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Case Report

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A Rare Case of Non-Secretory Multiple Myeloma Presenting with Dense Bone Marrow Infiltration by Plasma Cells with Intracellular Deposits of Immunoglobulin (Mott Cells)

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1. Abstract

Intracellular deposits of immunoglobulin (Ig) are seen occasionally in human B-cell lymphoproliferative disorders such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and various forms of lymphoma. Non-secretory multiple myeloma (NSMM) is a rare form of plasma cell neoplasm (PCN) characterised by a monoclonal plasma cell proliferation in the bone marrow with the same clinical and radiological manifestations of MM, but without monoclonal component in the serum and/or the urine. NSMM accounts for 1–5% of all cases of MM, and since plasma cells are unable to secrete Ig, serum and urinary electrophoresis are negative, and free light chain (FLC) measurement is unquantifiable. In a very few cases of NSMM, a large proportion of the proliferating cells synthesize complete Ig molecules but are totally unable to secrete them or to degrade them, although being still able to divide normally. As a consequence, Ig containing inclusion bodies accumulate in the cytoplasm of the plasma cells leading to the so-called Mott cells. These inclusions are made up of electron-dense material poorly or not delineated by a membrane and since its initial description, many pathologists clearly relate to an intracellular aggregation of non-secreted Ig. Due to its uncommon phenotype, this variant of MM usually poses a diagnostic challenge to clinicians because it requires the finding of a bone infiltration by atypical plasma cells. We report a NSMM with marked lymphoplasmocytosis and plasma cells containing inclusion bodies (Mott cells) in a 77-year-old woman with chronic anemia and the clinical suspicion of myelodysplastic syndrome (MDS) .

2. Case Report

A 77-year-old woman presenting with chronic anaemia and gradual, but progressive fatigue and weight loss, was clinically oriented as a myelodysplastic syndrome (MDS). The most significant finding was pallor but the examination of the head, neck, breasts, heart, abdomen, extremities and skin was unremarkable. Complete Blood Count (CBC) showed a moderate anaemia (Hb:100g/l), with leukopenia (2.3x109/l) and normal platelet count (202 x109/l). The anemia was slightly regenerative (Retics: 102x109/l) and peripheral blood smear examination showed normocytic normochromic red cells with moderate anisocytosis and few poikylocytes and ovalocytes. The differential leukocyte count (DLC) was as follows: segmented polymorphs 40%, non-segmented polymorphs: 3%, eosinophils 0%, basophils 2%, lymphocytes 50% and monocytes 5%. No immature cells were observed.

Serum protein electrophoresis showed a decrease of the γ region (Figure 1) and urinary Bence Jones protein was negative. General serum analytical data including immunoglobulin study are summarized in Table 1. Since the patient was initially oriented as a MDS a bone marrow (BM) morphology examination was performed and a marked cellularity with suppression of haematopoiesis with a up to 80% infiltration of lymphoplasmocytes and plasma cells was observed. These cells were characterised by a variable size, fairly condensed chromatin and multiple clear cytoplasmic inclusions mimicking metastatic deposits of clear-cell carcino-

ma/histiocytes with vacuolated cytoplasm (Figure 2). Large sized plasma cells without inclusions and few granulocytic precursors were also observed (Figure 3). Bone marrow immunohistochemistry (IHC) study demonstrated a marked positivity of plasma cells for CD138, providing a strong support to the diagnosis of plasma cell neoplasm (PCN).

