CASE REPORT

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Micromolecular multiple myeloma with chronic kidney failure in a young female patient on continuous hemodialysis

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Abstract

The maximum incidence of multiple myeloma appears in the 6th–7th decade of life and although the number of patients aged les than 60 years is increasing in recent years, the diagnosis of a monoclonal gammopathy in a young patient, under the age of 40 years remains a rarity. Literature data cite an incidence of approximately 2.2% in patients less than 40-year-old and an incidence of 0.3% in patients less than 30-year-old of all cases diagnosed with multiple myeloma. We present the case of a 32-year-old patient, being on continuous hemodialysis for chronic kidney failure for about a year, at the Hematology Clinic of Craiova, Romania. We investigate the origin of a serum monoclonal component revealed when performing serum protein electrophoresis. Bone marrow examination revealed the presence of a plasma cell infiltrate of 18%, which associated with the presence of a serum monoclonal component and in the conditions of renal failure as a complication of the disease, has allowed the diagnosis of multiple myeloma.

Keywords: multiple myeloma, chronic kidney failure, serum free chains.

Introduction

Multiple myeloma is a plasma cell dyscrasia, representing approximately 1% of all malignancies [1] and being the most common malignant monoclonal gammopathy; annually, there are diagnosed 4–5 new cases per 100 000 people, representing approximately 60 000 cases in Europe. It predominantly affects old patients, with a maximum incidence between 60 and 70 years [1, 2]. Young patients with multiple myeloma may have particular clinical presentations and indolent evolution with higher survival compared to old patients [3]. Multiple myeloma remains an incurable disease by conventional chemotherapy. The use of new molecules, having as target both myelomatous cells and bone marrow microenvironment, associated with high doses of cytostatic agents have changed the prognosis of these patients. The aim of the paper is to present the youngest patient diagnosed with multiple myeloma at the Hematology Clinic of Craiova, Romania.

Patient, Methods and Results

C.N. patient, aged 32 years, came to the doctor about a year ago because of physical asthenia, dizziness, and noticing the appearance of pale coloration of the skin. Investigations performed on this occasion revealed a severe normocytic normochromic normo-regenerative anemia (6.4 g/dL). Among the standard investigations that were made, we noticed the presence of an elevated value of serum creatinine (6.7 mg/dL). There was suspicion of collagenosis onset. The immunological investigations performed on this occasion are: anti-double stranded DNA antibodies-negative, serum complement C4 25 mg/dL, C3 48.4 mg/dL, rheumatoid factor 6.6 IU/mL, antinuclear antibodies-negative. Serum protein electrophoresis was not performed. Because the patient started suffering of anuria, dialysis was established, along with correction of anemia syndrome by transfusions with the same Rh blood group erythrocytes, then administration of erythropoietin.

Starting with March 2012, the patient complained of pain in the lumbar spine irradiated to lower limbs and paresthesia in the extremities. Serum protein electrophoresis performed on this occasion revealed a monoclonal peak in gamma region, the patient being guided to go at the Hematology Clinic of Craiova in May 2012 for further investigations.

Subjective findings: average general state, lower limb paresthesia, spontaneous pain and pain at the lumbar spine mobilization.

Objective findings: underweight, superficial sensibility disorders of the lower limbs.

Paraclinical testing: ESR 4 mm/h, Hb 12.4 mg/dL (the patient was treated with erythropoietin), T-cells 100 000/mm^2, normal leukocyte formula, GPT 7.2 U/L, bilirubin 0.27 mg/dL, blood glucose level 74 mg/dL, serum uric acid 2.63 mg/dL, creatinine 2.83 mg/dL, β-2 microglobulin 5.8 mg/L.

Serum protein electrophoresis: total protein 6.32 g/dL, albumins 55.4%, α1 2.2%, α2 9.2%, β-globulins 7.9%, γ-globulins 25.3%, A/G ratio 1.24. In the migration area of γ-globulins, there can be noticed the appearance of a monoclonal band (Figure 1).

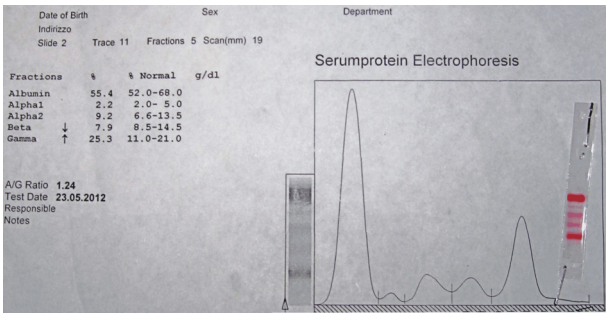

Figure 1 – ***Serum protein electrophoresis. There can be noticed an appearance of monoclonal peak in the gamma migration area.***

Dosage of serum free chains: kappa serum free light chains 1250 mg/L, lambda free light chains 26.1 mg/L; kappa/lambda ratio 47.89 (normal values 0.26–1.65).

