Myeloma cells with asurophilic granules - an unusual morphological variant – case presentation

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Abstract:

We present the case of an 80-year-old man who was admitted for anemia, back pain and progressive weakness. After a workup of clinical and laboratory data, the final diagnosis was multiple myeloma. The bone marrow aspirate revealed 53% myeloma cells with peculiar and rare morphological features: numerous large asurophilic–bright red granules – mucopolizaccharides and immunoglobulins secreted and accumulated in the endoplasmic reticulum, typically known as Russel bodies.

Key words: plasma cells, asurophilic granules, Russel bodies, Dutcher bodies.

1. Introduction

Multiple myeloma is a neoplastic plasma cell dyscrasia characterized by monoclonal proliferation of plasma cells with their accumulation in the bone marrow [1]. The malignant plasma cells produce an immunoglobulin (Ig) or protein M, a homogeneous Ig, formed of only one type of heavy chain and one type of light chain (kappa or lambda); the immunohistochemical particularities of this Ig establish the clinical features of the disease.

Diagnostic criteria for multiple myeloma include: more than 10% atypical plasma cells in the bone marrow, a monoclonal immunoglobulin in the serum or light chains in the urine and the presence of osteolytic lesions [2].

Anemia, renal insufficiency, hypercalcemia, metabolic dysfunctions and infections are all clinical features of the disease, with prognostic value [3, 4].

Myeloma cells have different morphological variants.

Usually, bone marrow aspirate shows *clusters* with a variable number of plasma cells; this underlines the need of careful examination of more than one smear. The bone marrow involvement is usually “focal”. Solitary plasma cell infiltration appears in rare cases [2].

Myeloma cells have distinct morphological criteria: [2, 5, 6]

Myeloma cells are larger than reactive plasma cells, with high nucleo/cytoplasmic ratio. The nucleus is displaced from the center of the cell, with nodular chromatin pattern; some of the cells may present a nucleolus and a perinuclear clear zone. Multi - or binucleated plasma cells are present. The cytoplasm is basophilic with large intracytoplasmic inclusions (mucopolysaccharides and immunoglobulins secreted and accumulated in the endoplasmic reticulum), known as Russell bodies, resembling a bunch of grapes [2, 7]. Dutcher bodies are PAS positive intranuclear inclusions seen in plasma cells. In myeloma, there is often discordance between nucleus and cytoplasm, the former appearing immature and the latter highly differentiated. There is often a high polymorphism – there are seen both abnormal plasma cells, and transitional forms – lymphoplasmacytoid – cells with intermediate features between lymphocytes and plasma cells [2].

Disorders to be considered in the differential diagnosis of multiple myeloma include monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, plasma cell leukemia, bone solitary plasmacytoma, extramedullar plasmacytoma, primary amyloidosis, chronic lymphocytic leukemia and bone marrow metastasis [1].

The median survival period after diagnosis is approximately three years. Among the prognostic factors identified in this disease are: plasma cell proliferation index, β2 microglobulin level, C reactive protein, creatinine, lactate dehydrogenase (LDH), low serum albumin, plasmablast morphology [8], abnormal karyotypes (the complete deletion of chromosome 13) or t (4; 14), t (14;16) translocation [1, 4].

Although there is virtually no prospect of a cure with current therapies (VMCP, VAD regimens etc, plus bisphosphonates) [9, 10, 11, 12, 13], there are several options under investigation that include combinations of drugs such as Thalidomide, Bortezomib and CC - 5013 - Lenalidomide. [12, 14, 15] Several groups have used VAD followed by intensive myeloablative therapy with autologous marrow transplantation in younger patients [12, 16].

2. **Full case presentation**

We present the case of an 80 - year - old man, P.N. with percutaneous vertebroplasty in February 2007; he was in his usual state of health until two months prior to presentation, when he began to complain of back pain and progressive weakness.

A complete blood cell count (CBC) revealed normochromic, normocytic anemia (hemoglobin 7.1 g/dl), rouleaux formation was appreciated on peripheral blood smear, biological inflammatory syndrome (ESR 60mm/hour, C reactive protein – positive), high lactate dehydrogenase (LDH 301U/l), creatinine 3.97mg/dl, BUN 157mg/dl, hypokaliemia (K 3.6mmols/l), hypercalcemia (Ca - 10.31mg/dl), hyperuricemia (8mg/dl). Serum protein electrophoresis detected a monoclonal peak limited to the gamma region of the electrophoretic strip (albumin 30%, alpha1 = 2.9%, alpha2 = 14.4%; beta = 8.7%; gamma = 44%); immunoelectrophoresis showed high values of IgG (35g/l), with low IgA (0.295g/l) and IgM (0.497g/l); urine immunofixation detected Bence Jones proteinuria.

Bone marrow aspiration was performed and revealed a hypercellular bone marrow with increased plasma cells (53%) with decreased granulocytic and erythrocytic components, with a slight megaloblastic deviation, and with present thrombocytogenic megakaryocytes (Figure 1)

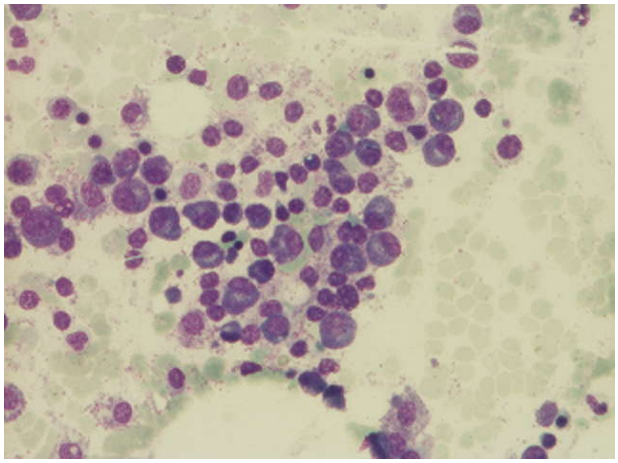


Figure 1: Clusters of plasma cells can be seen throughout this view of the aspirate – P.N. case (BM –MGG, objective 20X)

Flowcytometry analysis of the bone marrow aspirate is not included in the diagnostic criteria of multiple myeloma; in this case, no aberrant phenotype was noted – the profile of plasma cells was CD 38+ CD 138+ CD 56+ (favorable prognostic factor) and CD 19 - (Figure 2, 3).

