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MULTIPLE MYELOMA IN YOUNG WOMAN: CASE REPORT

Mieloma múltiplo em mulher jovem: relato de caso

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Abstract: Multiple Myeloma is a hematological neoplasm that typically affects the elderly population. It is rare in individuals under 40 years of age (2% of the total). The age group of the patient is fundamentally important in order to define the most appropriate treatment. Multiple Myeloma is characterized by dysregulated proliferation of plasma cells in the bone marrow, which produce and secrete monoclonal immunoglobulin. Patients commonly present symptoms such as anemia, hypercalcemia, renal failure and bone disease. The diagnosis is confirmed by detecting spinal cord plasma cytosis ≥ 10% and/or presence of plasmacytoma and at least one of the following criteria: presence of target organ lesion associated with Multiple Myeloma; presence of some biomarker. It is an incurable disease whose main goal of treatment is to increase the patient's survival and quality of life. Treatment is defined according to some parameters such as age and presence of comorbidities. Young patients with no comorbidities should preferentially perform high dose chemotherapy followed by autologous hematopoietic stem cell transplantation; while patients older than 65-70 years with comorbidities are treated with chemotherapy alone. Multiple Myeloma presents a heterogeneous evolution whose survival varies from a few months to more than a decade. The objective of this study is to report the case of a young patient diagnosed with Multiple Myeloma.

Keywords: Multiple Myeloma; Neoplasms; Plasma Cells; Bone Marrow.

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Resumo: O Mieloma Múltiplo é uma neoplasia hematológica que afeta tipicamente a população idosa, sendo raro em indivíduos com menos de 40 anos de idade (2% do total). A faixa etária do paciente é de fundamental importância para definição do tratamento mais adequado. O Mieloma Múltiplo caracteriza-se por proliferação desregulada de plasmócitos na medula óssea, os quais produzem e secretam imunoglobulina monoclonal. Os pacientes comumente se apresentam com sintomas de anemia, hipercalcemia, insuficiência renal e doença óssea. O diagnóstico é firmado ao se detectar plasmocitose medular ≥ 10% e/ou presença de plasmocitoma e no mínimo um dos critérios a seguir: presença de lesão de órgão alvo associado ao Mieloma Múltiplo; presença de algum biomarcador. Trata-se de uma doença incurável, cujo principal objetivo do tratamento é aumentar a sobrevida e qualidade de vida do paciente. O tratamento é definido de acordo com alguns parâmetros como idade e presença de comorbidades, sendo que os pacientes jovens e sem comorbidades devem realizar preferencialmente quimioterapia de altas doses seguida de transplante autólogo de células-tronco hematopoiéticas; enquanto os pacientes com mais de 65-70 anos, com comorbidades, são tratados somente com quimioterapia. O Mieloma Múltiplo apresenta evolução heterogênea cuja sobrevida dos pacientes varia de alguns meses até mais de uma década. Este estudo objetivou relatar o caso de uma paciente jovem diagnosticada com Mieloma Múltiplo.

Palavras-chave: Mieloma Múltiplo; Neoplasias; Plasmócitos; Medula Óssea.

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INTRODUCTION

Multiple Myeloma (MM) corresponds to 1% of all malignant neoplasms but represents the second most common hematological malignancy[1]. It is considered a disease of the elderly, with a median age at diagnosis between 65-74 years, with approximately 35% - 40% of the cases over the age of 75 years. Of the patients diagnosed with MM, less than 2% is below the age of 40 years, and the cases in patients less than 30 years are extremely rare[2]. This age distribution has implications in the population eligible for specific types of treatments, such as high doses of chemotherapy and stem cells transplantation[3]. MM is two times more common in African-caribbeans than white people, and the incidence is higher in males[4]. In recent years there has been an increase in the incidence of MM, which may be related to greater knowledge of the disease natural history and its pathogenesis, the improvement of laboratory resources, the increase in life expectancy worldwide and to chronic exposure to pollutants[1]. It is a disease with a heterogeneous development whose survival of patients is variable, from a few months up to 10 years[5].

