ACTA MEDICA TRANSILVANICA December27(4):18-20
Online ISSN 2285-7079

THE ACCIDENTAL DIAGNOSIS OF MULTIPLE MYELOMA OF A PATIENT SUFFERING NEUROLOGICAL SYMPTOMS

LIDIA MARIA MONDOC[1] , ALINA CĂTANĂ[2], ILIE MONDOC[3], ROMEO-GABRIEL MIHAILĂ[4]

[1,2,4]Sibiu County Emergency Clinical Hospital Sibiu, [3,4]"Lucian Blaga" University of Sibiu

Keywords: *multiple myeloma, stroke, immunelectroforesis, remission*

Abstract: *Multiple Myeloma is a malignancy of blood cells often discovered by chance that mainly affects elderly people. We present the case of a 75-year old female patient with a known history of neurological pathology presented to the department of Neurology for gait abnormality, dizziness and intermittent bone pain. Due to laboratory abnormalities the patient was referred to the hematology department for further investigation. An immunogram was made which showed an increase of IgA and low levels of immunoglobulin G and M. In the bone marrow aspiration the plasma cells were present between 34% and 42%. Further investigations were made and the patient was diagnosed with Multiple Myeloma type IgA with secretions of light kappa chains stage I A. Patient began treatment with chemotherapy, proteasome inhibitors, corticosteroids and zoledronic acide. Since Multiple Myeloma is not a curable disease, at some point, patients will relapse and new molecules should be considered.*

INTRODUCTION

Multiple myeloma is a cancer of the plasma cells, which normally are responsible for producing antibodies.(1)

Plasma clonal cells responsible for multiple myeloma come from post-germinal B lymphoid cells that later develop into progenitor cells in the bone marrow.(2) There are several forms of the disease, from the asymptomatic premalignant state of plasma cell proliferation (MGUS- monoclonal gammopathy of unknown significance), then the asymptomatic multiple myeloma (SMM- smoldering multiple myeloma), and finally the neoplastic disease (multiple myeloma) affecting various organs and tissues.(3,4) There are several types of multiple myeloma, but it is well known that IG A multiple myeloma is considered to have a poor prognosis.

Multiple myeloma is the second most common hematological neoplasm, after lymphoma, with a median age at diagnosis of 65-70 years, but cases diagnosed before the age of 60 have also been reported.(5) The occurrence of multiple myeloma is extremely rare before the age of 30, but cases have been reported with a frequency of 0.02% to 0.3%, especially in male patients.(6,7)

The causes of the cancer remain unknown, but recent studies have shown the existance of a familial predisposition, even though multiple myeloma is not considered to be a genetic disease.(8,9) The treatment for Multiple Myeloma is focused on chemotherapy regiments, corticotherapy, proteasome inhibitors, immunomodulators and monoclonal antibodies.

Although in multiple myeloma there are several innovative lines of therapy, the better response rate to treatment and especially the higher survival rate is due to the possibility of performing autologous stem cell transplant.(10,11) Multiple myeloma can be treated but remains an incurable disease.

CASE REPORT

We present the case of a 75-year old female patient, with a known history of neurological pathology (lacunar stroke due to occlusion of the right carotid artery, left hemiparesis, bilateral occlusions of the carotid arteries, aortic atheromatosis), presented to the department of Neurology for gait abnormality, dizziness and intermittent bone pain. The patient's responses to the neurological examinations performed were all within normal limits, with the exception of a mild gait disturbance.

Paraclinical laboratory investigations show changes in VEM-106,3 fL (81-102 fL), Hct-51% (35-47%) and the erythrocyte sedimentation rate-36 mm/h (< 20mm/h).

Because of these laboratory abnormalities and of a normal neurological examination the patient was referred to the hematology department for further investigation.

Clinically the patient was asymptomatic but with intermittent bone pain.

X-rays of the pelvis bones, spine, ribs and skull were performed and no osteolysis was observed. In our department the laboratory investigations were within normal limits except for a hyperuricemia. An immunogram was made which showed the following changes: Ig A-1000 mg/dL (70-400 mg/dL), Ig G-337 mg/dL (700-1600 mg/dL), Ig M-12 mg/dL (40-230 mg/dL).