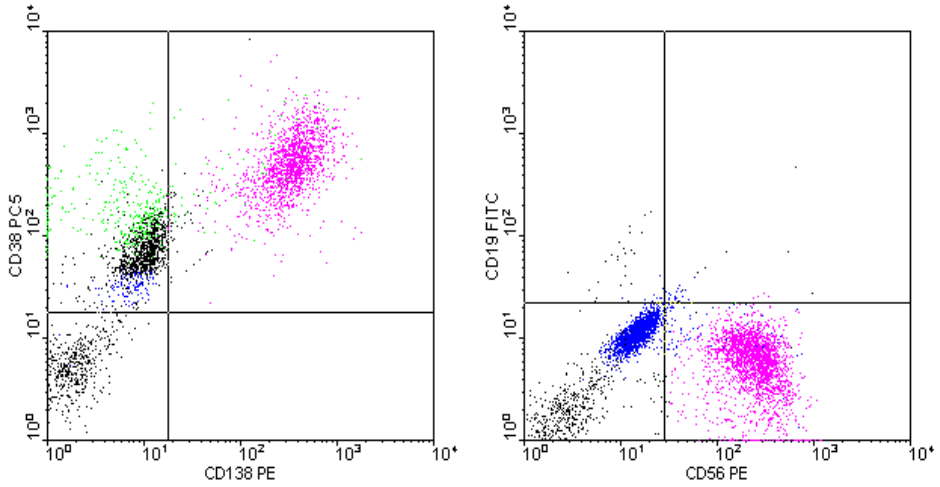


Figure 2: Dot - plot histograms: plasma cells (purple) positive for CD 38, CD 138, CD 56 and negative for CD 19 (BD Facs - Calibur, Software CellQuest version 3.3) - P.N. case.

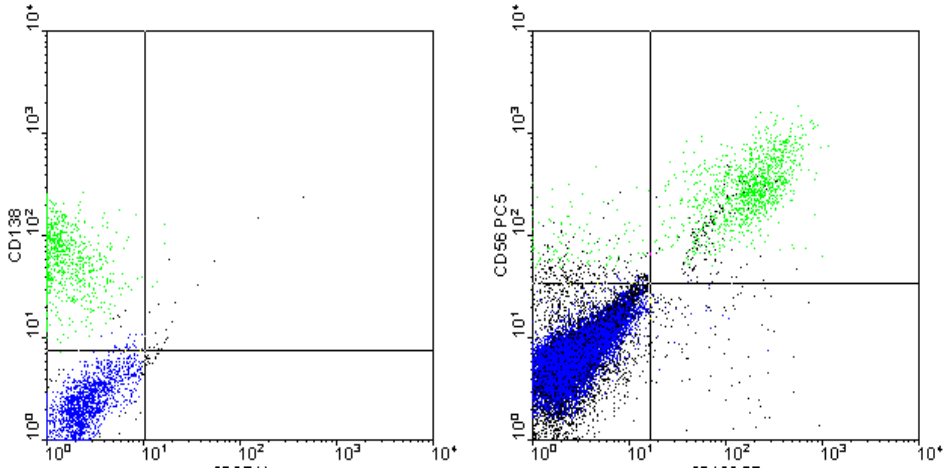


Figure 3: Dot - plot histograms: plasma cells (green) positive for CD 38, CD 138, CD 56 and negative for CD 65 (BD Facs - Calibur, Software CellQuest version 3.3) - P.N. case.

The particular aspect of this case resides in the morphological features of the myeloma plasma cells (Figures 4 to 7). These are large cells arranged in clusters, with basophilic cytoplasm, with excentrically placed nucleus and a perinuclear clear zone. The chromatin has a particular nodular pattern; an inconstant nucleolus may be observed. Plasma cells had numerous large azurophilic - bright red granules - mucopolysaccharides and immunoglobulins secreted and accumulated in the endoplasmic reticulum, typically known as Russel bodies [2, 5, 6].
Large bi - and multinucleated plasma cell were described.

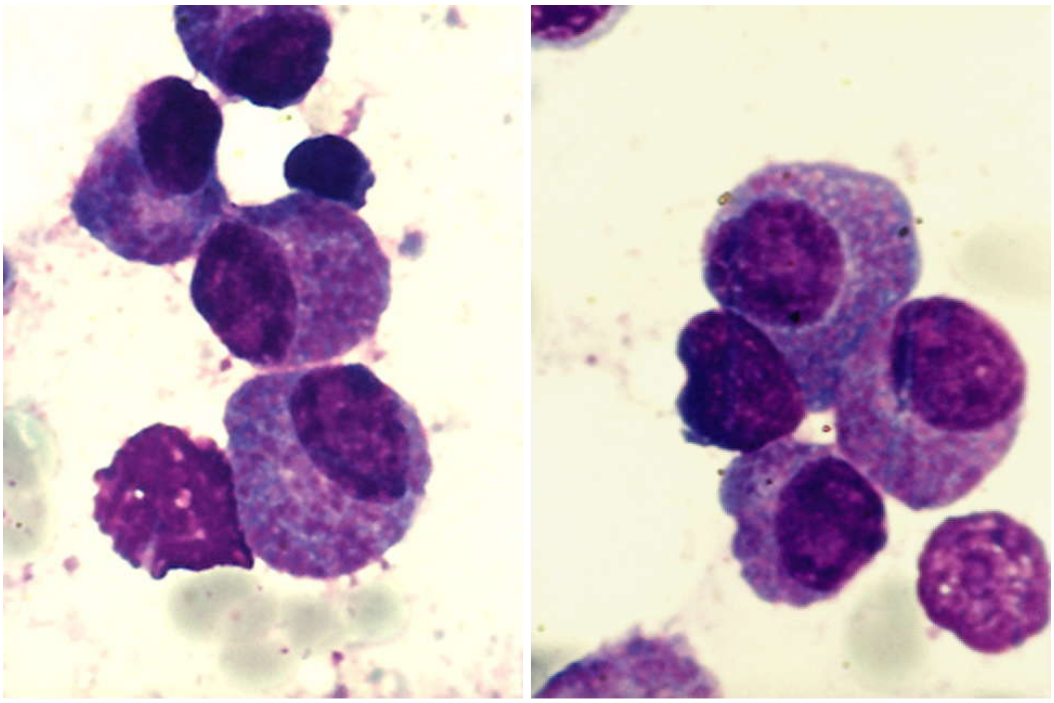
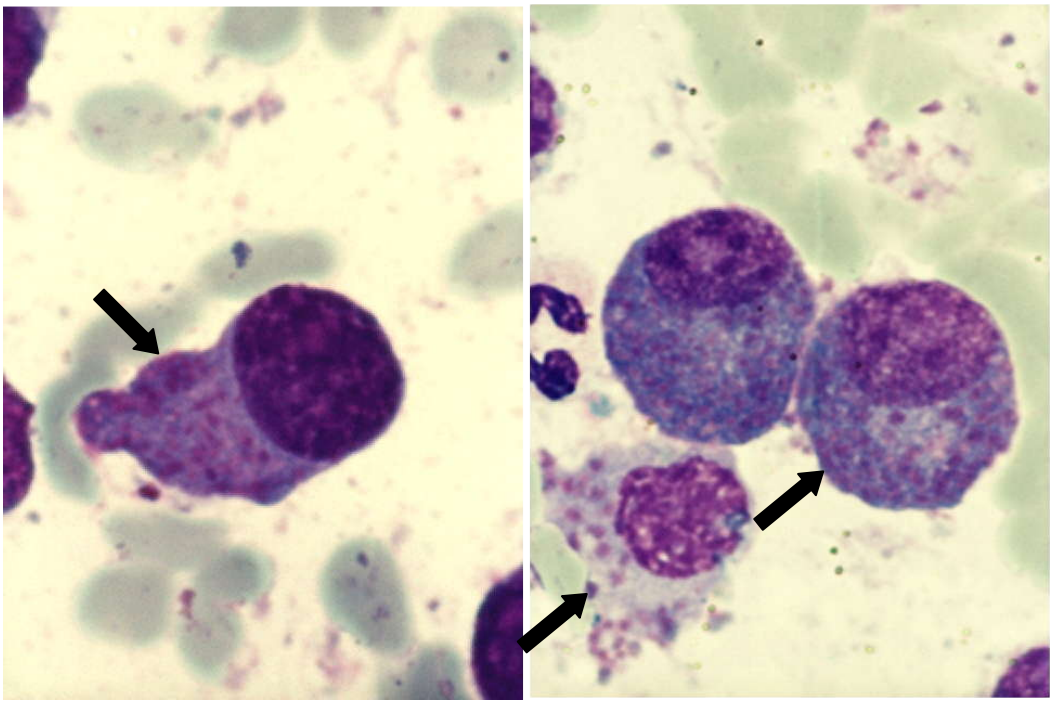