MM is a neoplasia arising from the lineage of B lymphocytes, characterized by the unregulated clonal plasmocytic proliferation in the bone marrow, being that these plasma cells produce and secrete monoclonal immunoglobulin or fragment of this, the M protein [1]. MM arises due to genetic mutations that occur during the differentiation of B lymphocytes into plasma cells. In about half of cases there is a chromosomal translocation that puts an oncogene in the gene of the heavy chain of immunoglobulin in chromosome 14. This results in overexpression of the oncogene and unregulated cell proliferation. The remaining cases are characterized by trisomies of several odd chromosomes (3, 5, 7, 9, 11, 15, 19 and 21). To the extent that the multiple myeloma develops, other genetic events, such as RAS mutations may occur[4].

Patients with MM commonly have symptoms of anemia (observed in 75% of patients at diagnosis), hypercalcemia (30%), renal insufficiency (25%) and bone disease (70%). The skeletal manifestations may present as painful lytic lesions, vertebral fractures or fractures of the long bones. High values of monoclonal protein can cause symptoms of hyperviscosity (headache, epistaxis, visual turbidity and mental confusion), while the reduced humoral immunity results in recurrent bacterial infections[4].

For the diagnosis of MM clinical history and detailed physical examination must be performed, proceed initially with routine laboratory tests: complete blood count, renal function, ions including calcium, protein electrophoresis of serum and urinary for quantification of monoclonal protein and then the serum and/or urine immunofixation in order to identify the subtype of monoclonal protein. The examination of the bone marrow (myelogram and/or biopsy with cytogenetic analysis) will help to confirm the diagnosis[6]. However, the criteria for the diagnosis of MM were revised in 2014 with the objective to allow an earlier recognition of the disease. Therefore, biomarkers were incorporated that in addition to elucidating the diagnosis can also infer the biological behavior of the disease in determining which patients will have a greater risk of unfavorable evolution. Thus, for confirmatory diagnosis of MM it is necessary, as a compulsory criterion, the medullary plasma cytosis ≥ 10% and/or presence of plasmacytoma confirmed by biopsy. In addition, it is necessary to have at least one of the following criteria: presence of any target-organ injury attributed to MM (hypercalcemia, renal insuf-

ficiency, anemia and lytic bone lesion); presence of a biomarker (medullary plasma cytosis ≥ 60%, ratio of serum free light chains in the serum involved and chains involved ≥ 100, more than 1 focal lesion checked by MRI)[7]. For all patients diagnosed with MM a skeletal survey is indicated with plain radiographs of the spine, skull, pelvis, chest, and upper bones of the limbs to determine the extention of the disease[4].

MM is considered an incurable disease. Therefore, the main objective of treatment is to increase the survival and quality of life of the patients[8]. The choice among the treatment options are based on patient characteristics such as age and presence of comorbidities, therapeutic options available and service experience. In patients aged less than 65-70 years, without comorbidities and with normal renal function the consolidation of treatment must be performed with high doses of chemotherapy followed by transplantation of autologous hematopoietic stem cells (TCTHa). On the other hand, elderly patients over 65-70 years or with comorbidities and/or with altered renal function usually are not eligible for transplantation, being then treated only with chemotherapy[9]. The traditional regien with vincristine-doxorubicin-dexamethasone was replaced by new therapeutic options and is currently in disuse. Therefore, the regimens that contain bortezomibe are suggested as first-line treatment associated with other drugs such as dexamethasone, thalidomide, doxorubicin and/or cyclophosphamide. The CTD regimen cyclophosphamide-thalidomide-dexamethasone, is widely used in the United Kingdom for those patients who are candidates for transplantation[4]. Whereas patients who are not candidates for transplantation, the chemotherapy regimen considered commonly used is the combination of melphalan, prednisone and thalidomide[6]. The support therapy for the control of the main clinical manifestations is essential for the improvement of the quality of life of patients with MM. Thus, bisphosphonates are used to reduce skeletal complications, the erythropoietin is used for the control of anemia and should be considered for prophylaxis for opportunistic infections[8]. For the treatment of bone pain, one should start with non-opioid analgesic agents (for example, paracetamol and/or dipyrone). The nonsteroid anti-Inflammatory drugs should be avoided by the potential risk of worsening renal function and the opiates should be introduced when the no-opioid analgesic agents are ineffective[6]. The majority of patients respond to initial treatment by acquiring a period of the disease stability, which is usually associated with the relative improvement of quality of life. Despite the impossibility of curative treatment, and relapse being inevitable, a large proportion of patients respond to Chemotherapies of second line with different drugs of the initial regimen, or even similar. However, the subsequent relapses become increasingly less sensitive to treatment[4].

