

A rare case of non-secretory multiple myeloma: a case report and literature review

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CASE REPORT

Non-secretory myeloma (NSM) is a rare form of myeloma. It is defined as monoclonal plasmocytic proliferation of the bone marrow with the same clinical and radiological manifestations of myeloma. However, plasma cells are unable to secrete immunoglobulin (serum and urinary electrophoresis are negative and free light chain measurement is unquantifiable).

This variant of multiple myeloma (MM) usually poses a diagnostic challenge to the biologist and clinician. We report a rare case of non-secretory myeloma in a 76-year-old patient who was diagnosed at the Mohammed V University Hospital Center in Oujda, Morocco.

INTRODUCTION

Multiple myeloma is a hematological malignancy characterized by the presence of clonal plasma cells in the marrow that typically secrete an abnormal immunoglobulin causing a monoclonal gammopathy. This serum protein is often characterized by an intact immunoglobulin (heavy and light chain), or it may be characterized only by the light chain. In the urine, an intact immunoglobulin is also often present [1].

Myeloma is characterized by end-organ damage as manifested by hematologic, renal, or bone complications [2].

Myeloma may be preceded by a premalignant phase in which clonal plasma cells are present but there is no evidence of end-organ damage: this is known as “monoclonal gammopathy of unknown significance” or “smoldering myeloma” [3].

Non-secretory myeloma (NSM) is a rare clinical form of multiple myeloma with monoclonal plasmocytic proliferation of the bone marrow and the same clinical and radiological manifestations. However, in the case of non-secretory myeloma, plasma cells are unable to secrete immunoglobulin (serum and urinary electrophoresis are negative and free light chain measurement is unquantifiable) [1].

CLINICAL-DIAGNOSTIC CASE

Mr. B.T., 76 years old, whose medical history includes:

- Chronic smoking for 25 years, weaned 35 years ago;
- Type 2 diabetes with oral antidiabetic drugs;
- Epilepsy treated with Phénobarbital, 0.75 mg/day.

The patient was admitted for mixed-type back pain, left intercostal neuralgia and left rib pain that was resistant to analgesics. Everything

evolves in a context of apyrexia and conservation of the general state.

The osteo-articular examination found pain in the palpation of the lower back spine. The rest of the clinical examination was without any particularities.

The patient has benefited from a biological assessment which did not indicate a biological inflammatory syndrome (normal erythrocyte sedimentation rate and CRP test) and the complete blood count with differential was without abnormalities. Serum protein electrophoresis showed hypogammaglobulinemia at 3.7 g/L and serum and urine immunofixations were negative with a normal Kappa/Lambda ratio. Renal and hepatic status was normal. (Table 1, Figure 1)

Magnetic resonance imaging (MRI) of the thoracic spine showed suspicious-looking D9 vertebral body compression with swollen pre-vertebral soft tissue swelling and posterior wall retraction, as well as a heterogeneous aspect of the cervical vertebrae.

The myelogram revealed 85% medullary plasmocytosis. (Figure 2)

Immunohistochemistry performed on osteomedullary biopsy showed medullary infiltration by myelomatous plasmocyte proliferation (CD138 positive) with a Kappa monotype.

Therapeutically, the patient was put on melphalan-prednisone-thalidomide (MPT)/Zometa protocol with a partial response (medullary plasmocytosis is of 18%).

DISCUSSION

Multiple myeloma is a hematological malignancy characterized by monoclonal plasmocytic proliferation invading the hematopoietic bone marrow. Serum protein electrophoresis shows either the presence of a narrow peak migrating most often in the gamma globulin

zone for secreting myelomas, or hypogammaglobulinemia associated with Bence-Jones proteinuria for light chain myelomas. The study of the myelogram shows a plasmocytosis greater than 10%. This plasmocytic proliferation is accompanied by hematological, bone and renal complications [4]. The contribution of Flow

Cytometry (CMF) in the initial evaluation is limited. However, it plays a more important role in the differential diagnosis of MM, where it can be a useful ancillary tool in identifying unusual morphologic variants of myeloma, cases of prominent reactive plasmacytosis, or B-cell non-Hodgkin lymphomas (NHLs) with extreme