Figure 4a, 4b - Clusters of plasma cells with azurophilic granules (MO – MGG, 100x objective) - P.N. case



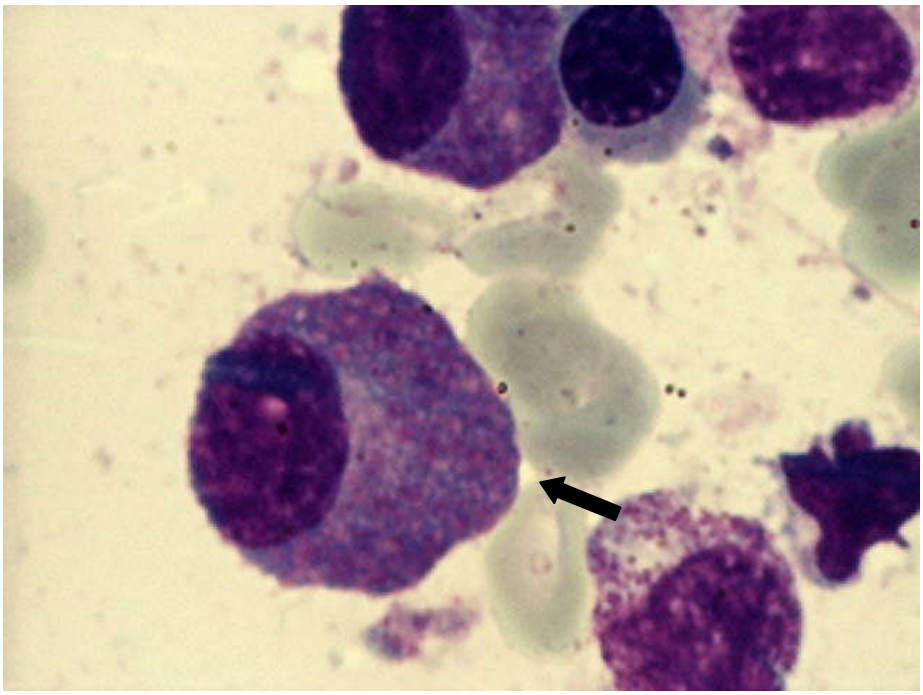


Figure 5a, 5b, 5c - Plasma cells with numerous azurophilic granules that tend to cover the nucleus, in some cases with cohesive appearance (Auer rods–like) - P.N. case

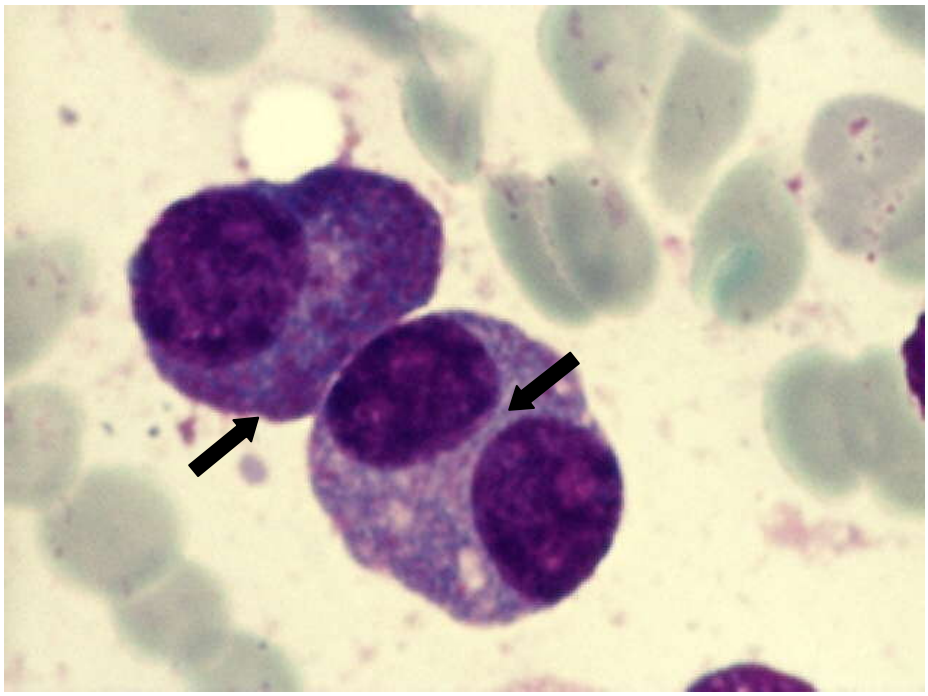


Figure 6 - Plasma cells with numerous azurophilic granules, one binucleated, some granules have foamy aspect (MO – MGG, 100x objective) - P.N. case