Thus, the present study aimed to report the case of a young patient diagnosed with MM, besides presenting the symptoms manifested at initial diagnosis, exposing the propaedeutic performed and the initial therapy used. Because this is an extremely rare disease in young adults it becomes necessary to know MM, establish an investigation strategy and more appropriate treatment to avoid an unfavorable evolution in this age range.

The design of this study was evaluated and approved by the Ethics and Research Committee of Faculdades Unidade do Norte de Minas (FUNORTE), with the opinion number 2.526.747.

CASE REPORT

Woman, 31 years old, born in Padre Carvalho, Minas Gerais, sought medical care in hospi-

tal, complaining of pain in the body, arthralgia and weakness four months ago. She had performed hemogram when anemia was identified, treated with noripurum without improvement. Evolved with diffuse abdominal pain, vomiting, episodes of diarrhea, loss of appetite, loss of weight (9 kg in 30 days), dry cough and fever in the afternoon with chills. Patient had no other complaints or comorbidities.

Upon physical examination, hemodynamically stable, vital data without changes, dehydrated 1+/4+, pale 2+/4+, regular general condition; the abdomen was flat, diffusely painful to palpation, splenomegaly; Blumberg, Rovsing and Murphy signs were negative. The patient was hospitalized, and laboratory exams were performed for investigation of clinical signs (Table 1). Chest radiograph: the pulmonary parenchyma without alterations. Total abdominal ultrasonography: moderate splenomegaly, kidneys increased dimensions (both of textural aspect suggestive of acute nephropathy), another abdominal organ studied were normal.

Table 1 - Results of laboratory examinations of a case study of MM, Montes Claros, MG, 2018.

Variable	Result
Hemoglobin	9.2 g/dL
Leukocytes	11.62/ mm3
Platelets	168,000/ mm3
AST	16 U/L
ALT	14 U/L
Amylase	39 U/L
Lipase	17 U/L
Gamma GT	22 U/L
PCR	8.6 mg/L
Creatinine	1.3 mg/dl

The patient evolved with dysuria and persistence of other complaints from the beginning of the clinical signs. It was arosen as diagnostic hypotheses pyelonephritis, intestinal parasitosis, hemolytic anemia. She received treatment with Ciprofloxacin and Albendazole. New examinations were performed and showed a drop in hemoglobin, hypercalcemia and increase in creatinine (Table 2).

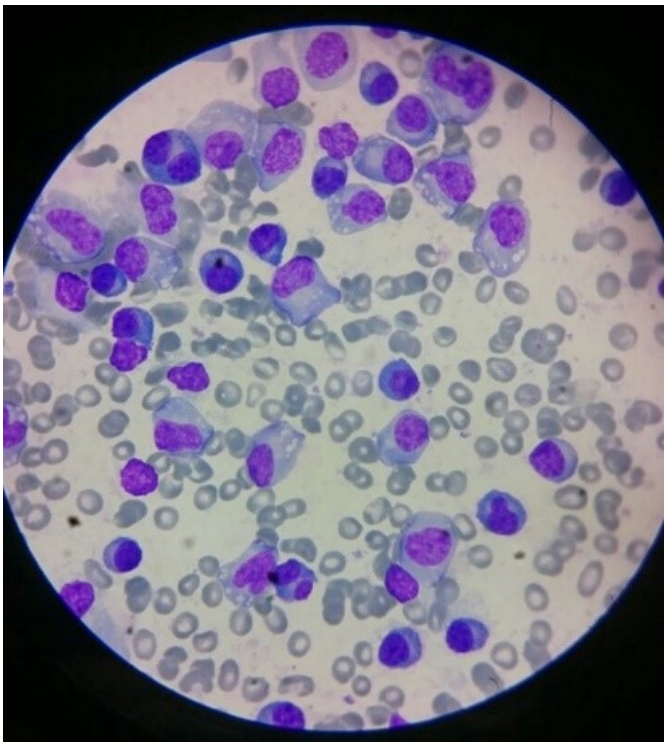
Table 2: Results of laboratory examinations of follow-up of case study of MM, Montes Claros, MG, 2018.