These results raised suspicion of a malignant proliferation so more investigations followed.

The protein electrophoresis was normal (without monoclonal peak), but the light kappa and lambda chain from the serum were modified: kappa chain-82,8 mg/L (3,3-19,4 mg/L), lambda chain-5,8 mg/L (5,7-26,3 mg/L) and the kappa/lambda ratio- 14,3 (0,26-1,65).

A bone marrow aspiration was made and the results confirmed the diagnosis of multiple myeloma (the presence of plasma cells between 34% and 42%. The plasma cells appeared smaller, some of them with nucleus and reddish cytoplasm).

The final diagnosis was Multiple Myeloma type IgA with secretions of light kappa chains stage I A.

Even if the patient did not present CRAB criteria we

[1]Corresponding author: Lidia Maria Mondoc, B-dul. Corneliu Coposu, Nr 2-4, Sibiu, Romania, E-mail: lidia2jc@yahoo.com, Phone: +40751 503855
Article received on 16.08.2022 and accepted for publication on 20.12.2022

decided to start treatment because the bone marrow was infiltrated with plasma cells between 34% - 42% and Multiple Myeloma type IgA is known to be an aggressive form of the disease.

With VAD protocol and Zolendronic Acid she responded well to the treatment with a decrease of seric Immunoglobulin A from 1000 mg/dL to 66 mg/dL. Patient continued the treatment with Bortezomib (1,3 mg/m2 on days 1,4,8 and 11) plus Dexamethasone (24 mg on the same days).

After four cycles of treatment the patient's response was excellent, the seric immunogram giving the following results: Ig A-156 mg/dL (70-400 mg/dL), Ig G-234 mg/dL (700-1600 mg/dL) and Ig M-15 mg/dL (40-230 mg/dL).

Because the patient presented with secondary peripheral neuropathy due to Bortezomib treatment, we reduce the dose (1 mg/m2).

Upon re-evaluation of the bone marrow aspiration the plasma cells were observed to be mature and within normal limits (1-2%).

During treatment the patient has not experienced severe side effects and her response to treatment was classified as stable disease (SD) until today.

DISCUSSIONS

Multiple myeloma represents approximately 1% of all existing neoplasias and approximately 10% of all malignant hemopathies. The median age at diagnosis is around 65 years, being more common among men.(12) Unlike bone metastases produced by other malignancies, osteolytic lesions from multiple myeloma are characterized by the lack of new bone tissue formation.(13) Often Multiple Myeloma is discovered by accident through routine blood screening and only rarely because of the clinical manifestations of the disease. Prodromal signs are in most cases: weakness, anemia, bone pain, pathologic fractures and in an advanced stage of the disease spinal compression and renal failure.(14) It is known nowadays that prior to the diagnosis of multiple myeloma, patients present a premalignant condition called MGUS (monoclonal gammopathy of undetermined significance) and only a small part of them (1% per year) turn into active multiple myeloma.(15)

What causes the premalignant cell to remain dormant even over 30 years remains unknown, but even in cases diagnosed with MGUS, genetic mutations such as del (17p13) and t (4;14) have been detected, which gives the patient a negative prognosis regarding the evolution of the disease towards progression but also a poor response to treatment.(16)

Recent studies have shown that not only the patient's mutational status has a negative impact, but also the interaction between tumor cells and the cellular microenvironment.(17) It seems that the cellular microenvironment plays an extremely important role regarding bone destruction, growth and survival of myeloma cells as well as in the problem of dealing with multidrug resistance.(18,19)

According to The Revised International Myeloma Working Group (IMWG), the diagnosis is based on the existence of CRAB criteria (one or more), together with at least 10% clonal plasma cells in the bone marrow or a plasmacytoma proven by biopsy. CRAB diagnostic criteria consist of: hypercalcemia, renal dysfunction, anemia or bone lesions.(20)

Patients suspected or already diagnosed with multiple myeloma require additional tests to highlight the monoclonal M protein in the serum by SPEP (serum protein electrophoresis), SIFE (serum immunofixation) and serum FLC.(21) In approximately 2% of the total number of patients diagnosed with multiple myeloma, there is no secretion of the monoclonal component and thus we speak of non-secretory myelomatous disease.(22)

There are five types of immunoglobulins in Multiple Myeloma that can be over-producted: A,G, M, D and E.