The bone marrow examination initially performed revealed the presence of a plasma cell infiltrate of 8–9%. The presence of a plasma cell infiltrate more than 10% in the bone marrow is a major criterion for diagnosis in multiple myeloma. On the terms of highlighting the presence of serum monoclonal component and the occurrence of complications (renal failure), there was suspicion of malignant monoclonal gammopathy, so we decided to repeat the bone marrow cytology.

Bone marrow cytology: bone marrow smears rich in nucleated cell elements. The lympho-plasmocyte series 18% polymorphic mononuclear and rarely multi-nucleated plasma cells (Figures 2 and 3).

Bone radiography (brain pan, costal plastron, lumbar spine) showed no osteolytic lesions.

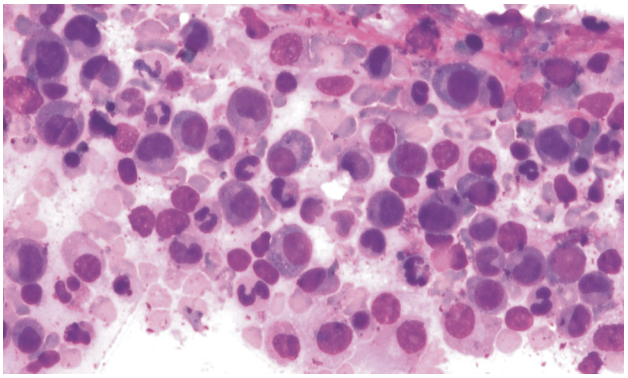

Figure 2 – ***Morphological examination of bone marrow smear. Bone marrow infiltration with plasma cells in 18%. May–Grünwald–Giemsa (MGG) stain, ob. 20×.***

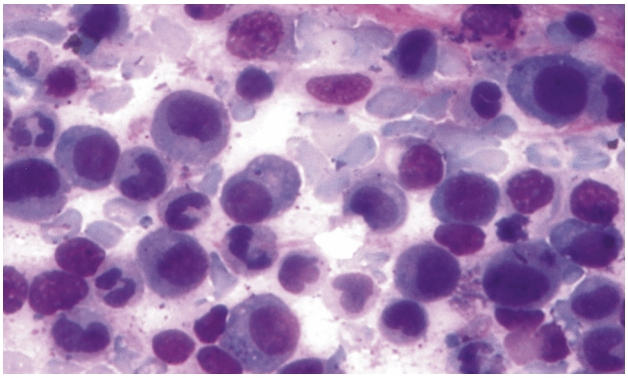

Figure 3 – ***Morphological examination of bone marrow smear. There can be noticed the presence of cells with round nucleus, eccentrically located, with condensed chromatin, abundant cytoplasm with perinuclear clear halo (plasma cells). MGG stain, ob. 40×.***

Lumbar spine NMR showed no evidence of osteolytic lesions.

The cytogenetic examination was not performed.

The case was interpreted as micromolecular multiple myeloma with light chains K, stage III according to the international staging system, respectively IIIB according to Durie–Salmon staging system. The case associates many negative prognosis factors. We initiated chemo-therapy with Velcade + Endoxan + Dexamethasone, the case being eligible for autologous bone marrow transplantation. The evaluation of the response to treatment will be done after four cycles of polychemo-therapy. If there is a favorable response, the patient will be guided to make the autologous bone marrow transplantation. Given the severe impairment of the renal function, there will be chosen a low-dose of Melphalan (100 mg/m^2) as conditioning regimen, to avoid toxicity.

Discussion

The results after the auto-TMO is similar to those using full-dose conditioning regimens (200 mg/m^2) [4, 5]. The maintenance therapy may be taken into account after the auto-TMO in case of a complete response (CR) (serum free chains undetectable by immunofixation and myelomatous plasma cells in the bone marrow under 5%) or stringent CR (complete response and normal ratio of free chains or absence of clonal cells in the red bone marrow detected by immunohistochemistry or immunofluorescence [6].

Multiple myeloma represents about 10% of hematological malignancies [7, 8]. Multiple myeloma is a heterogeneous disease, with survival between one year and over 10 years. Average survival in unselected patients is of three years. The survival rate at five years is of 35%. Survival is higher in younger patients compared to old patients [2, 3].

International staging system (ISS) identifies three stages: stage I (β-2 microglobulin <3.5 mg/L and serum albumin ≥3.5 g/100 mL: average survival of 62 months); stage II (β-2 microglobulin <3.5 mg/L but serum albumin <3.5 g/dL or β-2 microglobulin 3.5 to <5.5 mg/L regardless of the albumin serum level: average survival of 44 months); stage III (β-2 microglobulin ≥5.5 mg/L: average survival of 29 months) [9].

Our case came under stage III of disease, considering the value of β-2 microglobulin that was greater than 5.5 mg/L.

In patients diagnosed with multiple myeloma, before initiating the specific therapy, there should be identified the prognosis factors and established the prognostic risk affecting the therapeutic decision.

Prognosis factors in myeloma usually refer to cell proliferation (cell proliferation index), tumor mass

(clinical stage, bone marrow plasmocytosis), or patient status (hemoglobin, serum calcium, serum creatinine and serum albumin values). One of the most important prognostic markers is the value of β-2 microglobulin.