Variable	Result
Hemoglobin	6.7 g/dL
Hematocrit	19.4%
Leukocytes	7,584/ mm3
Platelets	125,000
Serum iron	244 mcg/dL
Ferritin	745.2 ng/ml
Saturation Index of transferrin	96.0%
Sodium	140 mEq/L
Albumin	3.3 g/dL
Globulin	1.7 g/dL
Rheumatoid Factor	Negative
Potassium	3.5 mEq/L
Ionic Calcium	1.45 mmol/L
Magnesium	2.5 mg/dL
Urea	38 mg/dL
Creatinine	1.57 mg/dL
PCR	36 mg/L
CPK	161 U/L
Total Proteins	5 g/dL
LDH	363 U/L
Direct Coombs	Negative
BAAR	Negative

EAS: bacterial flora slightly increased; GRAM of gout: presence of gram-negative rods; EPF: negative for protozoa and metazoan. Chest CT: osteolytic lesions at the level of the thoracic spine, ribs and sternum and scapula. Arose as diagnostic hypotheses MM and metastasis. Thus, the following were requested: myelogram; electrophoresis of serum and urinary protein and x-rays.

The myelogram showed the following description: bone marrow infiltrated by 85% of cells of Plasmacytic lineage (plasmocytes and plasmablasts) (Figure 1). Bone marrow biopsy: bone marrow hypercellularity.

Figure 1 - Myelogram evidencing Plasmacytosis of a case study of MM, Montes Claros, MG, 2018.



Regarding electrophoresis of serum proteins the following results were observed: total proteins: 7.50 g/dL; Albumin: 4.20 g/dL (56.0%); Albumin/ Globulin ratio: 1.37; alpha 1 globulin: 0.40 g/dL (5.3%); alpha 2 globulin: 0.89 g/dL (11.9%); beta 1 globulin: 0.44 g/dL (5.9%); beta 2 globulin: 0.39 g/dL (5.2%); gama globulin: 1.28 g/dL (17.1%). Urinary protein electrophoresis: proteinuria 24 hours: 28.84g/24h; albumin 32.5%; alpha 1 globulin 10.5%; alpha 2 globulin 19,5%; beta globulin 11.5%; gama globulin 25.7%; urinary volume 1350ml; monoclonal bands were not observed.

The results of radiographs of hip left and right femoral pointed multiple osteolytic lesions diffusely, bone demineralization, and osteopenia; reduction of articular spaces on coxofemorais, incipient osteophytosis. The radiographs of the left and right arms identified osteolytic lesions and osteopenia, as well as the x-rays of the left and right femur. Concerning the chest x-rays, the results indicated a cardiothoracic index increased bone structures with multiple osteolytic lesions. In the radiography of the skull there was skullcap with multiple osteolytic lesions and osteopenia.

After diagnosis of MM, the patient was referred to the onco-hematology service for treatment and follow-up. Therapy performed: 6 cycles of chemotherapy with CTD regimen (Cyclophosphamide, Thalidomide and Dexamethasone) associated to Pamidronate with prediction of performing TC-THa.

After initiation of chemotherapy, the patient showed significant improvement in all the symptoms. New laboratory examinations were performed after 6 cycles of chemotherapy (Table 3), showing significant improvement, as well as new electrophoresis of serum proteins (Table 4). Myelogram performed after 4 cycles of chemotherapy showed: bone marrow apparently normocelular and 4% of plasmocytes.

Table 3 - Results of laboratory examinations performed after chemotherapy of a case study of MM, Montes Claros, MG, 2018.

Variable	Values
Hemoglobin	14.1 g/dL
Hematocrit	44.5%
Leukocytes	14,400/mm3
Platelets	312,000
Urea	28 mg/dL
Creatinine	0.85 mg/dL
LDH	17 U/L
Total calcium	215 U/L

Table 4 - Results of serum proteins electrophoresis performed after chemotherapy of a case study of MM, Montes Claros, MG, 2018.

Variable	Values
Albumin	56.4% (3.84g/dl)
Alpha 1 globulin	5.3% (0.36g/dL)
Alpha 2 globulin	14.2% (0.97g/dL)
Beta 1 globulin	5.9% (0.40g/dl)
Beta 2 globulin	4.4% (0.30g/dL)
Gamma globulin	13.8% (0.94g/dL)
Albumin/Globulin ratio	1.29

DISCUSSION

MM is a malignant neoplasm originating from B lymphocytes infiltrating the bone marrow leading to bone destruction and bone marrow insufficiency[10], shows an incidence 50% greater in males when compared to females[4], being that in Brazil the average age at diagnosis is 61 years[1]. In the case reported there was a very atypical epidemiological presentation, because in addition to the patient being female, she is in an age range below the usual.