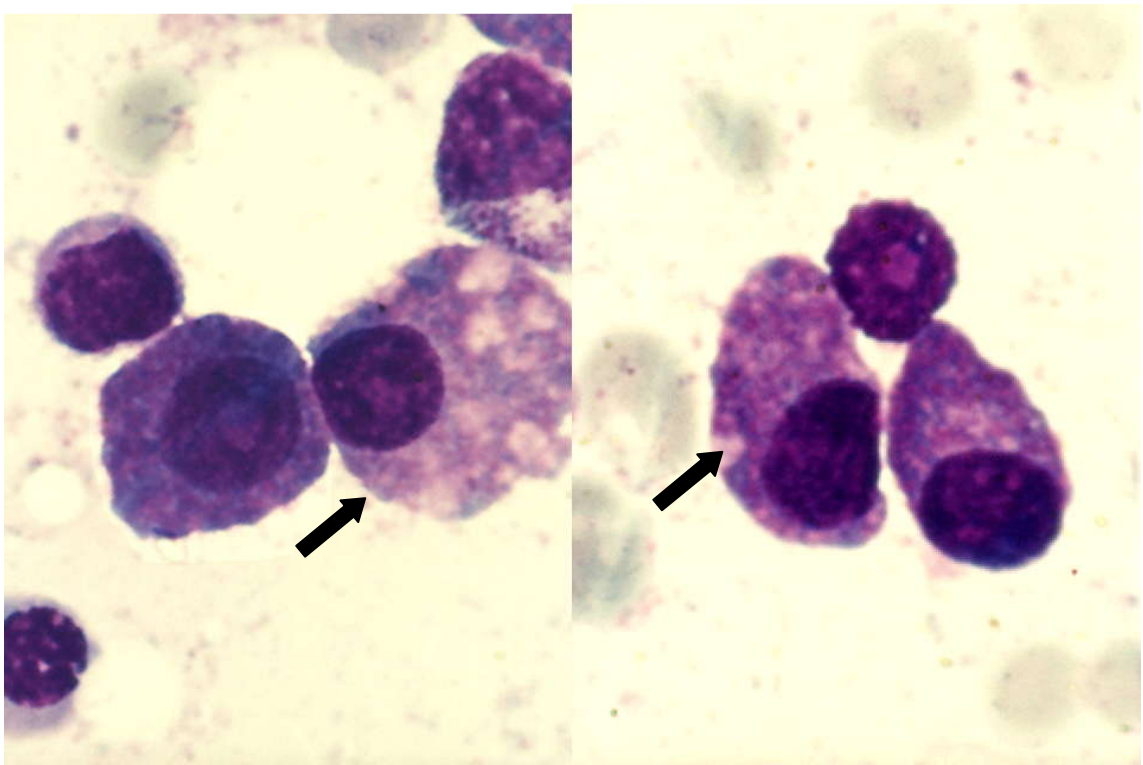


Figure 7a, 7b - Plasma cells with numerous azurophilic granules, so me granules have foamy aspect (MO – MGG, 100x objective) - P.N. case

The investigations were completed with X - rays of the skull which showed multiple lytic cranial lesions and diffuse osteoporosis (Figure 8). Spinal MRI scan identified of compression fracture of T12, L1, L2 with diffuse osteoporosis (Figure 9).

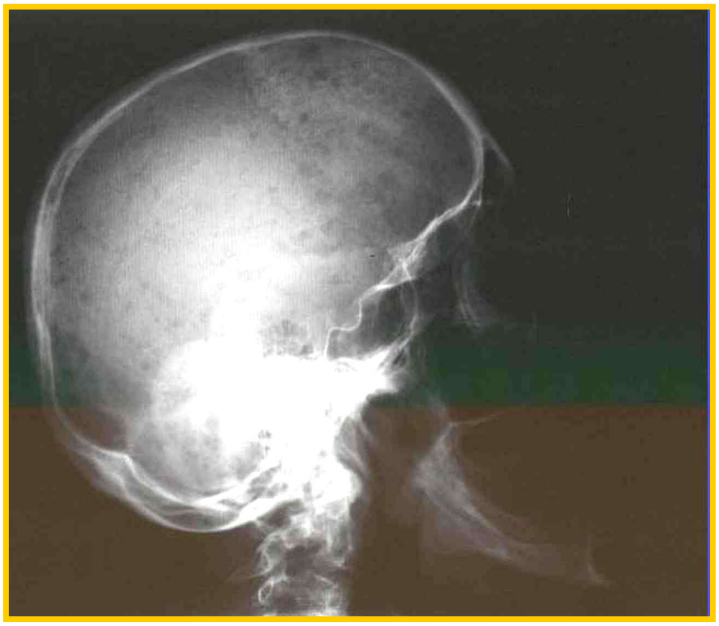


Figure 8 - Skull x - ray showing multiple lytic areas - P.N. case

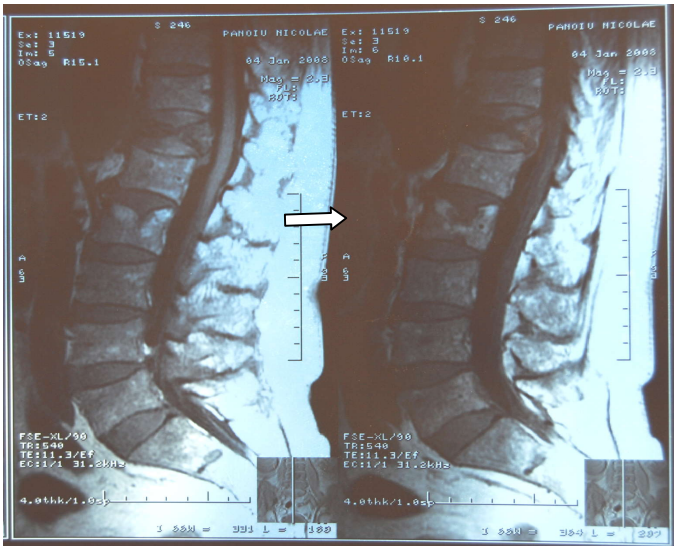


Figure 9 - Spinal MRI scan - compression fracture of T12, L1, L2 with collapsed plateau - P.N. case

The final diagnosis was **Multiple Myeloma IgG Kappa stage III B**; this was established according to Salmon-Durie Staging System [17] in the presence of major criteria: 53% myeloma plasma cells in bone marrow, monoclonal protein peak in serum, osteolytic lesions, corroborated with: anemia, renal failure, hypercalcemia. The multiple myeloma was complicated with compression fracture, secondary anemia, and possibly secondary amyloidosis. The renal failure may have a combined etiology: amyloidosis, myeloma kidney, excess NSAIDs treatment for back pain.