The most common over-production of Ig in Multiple Myeloma is G. All types of Myeloma are treated in the same way, but they respond to treatment differently and the prognoses are totally different.

Multiple Myeloma type Ig A is the second most frequent variation of the disease, and usualy does not respond well to treatment. The median survival of these patients is about 3 years. One of the most important prognostic factors in Ig A type is the presence of the chromosome 13 deletion.(23) The patients who have this cytogenetic status are less likely to respond to treatment, and the median duration of life is shorter.

Multiple myeloma is a chronic disease, with a slow evolution, in which the survival rate has improved significantly in the last 15 years.(24) This is due to the introduction into current practice of new therapeutic molecules such as: Bortezomib, Carfilzomib, Lenalidomide and Thalidomide.

The most recently approved drugs were: Pomalidomide, Ixazomib, Daratumumab and last but not least CAR-T (chimeric antigen receptor T) therapy.(25,26,27,28)

All these new molecules administered in specific combinations act in the myelomatous cell through various mechanisms. Thalidomide, Lenalidomide and Pomalidomide are immunomodulatory agents that induce the degradation of 2 B cell-specific transcription factors, directly causing myeloma cell cytotoxicity by inducing free radicals and destroying cellular DNA. They also have anti-angiogenic, immunomodulatory properties and inhibit tumor necrosis factor alpha.(29)

Bortezomib, Carfilzomib and Ixazomib are proteasome inhibitors.(30) On the other hand, Daratumumab is a monoclonal antibody that targets the CD 38 marked cell.(31)

Although we have many therapeutic options available today, patients are typically treated with 3-4 induction cycles before peripheral stem cell harvesting takes place.

Autotransplantation of peripheral stem cells remains the method of choice that can give the patient the longest free period of treatment.

However, recent studies have shown a significant improvement in cases where Lenalidomide was administered as maintenance therapy after stem cell autotransplantation.(32)

Although the therapeutic options in multiple myeloma are increasing, the choice of the appropriate treatment will be made depending on the eligibility or not of the patient for stem cell transplantation but also depending on the risk stratification factors. Another key element for the favorable prognosis of patients with multiple myeloma is negative minimal residual disease (MRD). However, additional studies are needed to determine if the treatment of patients with multiple myeloma can be decided according to the MRD status and if sustained MRD negativity can be considered as a marker of cure of the disease.(33)

In our case we were not able to investigate the cytogenetic status of the patient, nor the MRD status. However 1 year after her diagnosis of Multiple Myeloma she is still living and responding well to the treatment.

CONCLUSIONS

Multiple Myeloma is commonly diagnosed through routine blood screening and rarely because the patient is symptomatic, in an advanced stage of the disease. Most patients are elderly (over 60). Multiple Myeloma type Ig A is the second most frequent variation and responds poorly to the treatment. The treatment must be started immediately after diagnosis. Although Multiple Myeloma therapy improved significantly in recent years due to the new drugs (especially proteasome

inhibitors and immunomodulators) and autologous stem cell transplant, we can only speak about different types of transient remission of the disease, not a cure.

