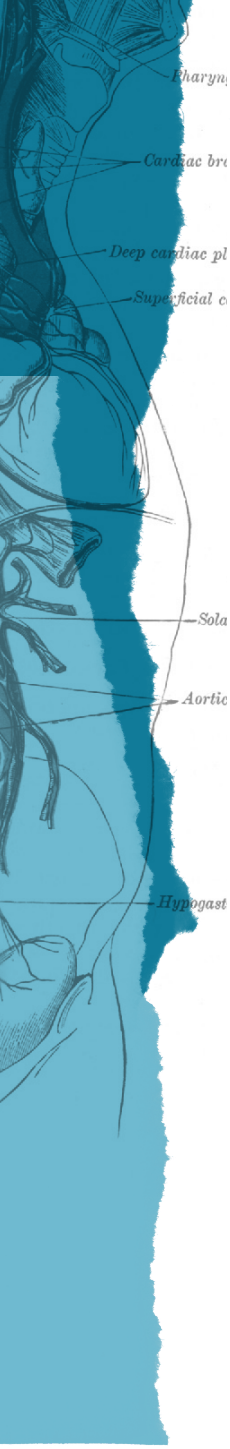

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Early-Onset High-Risk Multiple Myeloma: A Case Report from Bogotá (Colombia)

Mieloma múltiple de alto riesgo de aparición temprana: Informe de un caso en Bogotá (Colombia)

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ABSTRACT

Multiple myeloma (MM) is characterized by plasma cell overgrowth, typically affecting older individuals. However, it is exceptionally rare in young adults, accounting for only 2.2% of cases in those under 40. A 35-year-old female patient with recent-onset anemia requiring transfusion presented with gingival bleeding and ecchymosis. She presented severe anemia with no thrombocytopenia, elevated creatinine, and vertebral (T10 and T11) fractures. Electrophoresis revealed a monoclonal peak, bone marrow aspiration showed 80% infiltration by lambda plasma cells and cytogenetic studies identified t(4;14). Treatment included induction therapy with 4 cycles of bortezomib, lenalidomide, dexamethasone (VRd protocol) consolidation with daratumumab-VRd, and planned autologous transplantation. This case highlights the challenges and importance of diagnosing MM in young adults. Cytogenetic abnormalities, such as t(4;14) play a role in influencing prognosis and guiding treatment decisions. Thus, understanding the interplay between young age and cytogenetics is vital in this disease.

Keywords: Multiple myeloma, anemia, young adult, cytogenetics, case report.

RESUMEN

El mieloma múltiple (MM) se caracteriza por el crecimiento excesivo de células plasmáticas, y afecta típicamente a individuos de mayor edad. Sin embargo, es excepcionalmente raro en adultos jóvenes, representando solo el 2,2 % de los casos en aquellos menores de 40 años. Una paciente mujer de 35 años con anemia de reciente diagnóstico que requirió transfusión se presentó con sangrado gingival y equimosis. Presentó anemia severa sin trombocitopenia, creatinina elevada y fracturas vertebrales (T10 y T11). La electroforesis reveló un pico monoclonal, el aspirado de médula ósea mostró una infiltración del 80 % por células plasmáticas lambda, y los estudios citogenéticos identificaron una t(4;14). El tratamiento incluyó terapia de inducción con 4 ciclos de bortezomib, lenalidomida, dexametasona (protocolo VRd) y consolidación con daratumumab-VRd, con plan de trasplante autólogo. Este caso destaca los desafíos y la importancia de diagnosticar el MM en adultos jóvenes. Las anormalidades citogenéticas, como la t(4;14), desempeñan un papel crucial, influyendo en el pronóstico y orientando las decisiones terapéuticas. Por lo tanto, comprender la interacción entre la edad temprana y la citogenética es vital en esta enfermedad.

Palabras clave: Mieloma múltiple, anemia, adulto joven, citogenética, informes de casos.