Conventional cytogenetic tests reveal abnormal karyotype in only one third of the cases of multiple myeloma [10]. However, the presence of hypodiploidy [11] or the deletion of chromosome 13 are predictive factors of a short-term survival [12]. FISH technique reveals abnormalities in over 90% of patients with multiple myeloma [10]. In a clinical trial of the *Eastern Cooperative Oncology Group* (ECOG) [13], in which there were included 351 patients, the presence of t(4;14), t(14;16) or 17p were associated with a poor prognosis (average survival of 25 months). Monosomy and/or the deletion of chromosome 13 detected by FISH is a factor that is associated with reduced survival, especially when it is accompanied by a level of beta-2 microglobulin of over 2.5 mg/L [14].

In 2009, the *International Myeloma Workshop* concluded that cytogenetic test and FISH technique are important in risk stratification. Both FISH technique and cytogenetic test are performed on samples collected from the red bone marrow. Highlighting any cytogenetic abnormality suggests the presence of a high-risk disease, the abnormalities with poor prognosis being: the deletion of chromosome 13 or 13q, t(4;14) and 17p deletion; *in situ* hybridization detection of t(4;14), t(14;16) and 17p deletion. Patients suffering of a disease with a high proliferation rate are also included in the high-risk category. The problem is that these techniques are expensive and they are not always available for the clinician. The cytogenetic test for the female patient diagnosed at our clinic was not performed.

Serum kappa/lambda ratio seems to have a prognostic impact in multiple myeloma, too. Overall survival is significantly reduced in patients with ratio >32. Thus, the initial ratio of serum free chains at diagnosis is a predictive factor of prognosis in myeloma and it may be incorporated into the ISS in order to improve risk stratification [15]. Thus, 47.89 kappa/lambda ratio in the female patient diagnosed at our clinic is a negative prognosis factor.

High-risk patients are about 25% of newly diagnosed cases of multiple myeloma, with a survival rate of two years or less [16]. High-risk patients may have primary resistance to treatment or even though they respond to the conventional induction therapy followed by autologous bone marrow transplantation, they tend to relapse quickly. Thus, new therapeutic agents can be considered as first-line therapy in these patients, in the attempt to improve the response to induction therapy.

Because the cytogenetic test was not performed in our case, the main negative prognosis factors identified in our patient were: the value of β-2 microglobulin, the advanced stage, the presence of renal failure in the stage of continuous hemodialysis, and the kappa/lambda ratio of 47/1.

Renal failure in patients with multiple myeloma is a complication encountered in evolution to half of patients with myeloma, approximately 20–30% of patients presenting renal impairment since the diagnosis [17]. Its multifactorial pathogenesis includes: myelomatous tubulopathy secondary to the elimination of light chains in urine, hypercalcemia, dehydration, infections, use of non-steroidal anti-inflammatory drugs or of contrast agents used in radiology.

When treating patients with multiple myeloma there should be considered both therapy of the underlying disease and complications [18–20].

Therapy guides developed by *NCCN* in 2011 recommend the following therapeutic approach: the combination of Bortezomib / Cyclophosphamide / Dexamethasone as induction therapy for bone marrow transplantation candidates, the combination of Bortezomib / Dexamethasone (without Cyclophosphamide) or the combination of Melphalan / Prednisone / Lenalidomide as induction therapy in patients who are not candidates to bone marrow transplantation [21]. Young age that makes the patient eligible for autologous bone marrow transplantation and the presence of several negative prognostic factors were the reasons for the triple combination therapy (with Velcade + Cyclophosphamide + Dexamethasone) that was initiated according to the guides. The achievement of a complete response will be followed by peripheral stem cell harvest and autologous bone marrow transplantation.

FDA approved, in January 2012, the subcutaneous administration of Bortezomib. The effectiveness of therapy by subcutaneous administration is not inferior to that obtained by conventional intravenous administration, but the administration safety profile was improved. Thus, the incidence of neuropathy of grade 2 or higher was of 24% for subcutaneous administration compared with 41% for intravenous administration; there was found neuropathy of grade 3 or higher in 6% of cases with subcutaneous administration, compared to 16% with intravenous administration [22]. Initiating therapy with Bortezomib with subcutaneous administration may be considered in patients with preexisting peripheral neuropathy or peripheral neuropathy risk. The presence of preexisting neuropathy in our case and also the increased risk of neuropathy induced by Bortezomib therapy are arguments for choosing subcutaneous administration.

Conclusions

Although multiple myeloma is usually described as being the "old people's anemia", young age is not an exclusion criterion for the diagnosis. Our case presents the youngest patient with multiple myeloma diagnosed at the Hematology Clinic of Craiova, Romania. The standard of treatment in young patients is represented by 4–6 cycles of induction followed by auto-TMO and maintenance therapy when a complete response is obtained. Despite the progress of the therapeutic approach, which has led to an increased survival without signs of disease, and to the overall survival of these patients, and also to the improvement of the quality of life, multiple myeloma still remains an incurable disease.

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