Table 1 Laboratory results

Parameter	Case	Reference range
Hemoglobin	14,6 g/dL	13-18 g/dL
Erythrocyte sedimentation rate	24	-
CRP	8,82 mg/L	0-5 mg/L
ALT	22 UI/L	0-55 UI/L
AST	25 UI/L	5-34 UI/L
Gamma-GT	25 UI/L	12-64 UI/L
LDH	383 UI/L	125-243 UI/L
Creatinine	8,44 mg/L	7,2-12,5 mg/L
Ca ⁺⁺	93 mg/L	88-100 mg/L
24-h proteinuria	48,98 mg/24h	<500
Total protein	54 g/L	60-78 g/L
IgG	3,82 g/L	5,4-18,22 g/L
IgM	<0,20 g/L	0,22-2,40 g/L
IgD	<7 mg/L	7,7-132,10 mg/L
Free light chains Kappa-serum	6,57 mg/L	3,30-19,40 mg/L
Free light chains Lambda-serum	5,41 mg/L	5,71-26,30 mg/L
Kappa / Lambda Free light chains ratio	1,21	0,26-1,65

Figure 1 A: Serum protein electrophoresis showing hypogammaglobulinemia
 B: negative serum immunofixation
 C: negative urine immunofixation

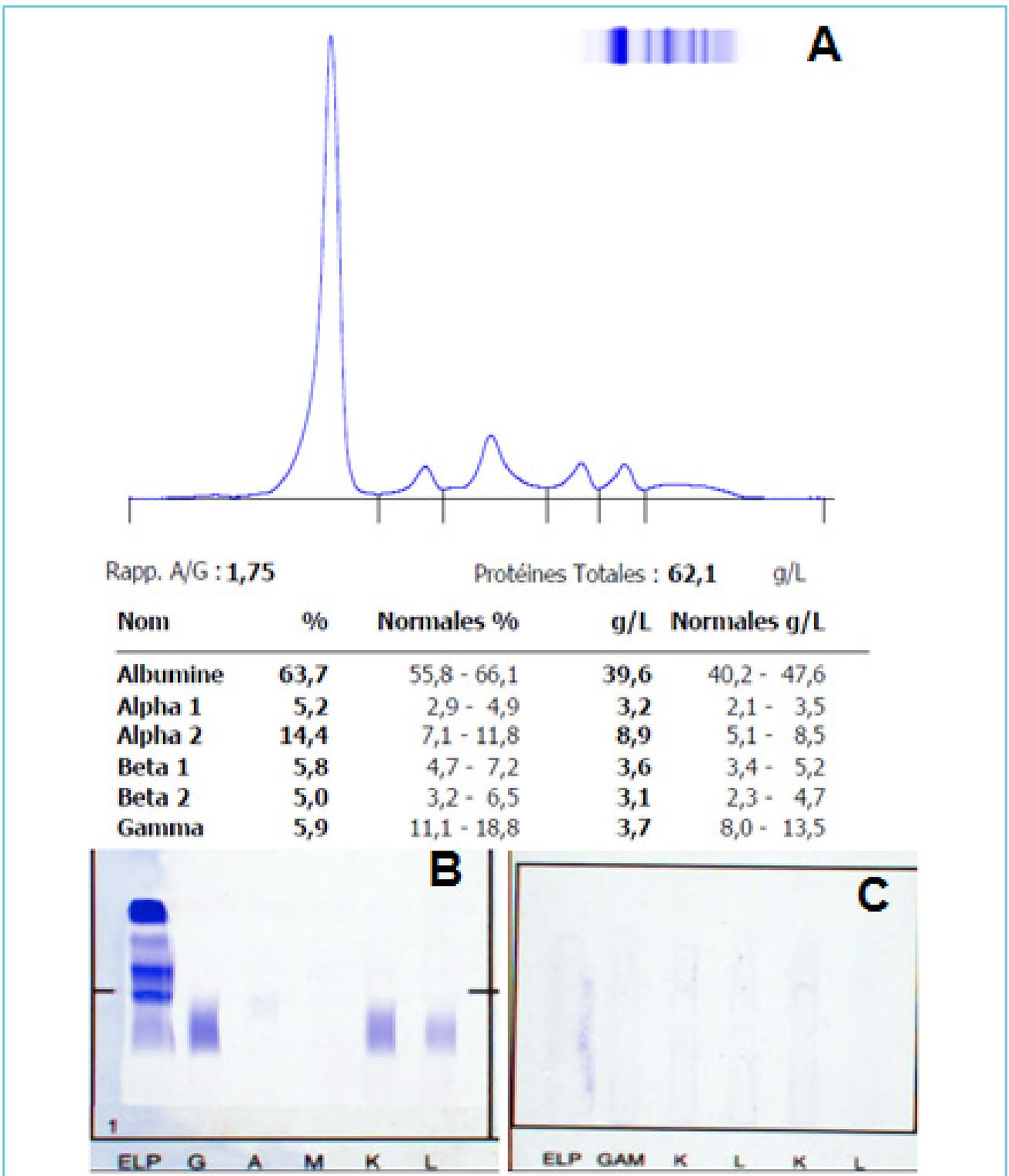
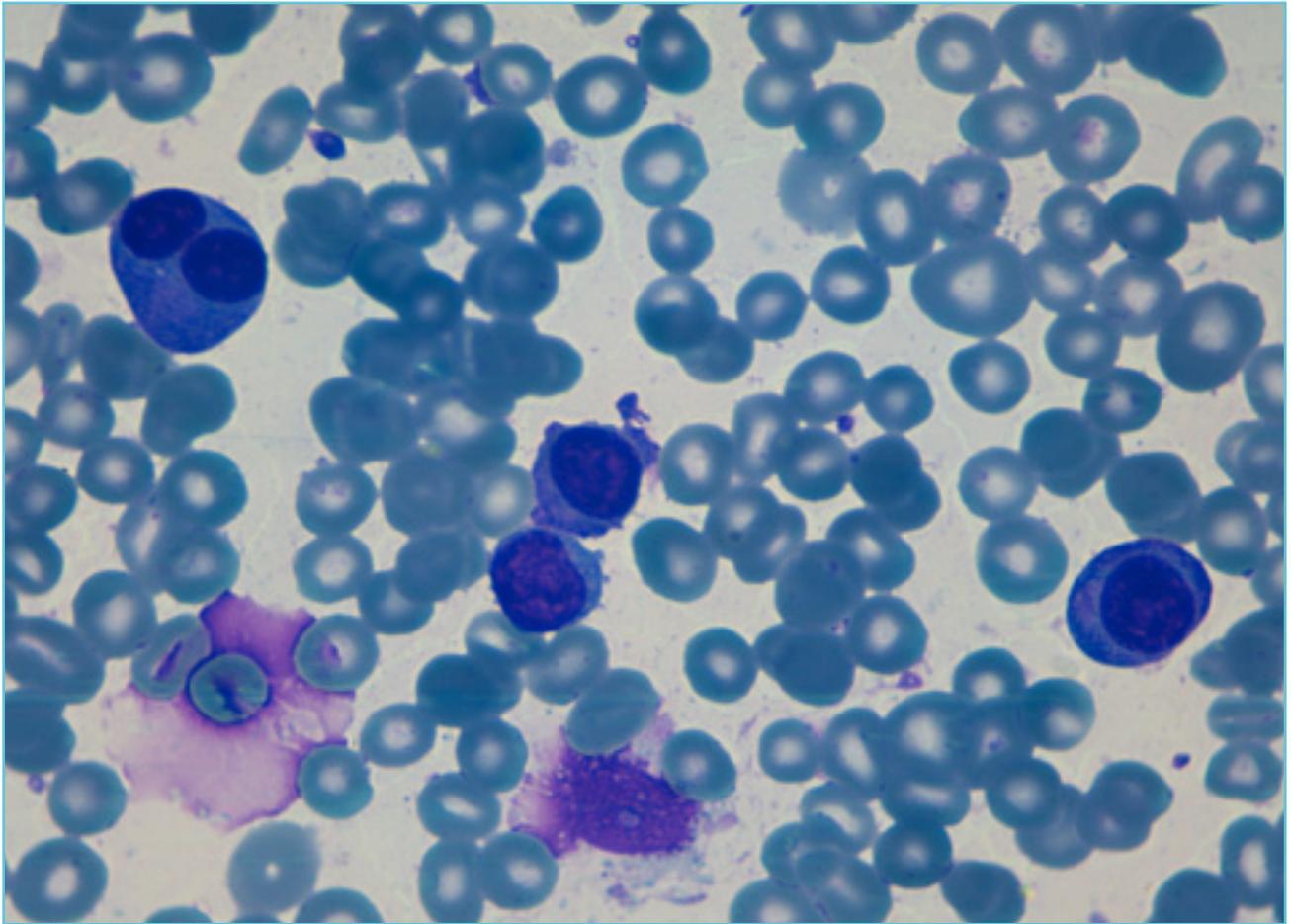


Figure 2 Myelogram showing a medullary plasmocytosis



plasmacytic differentiation, among others [5]. CMF has also shown interest in accurately quantifying medullary plasmocyte infiltration and the proportion of pathological plasma cells relative to total medullary plasma cells (ratio) [6].