MM has a heterogeneous presentation, which may correlate to different cytogenetic mutations that occur. However, the findings of anemia, hypercalcemia, renal and bone pain are the most common. For an initial evaluation complete blood count must be requested with platelet count; urea; serum creatinine and serum electrolytes; serum calcium; albumin; lactate dehydrogenase; beta-2-microglobulin and x-rays.[10] In the present case, the patient started the clinical sigs with symptoms of anemia, arthralgia and asthenia. Among the confirmatory diagnostic criteria of the disease it is observed that the patient had a myelogram with intense plasmocitose (85%), presence of lytic lesions (thoracic spine, ribs and sternum and scapula) and hypercalcemia.

Despite the significant advances, MM is still a disease considered incurable and the main objective of treatment is to achieve greater survival time free from the disease. The time to relapse of the disease can vary from months to years depending on the treatment regimen proposed[8]. The patient's age and the presence or not of comorbidities directly influences the choice of treatment and prognosis[10]. Thus, current therapy includes a phased approach, often consisting of induction therapy, consolidation and maintenance therapy. With a wider panorama and more treatment options, the approach of optimal therapy has become increasingly complex. Especially in young patients aged less than 50 years, less than 15% of the cases, where there are doubts whether more intense therapies could be incorporated in this population, which may have a greater tolerance to schemes of conditioning and, consequently, a greater survival time free from recurrence[11].

Upon defining the TCTHa as therapeutic option one should consider the initial exposure to chemotherapeutic agents that may affect the collection of stem cells and also contribute to the onset of secondary neoplasms. Thus, among the main schemes suggested for the first-line treatment of the bortezomibe is more indicated. As examples, the associations bortezomibe and dexamethasone; bortezomibe, cyclophosphamide and dexamethasone; bortezomibe, doxorubicin and dexamethasone; bortezomibe, lenalidomide and dexamethasone; bortezomibe, thalidomide and dexamethasone. However, bortezomibe is not available in the Sistema Único de Saúde (SUS) of Brazil for first-line regimens. For this reason, the CTD regimen was chosen, which has a reasonable response rate of 65%[13], associated to pamidronate and then

TCTHa.

TCTHa is mandatory for consolidation of treatment in eligible patients and has a mortality rate relatively low, approximately 5%[11 12]. Whereas the allogeneic transplantation has a high mortality rate, ranging between 30% and 50%, directly related to the bacterial and fungal infections, interstitial pneumonitis and graft versus host disease. Based on this evidence, TCTHa was chosen for the patient. In this modality of transplanting the stem cells are removed from the peripheral blood from the own patient after mobilisation by apheresis procedure, high doses of chemotherapy are performed and then the stem cells are reinfused into the patient. Therefore, the fundamental point of TCTHa is possibility of conducting an intense chemotherapy for eradication of neoplastic clones.

The assessment of response to treatment and follow-up of these patients must be done through the quantification of serum and or urine monoclonal protein, complete blood count with platelet count, urea, creatinine, ionic calcium and radiological study. According to the evolution and clinical indication myelogram and bone marrow biopsy, dosage of serum free light chains, MRI and PET\CT might also be necessary[10]. Until the moment of conclusion of this work, the patient had not performed the TCTHa, however, showed significant improvement in new examinations and on quality of life and is under propaedeutic for the completion of treatment of consolidation with TCTHa.

FINAL CONSIDERATIONS

The case report showed a young patient diagnosed with MM through compatible clinical history associated with bone marrow aspirate showing 85% plasmocytes; hypercalcemia and osteolytic lesions. The patient was treated with 6 cycles of CTD chemotherapy and is under propaedeutic for completion of TCTHa.

MM is an uncommon neoplasm in young people, which often can delay the initial diagnosis and, therefore, affect the outcomes. It is concluded that strategies for the early recognition in this population should be defined and with the therapeutic options currently generates a degree of uncertainty about the best option for a more lasting complete remission and control of the disease in the long term, especially when access to new drugs is restricted.

The authors declare not having interest conflict.

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