With an obvious diagnosis, the differential diagnosis was easy to establish [1, 2, 3], including: a) monoclonal gammapathy of undetermined significance (MGUS) and b) smoldering myeloma, both with monoclonal immunoglobulin in the serum less than 3g/dl, < 10% plasma cells in bone marrow, no evidence of myeloma end - organ damage - anemia, renal failure, hypercalcemia, lytic lesions; c) Waldenstrom's macroglobulinemia with IgM paraprotein peak and lymphoplasmacytic bone marrow infiltration [1].

The patient's prognosis is unfavorable [1, 4] because of multiple associated factors: age, aggressive onset of disease – with complications (acute renal failure, multiple lytic lesions, vertebral destructions that needed surgical intervention), associated cardiac pathology which limits the possible therapeutic regimens, other biological factors with prognostic value – severe anemia, increased LDH, positive PCR. We mention that neither the percentage of plasma cell involvement of the bone marrow, nor the morphological aspect of plasma cells represent prognostic factors – except for the case when plasmablasts are observed, or when plasma cells appear on the peripheral blood smear (PBS) [1, 4].

3. Discussion

Multiple morphological variants of plasma cells are described [2, 5, 6]:

- Plasma cells with abundant eosinophilic cytoplasm because of the presence of immunoglobulins as bright red granules - Flame Cells, frequently associated with IgA myeloma; however, they can also be associated with other types of myeloma.
- Plasma cells with globular inclusions (Russell bodies) in their cytoplasm – Mott cells – resembling a bunch of grapes
- Plasmablast – large cells with a very large nucleus and prominent nucleolus (adverse prognostic factor)
- Multiple intracellular mitosis and abnormal plasma cells with large nucleus

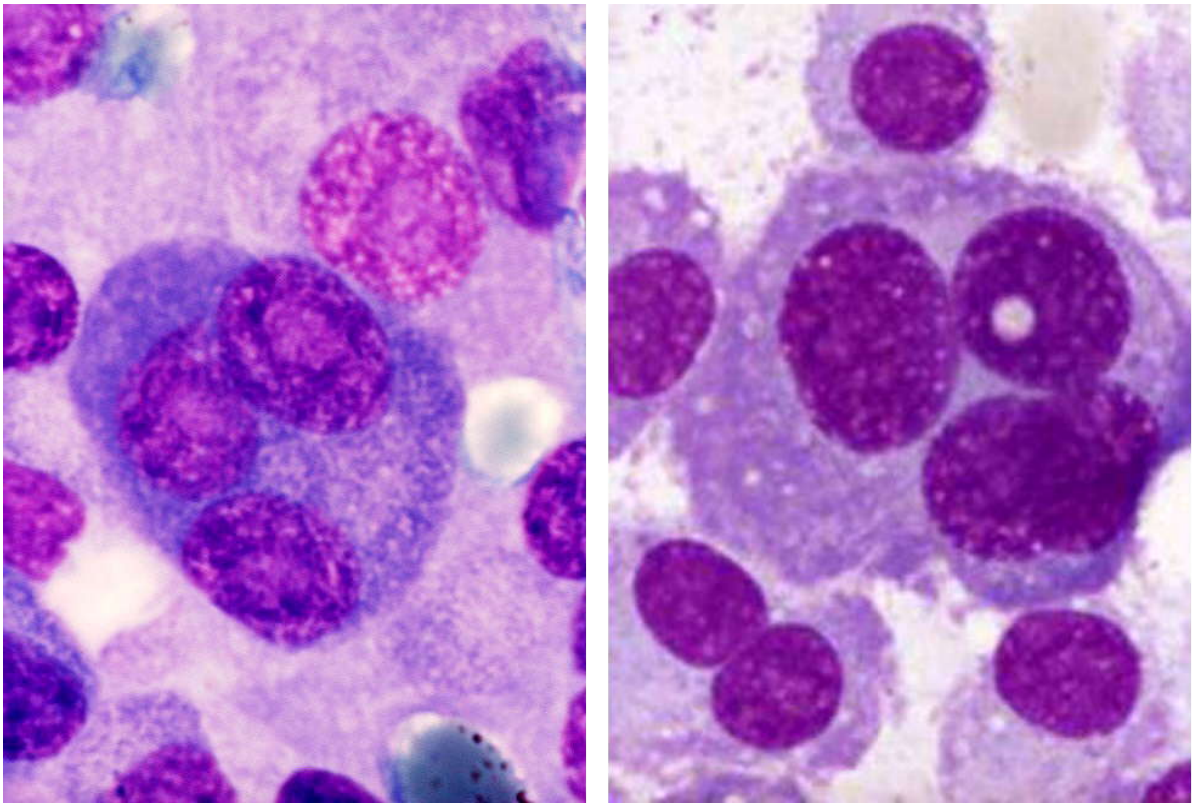
Plasma cells have a great variety of intracytoplasmic or intranuclear inclusions [2, 5, 6, 7]: Russell bodies (mucopolysaccharides and immunoglobulins secreted and accumulated in the endoplasmic reticulum), immunoglobulin granules and large vacuoles. These different globular intracytoplasmic inclusions are often mistaken for Auer rods or liposarcoma cells, or even adenocarcinoma cells – the typical aspect is of signet ring cells [6].

Because of the peculiar morphological aspect of plasma cells presented in this case (numerous large azurophilic - bright red granules), we considered necessary to have a careful differential diagnosis with other morphological variants [2, 5, 6, 7] - typical plasma cells (Figure 10, 11), sarcoma plasma cells like (Figure 13), plasmablasts (Figure 14, 15), foamy plasma cells (Figure 15), flame cells (Figure 16), Russell bodies (Figure 12) and reactive plasma cells.

The morphological variants of plasma cells are presented below in table 1 (adapted after 6):

Table 1: Different morphological aspects of plasma cells:

Type	***Characteristics***
Plasma cells with or without anaplastic	• high incidence; • nucleo/cytoplasmic asynchronism or dysplastic characteristics; • nucleolus plasma cells; • anaplastic morphological type includes: large nucleus, polymorphism, morphological aspects resembling immunoblastic lymphoma
Small/lymphocytic cells	• central nucleus, abundant or moderate basophilic cytoplasm; • small incidence
Lobulated/ folded/monocytoid/ convoluted	• small incidence; • lobulated nucleus and multiple irregularities; • differential diagnosis with T cell leukemia
Flame Cells	• polymorphic cells with eosinophilic cytoplasm (Flame Cells); • torn cytoplasm cells; • multinucleated cells, associated with IgA myeloma, but also present in other myeloma types
Plasmablast	• more than 2% blasts with high nucleo/cytoplasmic ratio, diffuse chromatin, variable nucleolus



