

Review Article with Case Study

Non-Secretory Multiple Myeloma- An Unusual Presentation With Review of Literature

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Abstract

Multiple myeloma is a B-cell malignancy caused by monoclonal proliferation of plasma cells which secrete immunoglobulins leading to a "M" protein spike on immunoelectrophoresis and lytic bone lesions or renal involvement or anaemia or hypercalcaemia and is not associated with organomegaly. Here we present a case with non-secretory multiple myeloma with lymphadenopathy and hepatosplenomegaly with review of literature.

A 75 year old male presented with low back pain, recurrent anaemia, recurrent pneumonia, raised ESR, lymphadenopathy and hepatosplenomegaly. With a haematological malignancy in mind, a bone marrow examination was done which revealed plasma cells which were CD 138 and monoclonal kappa chain positivity on immunohistochemistry. The serum protein electrophoresis with immunofixation did not show a "M" spike. Lytic lesions were seen on X-ray. Hence, a diagnosis of non-secretory multiple myeloma (NSMM) was made. However, the patient expired after four cycles of chemotherapy due to persistent pneumonia.

NSMM has varied clinical manifestations like plasma cell leukaemia, a higher incidence of neurological presentation, minimal lytic bone disease, a lower median percentage of plasma cells in the marrow and a lower incidence of hypogammaglobulinaemia. Various studies have differing experiences on the survival of patients with NSMM. Morphologically, plasma cells have shown rough endoplasmic reticulum and a clear Golgi apparatus on electron microscopy or with distended endoplasmic reticulum. A case of NSMM presenting with pancytopenia has been reported. This patient had plasma cell infiltration of the bone-marrow. The plasma cells were multinucleated and showed erythrophagocytosis and phagocytosis of granulocytes. These are true non-secretors who do not excrete the light chains and can be identified by immunohistochemistry using CD 138 and kappa and lambda light chain. The conventional methods of detection of free light chains (FLC) are not sensitive; hence, FLC assay is now used for the detection of light chains in oligo-secretors. Patients are prone to infections especially with *Pneumococcus*. Amyloidosis has also been reported in secretory cases.

A high degree of suspicion for a haematological malignancy is warranted in a case of recurrent anaemia despite blood transfusions, repeated infections, generalised lymphadenopathy and hepatosplenomegaly. A bone-marrow examination with immunohistochemistry is helpful in such cases, which can be supported by ancillary tests like serum protein electrophoresis with immunofixation, Free-Light Chain assay and X-ray for lytic lesions in bone, where indicated.

Key Words: Non-secretory multiple myeloma, M-band, Anaemia, Recurrent pneumonia, Lytic bone lesions, Plasmacytosis.

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Introduction

Multiple myeloma is a B-cell malignancy caused by monoclonal proliferation of plasma cells which secrete immunoglobulins leading to "M" protein spike on immunoelectrophoresis and lytic bone lesions or renal involvement or anaemia or hypercalcaemia and is not associated with organomegaly.

Non secretory multiple myeloma is a rare disease (1-5% of all myelomas) and is characterised by the increase in

plasma cells, lytic bone lesions with or without hypercalcaemia and renal involvement. There is absence of M band in the serum or urine¹. The diagnosis rests on the demonstration of plasma cells in the bone-marrow. A search in "PubMed", showed less than 80 case reports since 1972 following which the incidence of non-secretory multiple myeloma has declined, probably as a result of more sensitive methods of detection of light chains. A high index of suspicion is needed to diagnose such cases¹. We report here a rare

case of non-secretory multiple myeloma with an unusual presentation of lymphadenopathy and hepato-splenomegaly, lytic bone lesions and a bone-marrow plasmacytosis. A literature review of cases of non-secretory multiple myeloma, its clinical manifestations and investigations has been done.

Case report

A 75 yr old male came with complaints of fever and cough for 20 days, shortness of breath for four days, history of chest pain, left sided, non radiating, not associated with sweating. There was no history of palpitations or pedal oedema.

Patient had a past history of Hansen's disease 40 years ago, which was treated with dapsone and clofazimine. Patient was operated for epigastric hernia one year back when he was treated for anaemia while admitted in surgical ward. Six units of packed RBC was transfused. He had a past history of recurrent pneumonias. He was a non smoker and a non-alcoholic.

On examination, the patient was pale, had bilateral pitting oedema and bilateral lymph node enlargement, cervical & inguinal group of nodes, 1-1.5cm in size, firm in consistency. His blood pressure was 140/80 mm hg, respiratory rate was 32 / min. Patient was dyspnoeic. His abdomen was distended. He had hepatomegaly, 5 cm below right costal margin and splenomegaly 7cm below the costal margin. On auscultation, bilateral fine basal crepitations were heard. Heart sounds were normal. CNS examination showed no focal neurological deficit.

Laboratory investigations revealed anaemia (Hb - 6.3 g/dl), neutrophilic leucocytosis (Tlc - 14,900, Dc - N-87.1, E-0.6, L-10.6, M-1.7, B-0). He had slight thrombocytopenia (platelet count - 1.30 lac/cu.mm). The ESR was 136 mm at one hour. His renal parameters and serum electrolytes were normal. Urine analysis revealed- albumin 1+, pus cells 5-10/hpf, epithelial cell- 2-4/hpf. His liver function tests revealed mild hyperbilirubinemia (total bilirubin-2.2mg/dl, direct bilirubin-0.3 mg/dl) with mild increase of serum alkaline phosphatase - 177 u/l. The total protein (7.4 g/dl) was normal with a lowered serum albumin (2.2 g/dl). The serum globulin was raised (5.2 g/dl). The serum LDH was slightly raised at 257 u/l. The reticulocyte count was slightly raised at 3.2%, the indirect Coombs test being negative. HIV 1 & 2 and HBsAg were non reactive. The echocardiography showed normal LV function and no regional wall abnormality.

