(7q32); (b)-(d) cell showing 50 chromosomes and multiple abnormalities detected by SKY: 50,XY,rea(1),der(2)t(2;21)(q27;q11),ins(3;?8or1)(p21;?), +5,der(6)t(X;6)(?q24;q27),del(7)(q32),der(8)t(3;8)(q12;p11.2), +9,-10,add(13)(p11),del(19)(?p11.2), +der(19)t(10;19)(q11.2;p13.3) - the add(13) is indicated by an arrow.