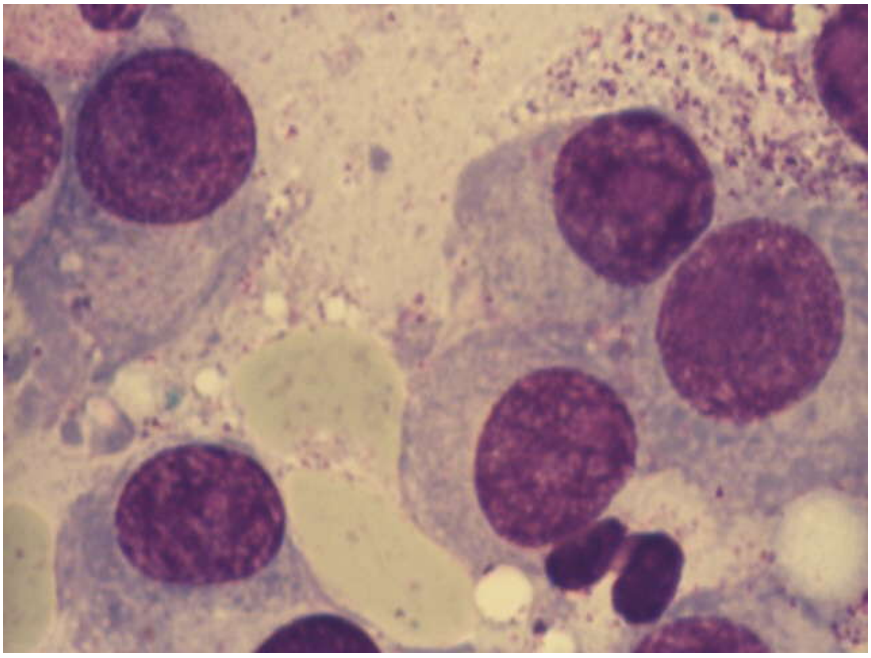


Figure 10a, 10b, 10c – Typical plasma cells - cluster cells, eccentrically placed nucleus, nodular chromatin, basophilic cytoplasm, perinuclear clear zone, some multinucleated, others with nucleolus (B.M. – MGG, 100x objective) *– images from "Diagnosis of Hematologic Malignancies - Atlas Notes and Images", Ana Maria Vlădăreanu, Carol Davila Universitary Publishing House, Bucharest, 2007 - Hematology Department – Emergency Universitary Hospital Bucharest, with the author's permission*

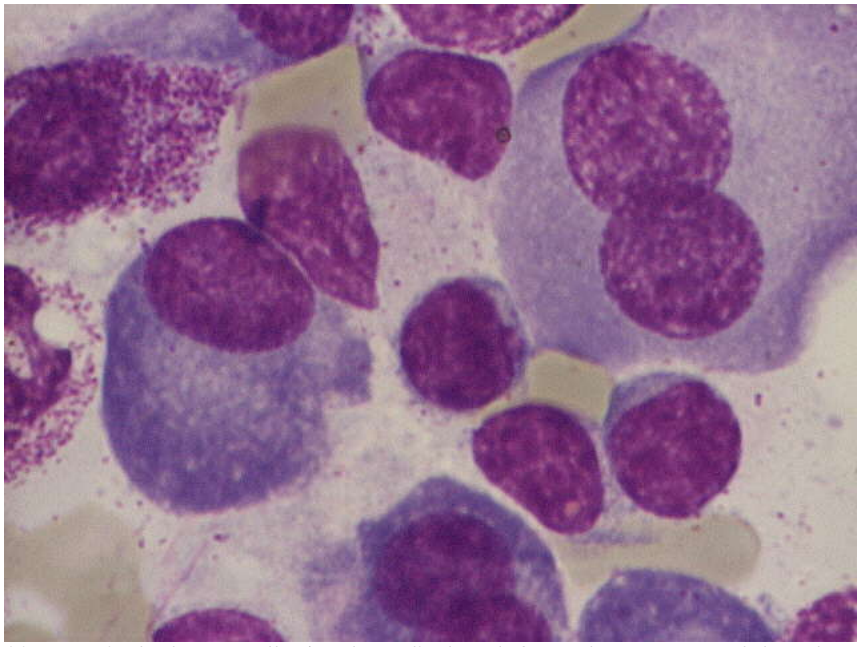


Figure 11 – Typical plasma cells (nucleus displaced from the center, nodular chromatin, basophilic cytoplasm, a perinuclear clear zone, some multinucleated) and lymphoplasmacytoid cells (reduced basophilic cytoplasm, with high nucleo/cytoplasmic ratio) – (B.M. – MGG, 100x objective) *– image from "Diagnosis of Hematologic Malignancies - Atlas Notes and Images", Ana Maria Vlădăreanu, Carol Davila Universitary Publishing House, Bucharest, 2007 - Hematology Department – Emergency Universitary Hospital Bucharest, with the author's permission*

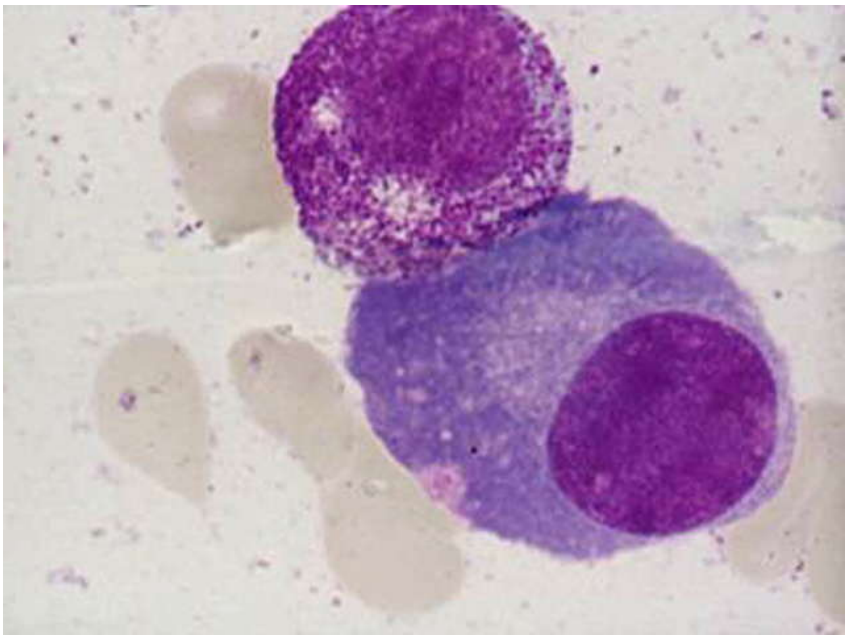


Figure 12 – Plasma cells with Russell rods (B.M. – MGG, 100x objective) *– image from "Diagnosis of Hematologic Malignancies - Atlas Notes and Images", Ana Maria Vlădăreanu, Carol Davila Universitary Publishing House, Bucharest, 2007 - Hematology Department – Emergency Universitary Hospital Bucharest, with the author's permission*