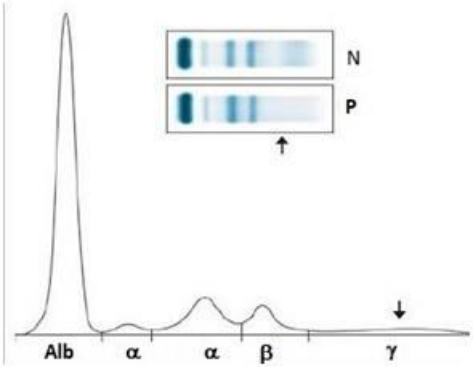

Figure 1: Serum protein electrophoresis

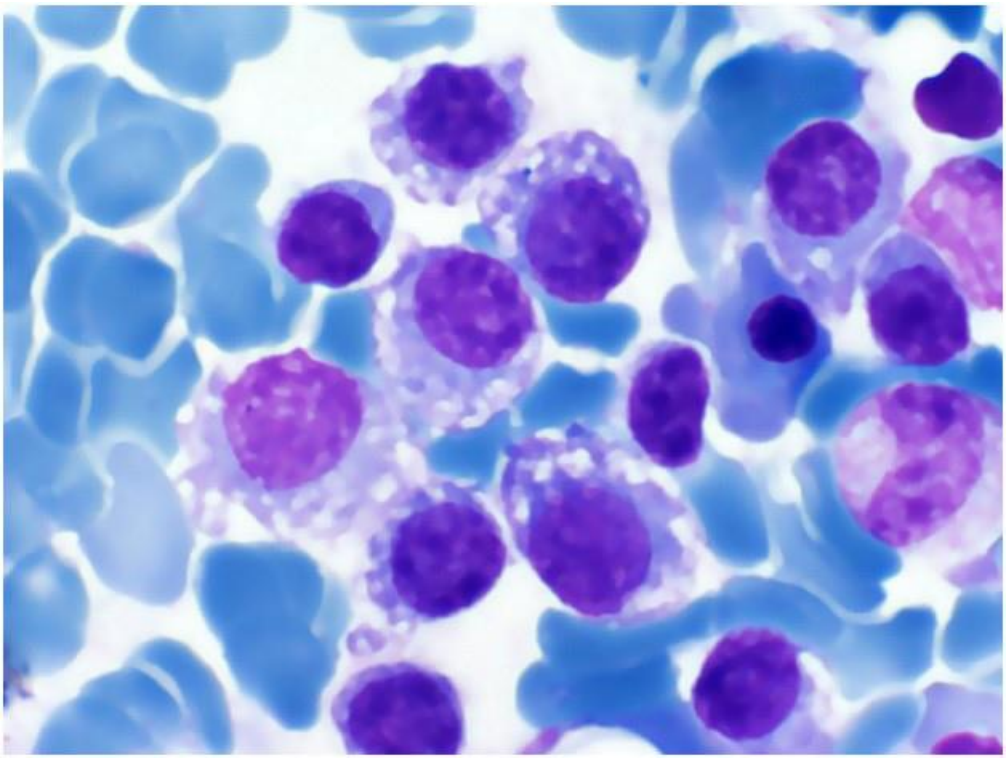

Figure 2: Lymphoplasmocytosis and plasma cells with cytoplasmic Ig inclusions (Mott cells).

Table 1: Basic Haematology Data and Serum Biochemical Parameters of the Patient with NSMM.

Parameter	Result	Reference range
Hemoglobin	101 g/l	130-170 g/l
Erythrocyte Sedimentation rate (ESR)	20 mm/h	8-12mm/h
C reactive protein (CRP)	6.8 mg/l	0.1- 5 mg/l
ALT	32 IU/l	2- 55 IU/l
AST	25 IU/l	5- 34 IU/l
Gamma-GT	23 IU/l	12-64 IU/l
LDH	180 IU/l	125-243 IU/l
Creatinine	9.44 mg/l	7.2-16.5 mg/l
Calcium (Ca^{++})	98 mg/l	88-100 mg/l
24-h proteinuiria	49.1 mg/24h	<500 mg/24h
Total protein	46 g/l	52-78 g/l
IgG	3.56 g/l	5.5-16.3 g/l
IgM	<0.25 g/l	0.3-2.93 g/l
IgA	<0.25 g/l	0.7-2.10 g/l
Serum free light chains Kappa	1.12 g/l	1.7-3.70 g/l
Serum free light chains Lambda	0.35 g/l	0.9-2.19 g/l
Kappa/Lambda free light chains ratio	3.20	1.8-3.65

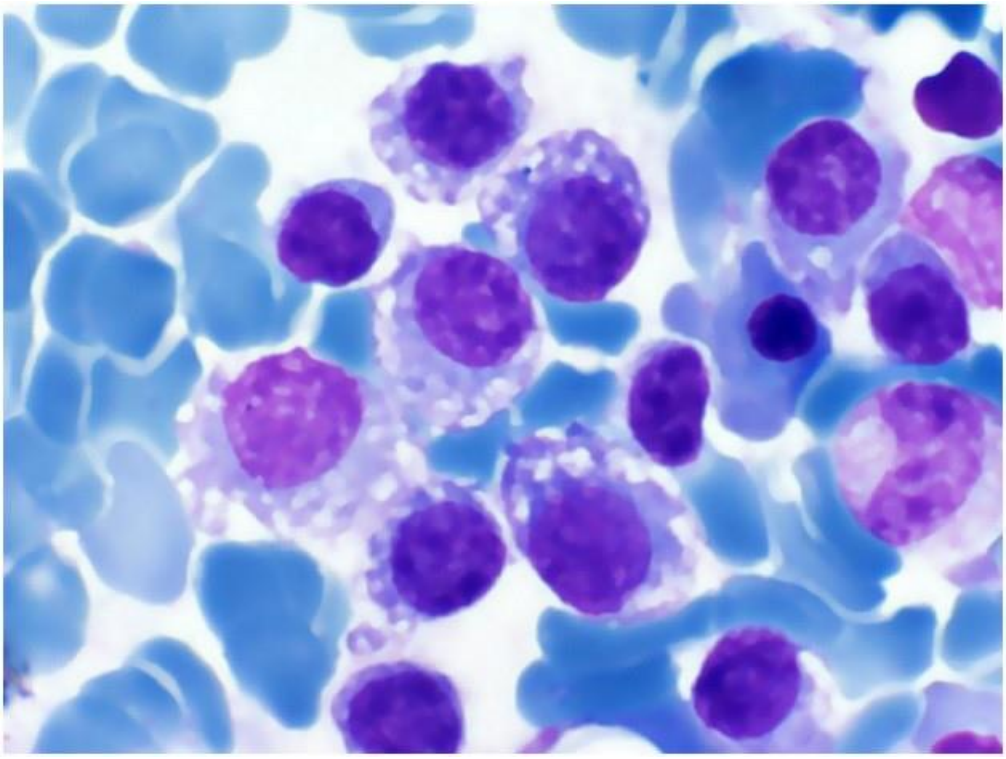

Figure 3: Atypical plasma cells and a large sized promyelocyte.