REFERENCES

1. Kyle RA, Rajkumar SV. Multiple Myeloma. Blood. 2008;111(6):2962-72.
2. Kazandjian D, Mailankody S, Korde N, Landgren O. Smoldering multiple myeloma: pathophysiologic insights, novel diagnostics, clinical risk models, and treatment strategies. Clinical advances in hematology & oncology: H&O. 2014;12:578-87.
3. Palumbo A, Anderson K. Multiple Myeloma. New England Journal of Medicine. 2011;364:1046-60.
4. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. ASH Education Program Book. 2013;2013:478-87.
5. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78:21-33.
6. Blade J, Kyle RA, Greipp PR. Multiple myeloma in patients younger than 30 years. Report of 10 cases and review of the literature. Archives of internal medicine. 1996;156:1463-8.
7. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
8. Koura DT, Langston AA. Inherited predisposition to multiple myeloma. Ter Adv Hematol. 2013 Aug;4(4):291-7.
9. Lynch HT, Sanger WG, Pirruccello S, Quinn-Laquer B, Weisenburger DD. Familial Multiple Myeloma: a Family Study and Review of the Literature. Journal of the National Cancer Institute. 2001;93:1479-83.
10. Kristinsson SY, Landgren O, Dickman PW, Derolf ÅR, Björkholm M. Patterns of Survival in Multiple Myeloma: A Population-Based Study of Patients Diagnosed in Sweden From 1973 to 2003. Journal of Clinical Oncology. 2007;25:1993-9.
11. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of Improved Survival in Patients With Multiple Myeloma in the Twenty-First Century: A Population-Based Study. Journal of Clinical Oncology. 2010;28:830-4.
12. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: A Cancer Journal for Clinicians 2021;71:7–33.
13. Roodman GD. Pathogenesis of myeloma bone disease. Leukemia. 2009;23:435–41.
14. Longo, Dan. Harrison's Principles of Internal Medicine 18th Edition. Mc Graw Hill Medical. 2012. p. 938.
15. Kyle RA, Larson DR, Therneau TM, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. N Engl J Med. 2018;378(3):241–9.
16. Bustoros M, Sklavenitis-Pistofidis R, Park J, et al. Genomic Profiling of Smoldering Multiple Myeloma Identifies Patients at a High Risk of Disease Progression. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(21):2380–9.
17. Das R, Strowig T, Verma R, et al. Microenvironment-dependent growth of preneoplastic and malignant plasma cells in humanized mice. Nat Med. 2016;22 (11):1351–7.
18. Alameda D, Saez B, Lara-Astiaso D, et al. Characterization of freshly isolated bone marrow mesenchymal stromal cells from healthy donors and patients with multiple myeloma: transcriptional modulation of the microenvironment. Haematologica. 2020;105(9):e470–3.
19. Damasceno D, Almeida J, Teodosio C, et al. Monocyte Subsets and Serum Inflammatory and Bone-Associated Markers in Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma. Cancers (Basel). 2021;13(6).
20. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group Updated Criteria for the Diagnosis of Multiple Myeloma. Lancet Oncol. 2014;15:e538–48.
21. Katzmann JA, Dispenzieri A, Kyle R, et al. Elimination of the Need for Urine Studies in the Screening Algorithm for Monoclonal Gammopathies by Using Serum Immunofixation and Free Light Chain Assays. Mayo Clin Proc. 2006;81:1575–8.
22. Chawla SS, Kumar SK, Dispenzieri A, et al. Clinical course and prognosis of non-secretory multiple myeloma. European journal of haematology; 2014.
23. Dutta AK, Hewett DR, Fink JL, Grady JP, Zannettino AC. Cutting edge genomics reveal new insights into tumour development, disease progression and therapeutic impacts in multiple myeloma. British Journal of Haematology; 2017.
24. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122–8.
25. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. The New England journal of medicine. 2016;375:754–66.
26. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017;130:974–81.
27. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020;396:186–97.
28. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021;397:2361–71.
29. Krönke J, Udeshi ND, Narla A, et al. Lenalidomide Causes Selective Degradation of IKZF1 and IKZF3 in Multiple Myeloma Cells. Science. 2014;343:301–5.
30. Rajkumar SV, Richardson PG, Hideshima T, Anderson KC. Proteasome Inhibition as a Novel Therapeutic Target in Human Cancer. J Clin Oncol. 2004;23:630–9.
31. Lonial Sagar, Weiss Brendan M., Usmani Saad Zafar, et al. Single-agent daratumumab in heavily pre-treated patients with Multiple Myeloma: An Open-Label, International, Multicentre Phase 2 trial (Sirius). Lancet 2016;Prepublished online DOI: 10.1016/S0140-6736(15)01120-4.
32. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017;376:1311–20.
33. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17:e328–46.