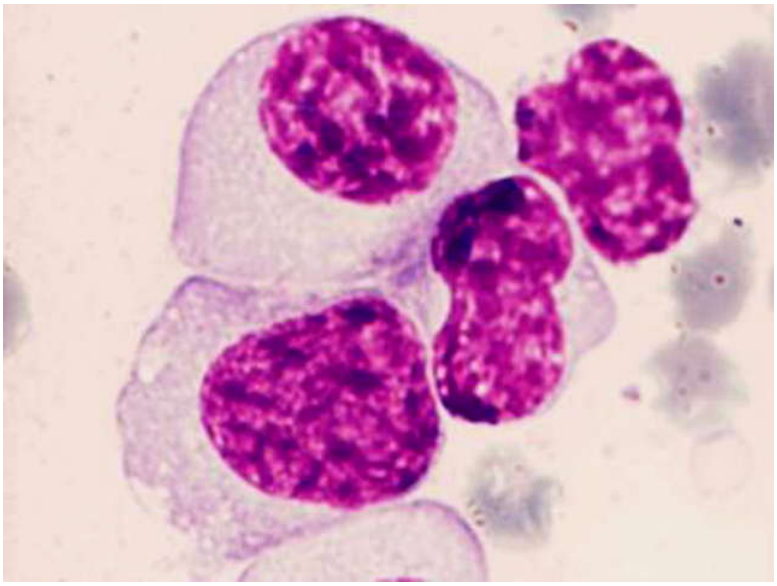


Figure 13 – Plasma cell sarcoma like (B.M. – MGG, 100x objective) *– image from "Diagnosis of Hematologic Malignancies - Atlas Notes and Images", Ana Maria Vlădăreanu, Carol Davila Universitary Publishing House, Bucharest, 2007 - Hematology Department – Emergency Universitary Hospital Bucharest, with the author's permission*

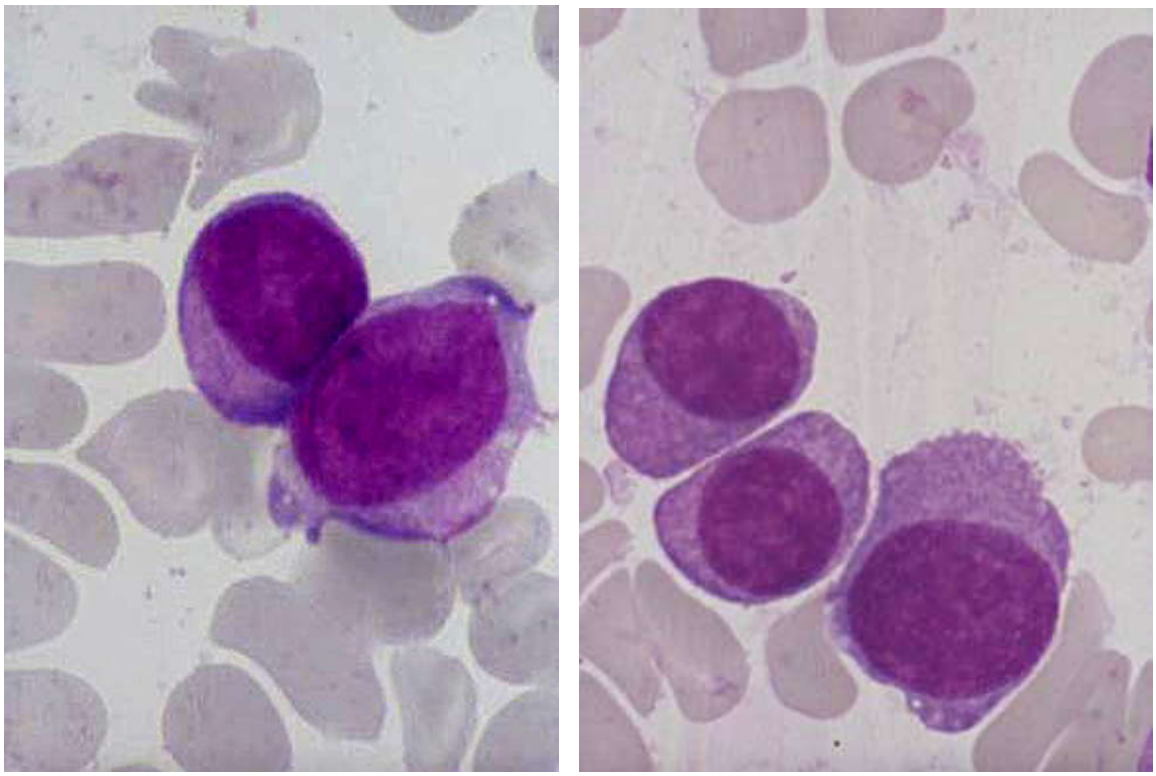


Figure 14a, 14b – Plasmablasts - high nucleo/cytoplasmatic ratio, some with nucleolus (P.B.S. – MGG, 100x objective) *– images from "Diagnosis of Hematologic Malignancies - Atlas Notes and Images", Ana Maria Vlădăreanu, Carol Davila Universitary Publishing House, Bucharest, 2007 - Hematology Department – Emergency Universitary Hospital Bucharest, with the author's permission*