INTRODUCTION

Multiple myeloma (MM) is a hematological neoplasm characterized by the clonal proliferation of plasma cells producing immunoglobulins, primarily IgG (1,2). This condition gives rise to a range of organ dysfunctions and symptoms, including bone pain or fractures, renal failure, susceptibility to infections, anemia, hypercalcemia, and sometimes, neurological symptoms and manifestations of hyperviscosity (1,2). Despite being the second most common hematological malignancy, MM is relatively rare in individuals under 40 years old, comprising only 2.2% of cases in this age group (3,4). Cytogenetic abnormalities play a crucial role in MM's pathogenesis and have a significant impact on patient prognosis. Chromosomal translocations, such as t(4;14), have been associated with high-risk MM and can guide therapeutic decision-making and affect the prognosis (2). This case presentation highlights a compelling instance of a 35-year-old patient diagnosed with high-risk MM harboring t(4;14) aberration. We aim to emphasize the challenges and importance of diagnosing MM in young adults and shed light on the implications of cytogenetic abnormalities on the disease's clinical course. Understanding the complex interplay between cytogenetics and MM pathogenesis is crucial in optimizing treatment strategies and improving patient outcomes.

CASE PRESENTATION

A 35-year-old Caucasian female patient presented to the emergency department with a 3-day history of self-resolving gingival bleeding and ecchymoses on her legs, as well as a laboratory finding of severe anemia from an outpatient evaluation. One year before the current consultation, the patient had experienced increased menstrual bleeding and abnormal bleeding during a molar extraction procedure. Three months prior, she had presented to another institution with fatigue and asthenia and was found to have severe anemia that required a blood transfusion. Abnormal uterine bleeding was attributed as the cause, and the outpatient management was with oral iron supplementation. She denied experiencing arthralgia or alopecia, and there was no fever, weight loss, or any gastrointestinal symptoms.

On admission, she had normal vital signs, pale conjunctiva, and generalized pallor, with multiple ecchymosis, especially in her legs. The oral cavity did not have any ulcers or cheilosis. There was also no cervical, axillary, or inguinal lymph node enlargement presence. The abdomen was soft, and there were no signs of hepatosplenomegaly. The cardiopulmonary and neurological exami-

nations were normal. The initial laboratory workout revealed severe anemia of normal volumes (Hb: 5.8 g/dL), the platelets and leukocytes were within normal value, and creatinine elevation (creatinine 2.3 mg/dL) was presumed to be acute. For the hemoglobin level and symptoms, a transfusion of 3 units of filtered red blood cells was decided.

The patient's anemia etiology was unclear, and a positive direct Coombs test with indirect hyperbilirubinemia (total: 3.0 mg/dL, indirect: 2.89 mg/dL) and an LDH of 87 UI/L raised suspicion of an autoimmune cause. Further investigations, including ANAs, ENAs, lupus anticoagulant, and anti-DNA, all were negative. It was attributed to the recent previous transfusion. Given the patient's altered kidney function, a kidney biopsy was ordered.

During hospital evaluation, the patient developed a cough with expectoration, and a polymerase chain reaction test for SARS-CoV-2 came back positive. A chest X-ray ruled out parenchymal involvement but incidentally revealed a vertebral fracture at T10 and T11. Monoclonal gammopathy was suspected as the underlying condition affecting the erythrocyte line, renal function, and bone system. Serum protein electrophoresis revealed the presence of a gamma monoclonal peak. Bence Jones protein was positive, serum IgG was elevated, while serum IgA and IgM levels were normal. There was also an increase in urine and serum lambda-free light chain levels, with normal kappa values. Also, the serum-corrected calcium was normal (table).

Table. Laboratory findings of the patient. "*" express abnormal values

Laboratory	Patient's Value	Normal Value
Serum calcium	9.0 mg/dL	8.8-10.3 mg/dL
Serum Albumin	2.5 g/dL *	3-4 g/dL
ß2-microglobulin	5.93 mg/L*	1.5-3.0 mg/L
Lactate Dehydrogenase	87 UI/L	140-280 UI/L
Serum IgG	11757 mg/dL *	700-1600 mg/dL
Serum IgA	< 10 mg/dL	70-400 mg/dL
Serum IgM	< 25 mg/dL	40-230 mg/dL
Serum Lambda free light chain	12.77 mg/L *	0.26-1.65 mg/L
Serum Kappa free light chain	12.03 mg/L	3.3-19.4 mg/L
Urine Lambda free light chain	37.95 mg/L *	0-4.99 mg/L
Urine Kappa free light chain	14.58 mg/L	0.01-32.71 mg/L

Source: own elaboration.