MM is almost always preceded by an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS) [7-9]. MGUS is defined as a serum monoclonal protein (non-IgM type) <30 g/L, Clonal bone marrow plasma cells <10%, and absence of end-organ damage such as hypercalcaemia, renal failure, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder [9]. About 80% of multiple myeloma originates from non-IgM immunoglobulin MGUS

(non-IgM MGUS), and 20% from light-chain immunoglobulin MGUS (LC-MGUS). In the event of progression, IgM immunoglobulin MGUS (IgM MGUS) usually evolves into Waldenstrom macroglobulinaemia, but in rare instances IgM MGUS can progress to multiple myeloma (IgM myeloma) [9-14].

Non-secretory myeloma is a rare clinical form of multiple myeloma (2% to 4% of all cases) [1] with monoclonal plasmocytic proliferation of the bone marrow and the same clinical and radiological manifestations. However, in the case of non-secretory myeloma, plasma cells are unable to secrete immunoglobulin (serum and urinary electrophoresis are negative and free light chain measurement is unquantifiable). (Table 2)

Table 2 Criteria for Non-Secretory Myeloma [1]

Biopsy-proven clonal plasma cells
<0,5 mg/dl serum protein by serum protein electrophoresis
<200 mg/24hrs of light chain proteinuria by urine protein electrophoresis
Unquantifiable free light chain measurement
Evidence of CRAB criteria (hypercalcemia, renal dysfunction, anemia, bone disease) for symptomatic myeloma (which must be attributable to clonal plasma-cell infiltration)

This rare entity (NSM) must be distinguished from oligosecretory myeloma, in which proteins are produced but at very low levels that make reliable measurement more challenging. Oligosecretory multiple myeloma is often characterized by serum protein <10 mg/dL, urine protein <200 mg/24 hrs, and free light chain values <100 mg/L (or 10 mg/dL) [15].

Two distinct types of NSM have been described. The first group consists of patients who are “non-producers.” These are patients whose tumors may have defects in immunoglobulin synthesis. These tumors are not able to synthesize or secrete a protein even though they might have all the features of a plasma cell disorder [16]. In this category, we include the patients who have no measurable protein in the blood or urine, yet who still have a significant plasma cell burden in the marrow and evidence of end-organ damage. In addition, even the dosage of the free light chain will not reveal measurable disease as currently defined. The next category of non-secretory myeloma patients consists of those whose tumors produce a protein but have defects in secretion, possibly due to a mutation of the immunoglobulin gene thus explaining the absence of secretion in a patient with non-secretory myeloma.

According to the recommendations established by the International Myeloma Workshop[3], the

workup for all newly diagnosed myeloma patients includes: routine chemistries including LDH and beta-2-microglobulin, complete blood cell count with differential, serum protein electrophoresis with immunofixation, quantitative immunoglobulins (including IgD or IgE if suspected), 24-hr urine test with protein quantification and immunofixation, serum free light chain assay, skeletal survey and positron emission tomography scan[1].

Response assessment in myeloma is typically based on the absence of a detectable protein in the blood or urine and a normal free light ratio. Even with a response that meets these criteria, a more in-depth assessment using molecular techniques, such as multi-parameter flow cytometry (MPF) [1,17,18], is able to evaluate the minimal residual disease (MRD) that likely will contribute to relapse. Therefore, the IMWG included the evaluation of the residual disease of MM by MPF in the therapeutic response criteria. However, MPF alone is probably not sufficient to assess total body myeloma burden. For this reason, the pairing of imaging and more sensitive marrow assessment represents an optimal method by which to assess response to therapy and MRD, and will likely be applied to all myeloma patients, not just non-secretory patients in whom the inability to use SPEP or UPEP limits methods of response assessment [1].

CONCLUSION

In conclusion, the absence of a monoclonal protein in serum and/or urine does not rule out the diagnosis of MM. Indeed, the diagnosis of non-secreting myeloma should be made in patients with clinico-biological and radiological characteristics of MM with a ratio of normal Kappa/Lambda free light chains. As a result, this report has now become a standard for the diagnosis of non-secreting myeloma.

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