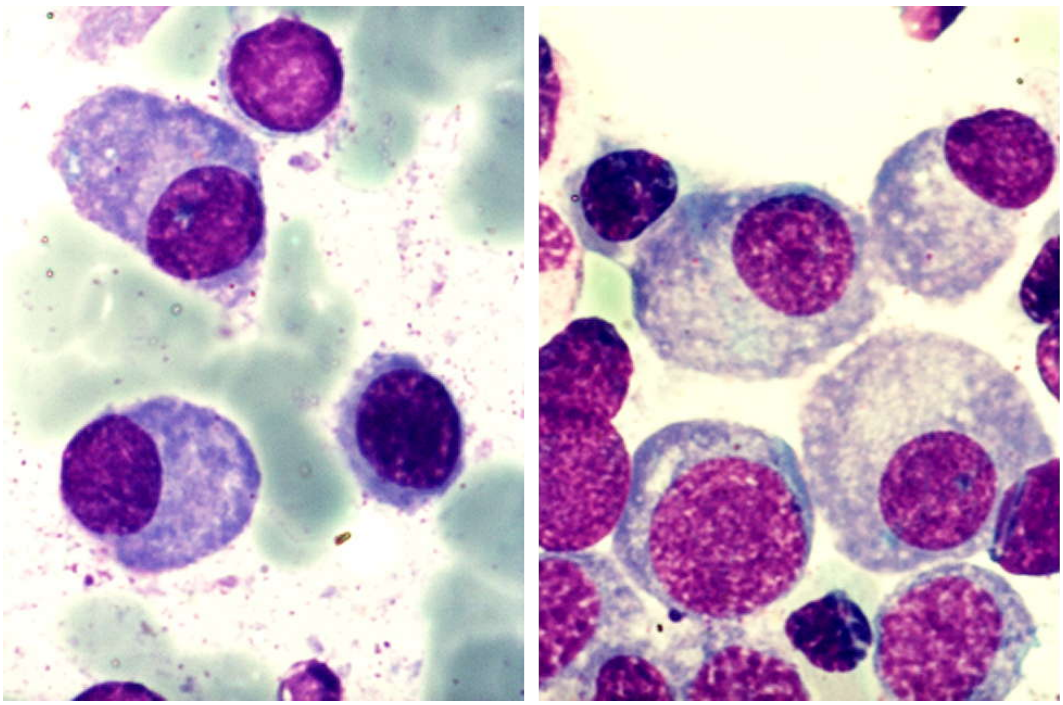


Figure 15a, 15b – Foamy plasma cells, plasmablasts with high nucleo/cytoplasmic ratio (B.M. – MGG, 100x objective *– images from the cases diagnosed in the Hematology Department – Emergency Universitary Hospital Bucharest)*

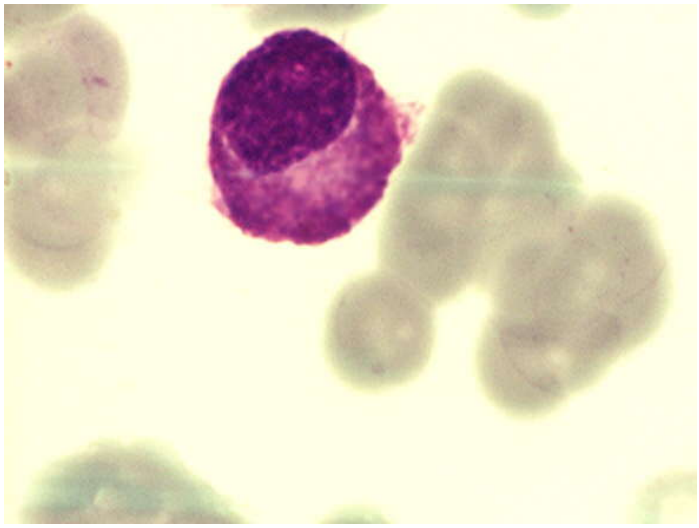


Figure 16 – Flame plasma cell (B.M. – MGG, 100x objective *– images from the cases diagnosed in the Hematology Department – Emergency Universitary Hospital Bucharest)*

There is a classification of multiple myeloma based on morphology, with important implications in evolution and prognosis (table 2) (after 2, adapted after 5):

Table 2: Morphological and prognostic value classification of multiple myeloma [2, 5]:

- Reduced malignancy MM: plasmocytic type
  - Small cells
- Intermediate malignancy MM: folded type
  - Polymorphous type
  - Asynchronic type

- High malignancy MM: plasmablastic type.

There are situations when it is necessary to make a differential diagnosis between plasma cells and blast cells in acute leukemia, and other hematopoietic precursors - osteoblast - or nonhematopoietic cells (bone marrow metastasis) [2, 5, 6]

4. Conclusions:

The presented case illustrates the necessary diagnostic steps, a typical combination of clinical features and laboratory tests.
It is a clear diagnosis: IgG Kappa multiple myeloma stage III B with compression fractures of T12, L1, L2, secondary anemia, possibly secondary amyloidosis and renal failure.

The unusual aspect of this case is the morphological facet of myeloma cells – with numerous large azurophilic-bright red granules; this characteristic, in the light of the multiple associated complications, may be regarded as an unfavorable prognostic factor in this particular case.

References:

1. Kyle RA, Rajkumar SV. Plasma cell disorders. In: Goldman L, Ausiello DA, eds. Cecil textbook of medicine. 22nd ed. Philadelphia: W.B. Saunders, 2004:1184-95
2. Ana Maria Vlădăreanu: Diagnosticul hemopatiilor maligne in note si imagini de atlas – Editura Universitara Carol Davila Bucuresti, 2007
3. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749-757.
4. Rajkumar SV, Greipp PR. Prognostic factors in multiple myeloma. Hematol Oncol Clin North Am 1999;13:1295-1314.
5. Begemann M. Praktische Hamatologie. Klinic. Therapie. Methodik. Georg Thieme Verlag, New York 1999
6. Foucar K. Bone Marrow Pathology: ASCP Integrative Hematopathology Series 2. ASCP Press, Chicago 2001.
7. Barlogie B, Alexanian R, Pershouse M, Smallwood L, Smith L. Cytoplasmic immunoglobulin content in multiple myeloma. J Clin Invest 1985;76:765-769.
8. Graham RC Jr, Bernier GM. The bone marrow in multiple myeloma: correlation of plasma cell ultrastructure and clinical state. Medicine (Baltimore) 1975;54:225-243.
9. Pavlovsky S, Saslavsky J, Tezanos Pinto M, et al. A randomized trial of melphalan and prednisone versus melphalan, prednisone, cyclophosphamide, MeCCNU, and vincristine in untreated multiple myeloma. J Clin Oncol 1984;2:836-840.
10. Monconduit M, Menard JF, Michaux JL, et al. VAD or VMBCP in severe multiple myeloma: the Groupe d'Etudes et de Recherche sur le Myelome (GERM). Br J Haematol 1992;80:199-204.
11. Alexanian R, Barlogie B, Tucker S. VAD based regimens as primary treatment for multiple myeloma. Am J Hematol 1990;33: 86-9.
12. Rajkumar SV, Gertz MA, Kyle RA, Greipp PR. Current therapy for multiple myeloma. Mayo Clin Proc 2002;77:813-22.
13. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate treatment in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:448-493.
14. Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for earlystage myeloma. Leukemia 2003;17:775-9.
15. Weber D, Rankin K, Gavino M, Delasalle, K. Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003;21: 16-9.
16. Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. N Engl J Med 1991;325:1267-1273.
17. Greipp PR, San Miguel JF, Durie BG, et al. A new international staging system (ISS) for multiple myeloma (MM) from the International Myeloma Working Group. Blood 2003;102:190a.