The renal biopsy confirmed the presence of linear lambda light chains deposited in the glomerular basement membrane. The bone marrow biopsy revealed a myelogram with 62% plasma cells. Flow cytometry analysis showed that 3% of the plasma cells had weak expression of CD38 and were negative for CD138, CD56, and CD19. The bone marrow revealed hypercellularity for the patient's age, with 80% diffuse infiltration by lambda plasma cells. Immunohistochemistry of these cells showed positive expression of CD38, CD138, and CD56 while being negative for CD20 and CD117. Red Congo staining was negative for amyloid deposits. Karyotyping revealed a normal female karyotype of 46, XX. Cytogenetic studies identified a t(4;14) translocation (high risk), with negative del(17p) and t(14;16). This confirmed the diagnosis of lambda IgG multiple myeloma. The patient's disease was classified as stage III according to the Revised Multiple Myeloma International Staging System (R-ISS), indicating a mean progression-free survival of 29 months.

Treatment was initiated with the VRd protocol (bortezomib, lenalidomide, dexamethasone), with the first cycle administered intrahospital and the following three cycles managed on an outpatient basis without complications. Before hospital discharge, kidney function returned to her normal values (creatinine: 0.93 mg/dL) and hemoglobin was stable at 12.3 g/dL. The patient was assessed by the hematopoietic stem cell transplantation group and deemed a candidate for consolidation with autologous transplantation. During follow-up, a significant 80% decrease in the monoclonal peak was documented; however, as it did not return to normal value and considering the high-risk status given by the cytogenetic alteration and her age, daratumumab was added to the fifth and sixth cycles (Dara-VRd) without complications. The patient is currently undergoing admission to the transplant unit, with plans for four additional cycles of chemotherapy for consolidation before starting maintenance therapy.

DISCUSSION

Multiple myeloma (MM) is a neoplasm caused by clonal plasma cell proliferation, resulting in the production of specific immunoglobulins in affected individuals (1,2). In this case, the patient presented with IgG type MM, which is the most common subtype, accounting for approximately 52% of cases followed by IgA at 21%, Kappa (κ) - lambda (λ) at 16%, IgD at 2%, biclonal at 2%, and IgM at 0.5% (1,5). Globally, MM constitutes 0.9 % of all neoplastic diseases, while in Colombia, it accounted for 1.46% of cases in 2018 (6). Ranking as the second most prevalent hematological malignancy in high-income countries, comprising 10% of such cases (4,7). MM can occur across

different age groups; however, this case is notable due to the patient's young age. This aspect warrants special attention, as MM typically manifests in older individuals.

MM typically affects older adults, with the mean age of presentation being 71 years in men and 74 years in women (8). However, the occurrence of MM before the age of 45 is exceptionally rare, constituting merely 2% of cases within this age category (8). In addition, the frequency for those under 40 years of age is 2.2% and for those under 30 years of age, it is 0.3% (3). The precise etiology of MM remains uncertain, although potential associations were observed in various factors, including radioactive exposure (e.g., nuclear warheads), petroleum products, and specific occupational groups such as farmers, woodworkers, and leather workers(1). As such, a comprehensive evaluation of potential risk factors and genetic markers assumes major importance, particularly in the context of a young patient as presented here.

Notable characteristics emerge within this age group. For instance, in individuals under 55 years of age, extramedullary MM is more prevalent (43% vs. 13%) (5). Likewise, a study conducted in Uruguay revealed that patients under 65 years of age tend to exhibit a more aggressive clinical presentation compared to those over 65 years of age. This includes a higher incidence of extramedullary disease (12% vs. 0%), osteolytic lesions (78.7% vs. 57.6%), and bone plasmacytoma (25.3% vs. 11.4%) (9).

Risk assessment and stratification have been extensively studied to determine their impact on the survival, relapse, and prognosis in patients diagnosed with MM (10). The International Staging System (ISS) is commonly employed for this purpose, primarily relying on β2 microglobulin and serum albumin levels, although other markers are also associated, such as lactate dehydrogenase (LDH) and FISH (Fluorescence in situ hybridization) studies. It is noteworthy that these markers were subsequently incorporated into the revised version of the scale, known as the Revised International Staging System (R-ISS) (10).