3. Discussion

Multiple myeloma (MM) is a malignancy of terminally differentiated, bone marrow plasma cells (PCs), which normally function to support long-term humoral immunity [1]. The diagnosis of MM is based on the demonstration of bone marrow plasmacytosis, monoclonal band (M protein) in the γ region on either urine or serum protein electrophoresis, and myeloma related organ dysfunction (hypercalcaemia, renal insufficiency, anaemia, and lytic bone lesions). Since the 1950s, it has been observed a very small subset of MM characterized by the absence of detectable M protein in serum and urine called non-secretory multiple myeloma (NSMM). Several cases of NSMM were first described in 1958 and since then a retrospective study of 869 cases of MM, suggested that the prevalence of NSMM was about 1% [2]. After 1979, there have been published several reports describing this variant of MM [3-5] estimating that these represented anywhere from 3% to 5% of the total MM population. Using IHC, approximately a 85% of NSMM stain for cytoplasmic M protein, indicating immunoglobulin synthesis These cases may be considered to be minimally secretory, hyposecretory, or oligosecretory, and advances in the detection of serum free light chains by ELISA have demonstrated that most of these cases were probably oligo secretors MM producing free light chains (FLC) in the absence of heavy chains [6,7]. Moreover, some of these cases exhibit variations in microscopic appearances of the tumour cells and its pathophysiology have been postulated to be a reduced protein synthesis or an increase in breakdown of abnormal immunoglobulin chains, either intracellular or extracellular. With the newer serum FLC assays, approximately three-fourths of these NSMM were found to have elevated FLC levels and/or abnormal FLC ratios [3]. Since these patients do not present with classical MM symptomatology, the diagnosis may be delayed.

We present hereby a case of NSMM with very low M protein and bone marrow plasma cells containing numerous cytoplasmic inclusion bodies or Mott cells. The rare and unique clinical presentation of this case, and the bone marrow lymphoplasmocytosis with a high percentage of Mott cells, prompted us to report this case. It may be postulated that Mott cells synthesize complete Ig molecules but are totally unable to secrete them or to degrade them, and as a consequence, Ig containing inclusion bodies accumulate in the cytoplasm [8-10]. Such inclusions are usually surrounded by membranes in dilated portions of the ER called Russell bodies [11]. It also appears likely that Ig accumulating into the ER could well be transported to the cytoplasm before their aggregation into inclusion bodies. In addition to PCNs the Mott cells, originating from the CD5+ auto reactive B cell population, are frequently encountered in the course of autoimmune diseases without a clear proof of its mechanism [10]. Although the formation of the inclusion bodies is not totally explained, a study performed on thymectomised autoimmune mice suggested that Mott cells were thymodependent plasmacytoid cells resulting from chronic B cell activation accompanied by impaired Ig secretion [11]. This activation would lead to exaggerated Ig hyper mutation and to the appearance of nonsecretable, misfolded, or aggregated Ig molecules [12]. Among the few reported cases, the observation plasma cells characteristics led to define two distinct types of NSMM. In the first type, the plasma cells produce Ig but are unable to secrete it out of the cell, possibly due to reduced permeability or absence and alteration of intracellular light chains. This form of NSMM is known as the “producer”

type or true NSMM. In the second type, plasma cells are unable to produce Ig and this form of NSMM is known as "non-producer" [13-15]. As in MM, the diagnosis of NSMM relies on skeletal, radiological studies and bone marrow examination, characterised by the classical infiltration by monoclonal plasma cells and its pathological consequences (bone pain, skeletal lesions). Due to the absence of circulating monoclonal protein, the diagnosis of NSMM is more difficult than for MM and, for this reason, it is frequently underestimated from the clinical point of view. Interestingly, in a minority of NSMM, a variable proportion of proliferating cells are typical Mott cells. In our patient with chronic refractory anemia initially oriented as a MDS, an unexpected NSMM was found after bone marrow morphology examination that exhibited a marked infiltration of atypical plasma cells with cytoplasmic inclusions (Mott cells). This was associated with a low concentration of M component in serum and the absence of FLCs in the urine. Since the patient meet the criteria of the International Myeloma Working Group [16] she was referred to a Reference Hospital for treatment and clinical follow-up. All authors have read and agreed to the published version of the manuscript and no conflict of interest is declared. No funding support was available for this case report, and the study was conducted according to the guidelines of the Declaration of Helsinki.

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