Genetic alterations generally occur during the differentiation process of B lymphocytes, including the recombination events related to immunoglobulin class switching and gene activation (4,11). Considering this, conventional cytogenetic and FISH studies have gained significance and are widely employed, since abnormalities in these are consistently associated with lower survival rates(10). Their importance extends to the evaluation of prognosis and treatment, as gene-

tic alterations are detectable even in the early stages of monoclonal gammopathy of uncertain significance (MGUS) (12). Genetic alterations have a prevalence of 10% in MGUS and 40 to 50% in MM (13).

Regarding FISH, it allows better identification compared to conventional cytogenetic studies (10). This technique assesses the presence of alterations such as t(4;14), del(17p) or t(14;16), which in MM have shown a prevalence of 10-15%, 8-10%, and 2-4% respectively, attributing their presence with a higher risk of treatment refractoriness and lower survival (10,14). Other translocations, such as t(11;14) are observed in 15% of cases, while t(6;14) in 4%. In approximately 10-15% of cases, the specific genetic abnormalities remain unidentified (13). Additionally, some studies have explored other markers such as ins1q and del(1p), del(17p), ins(1q), or P53 mutation, although these are less prevalent (14). It is important to note that the addition or deletion of 1p is associated with decreased survival (13). A meta-analysis confirmed poor prognosis in those having t(4;14), t(14;16), t(14;20), del(17dp), and gain(1q21) with hazard ratios (HZ) ranging between 1.6 and 2.1, all statistically significant (15). The inclusion of all these cytogenetic markers has expanded the disease classification in these patients, introducing terms like "double hit" MM when there is more than one cytogenetic marker and "triple hit" when there are more than two, which is relevant as it is associated with decreased survival (14).

In this case report, the presence of t(4;14) was found and documented, which is noteworthy since translocation involving chromosome 14 is related to the activation of multiple oncogenes and is associated with worse outcomes (4). The most frequent translocation is t(11;14), followed by t(4;14) and less frequent t(14;16), t(14;20) and t(6;14) (4). Regarding t(4;14), it serves as an independent predictor of survival, with a HR of 7.58 (95% CI 1.43 – 39.9; $p < 0.05$), and patients with this translocation exhibit a lower 3-year survival rate compared to those without it (81.2% vs. 66.7%, p=0.04) (11). However, in a study carried out in Japan, between 2012 and 2018, no significant association was found between the age of presentation and the presence or absence of t(4;14) cytogenetic abnormality (11). In contrast, in the United States, a cohort study spanning from 2004 and 2018, identified a higher prevalence of t(11;14) in young patients with MM, representing 27%, and t(6;14), representing 31% (16).

In another retrospective study involving 2027 patients, the presence of cytogenetic abnormalities, including t(4;14), t(14;16), t(6;14), and/or t(14;20) was associated with anemia, thrombo-

cytopenia, elevated β2 microglobulin (> 5.5 ug/mL), ISS III stages as well as a higher percentage of plasma cells in bone marrow (16). Furthermore, specific translocation, including t(14;16), t(6;14), or t(14;20), were linked to more significant renal impairment, while patients with t(4;14) often exhibit lower albumin levels, with the IgA isotype being particularly prevalent in this subgroup (16). Thus the evaluation of age and cytogenetic abnormalities shows their impact on clinical outcomes and informs the prognosis for patients with multiple myeloma.

CONCLUSIONS

This report presents the clinical case of a young patient with MM and high-risk cytogenetic abnormalities. This case highlights the importance of considering the diagnosis possibility of MM in young patients, even if it is rare. Knowledge of diagnostic algorithms, classification, and staging, especially about cytogenetic risks, is crucial to guide the appropriate therapeutic approach. It is essential to understand the underlying mechanisms of the disease, as this provides a solid scientific basis for the development of therapeutic strategies. Cytogenetic abnormalities, such as the t(4;14) identified in this case, are associated with a poorer prognosis and require special consideration in clinical management. Furthermore, this case highlights the importance of induction, consolidation, and maintenance regimens in young patients with high-grade cytogenetic abnormalities. Further research is needed in this population to optimize therapeutic approaches and improve outcomes.

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