In view of the raised temperature, breathlessness and elevated WBC counts the patient was started on oxygen, diuretics and antibiotics. The breathlessness suddenly increased and saturation dropped to less than 60%, at which point he was intubated and put on ventilator. The repeat haemoglobin was 7.5 gm/dl and repeat total leucocyte count was 60,000 cells/cu mm of blood. ABG revealed hypoxaemia & hypercapnia. Blood culture and sensitivity showed no growth. Urine culture showed insignificant bacteriuria. Endotracheal tube aspirate Gram stain showed few pus cells, occasional Gram positive cocci in pairs, numerous Gram negative bacilli.

On re-evaluation of patient's history & examination, with history of chronic low back pain, recurrent pneumonia, generalised lymphadenopathy, hepatosplenomegaly, anemia despite repeated blood transfusions & taking into consideration other lab parameters, serum protein electrophoresis with immunofixation was done. The total protein was 6.61 g/dl, albumin - 3 g/dl, alpha 1 globulin - 0.13 g/dl, alpha 2 globulin - 0.35 g/dl, gamma globulin - 0.36 g/dl. The immunoelectrophoresis did not show a M Band. With clinical features pointing to hematological malignancy, i.e., high ESR (136 mm), a bone marrow aspiration and biopsy were performed. The bone marrow showed a hypercellular marrow with an increase in plasma cells, plasma blasts, binucleated plasma cells with a bone marrow plasmacytosis (25%) (Figs 1&2).

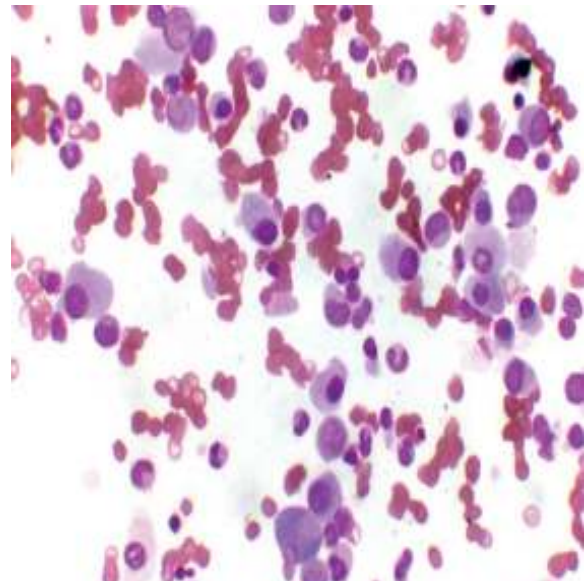


Fig 1- Bone marrow aspiration showing infiltration by plasma cells (Leishman's stain 40X10X)

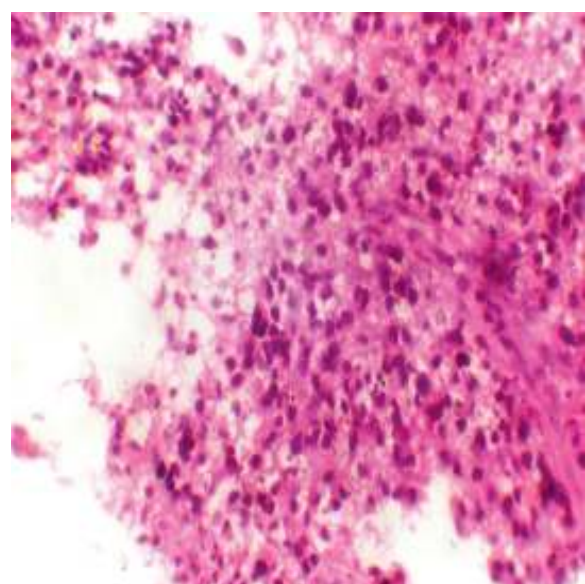


Fig 2- Bone marrow trephine biopsy showing plasma cells infiltrating the marrow (Haematoxylin and eosin staining 40X10X)

The erythroid series was normoblastic & myelopoiesis was normal. Immunohistochemistry on the bone marrow biopsy showed CD 138 and monoclonal kappa chain positive cells. The X-ray skull showed a lytic lesion. The urine did not show the presence of light chains or M protein spike. In view of the raised ESR, bone marrow plasmacytosis and an absence of M band on serum immune-electrophoresis, a diagnosis of non-secretory multiple myeloma was made. The serum calcium and renal parameters were normal. Ultrasound of the liver showed diffuse homogenous deposition and amyloidosis was suspected. However, an abdominal fat biopsy was negative for amyloid. The patient was started on melphalan, prednisolone & allopurinol. After 4 cycles of chemotherapy the patient passed away due to persistent pneumonia.

Discussion

Multiple myeloma is the malignant disorder of plasma cells accounting for 10-15% of all haematological malignancies and one to two percent of all malignancies. Non secretory multiple myeloma is characterized by bone marrow plasmacytosis, lytic bone lesions and an absent M band either in the serum or urine on immuno electrophoresis with or without organ damage². Two cases of NSMM below the age of 30 years have been described in literature. The monoclonal immunoglobulins were demonstrated by immunohistochemistry³. The disease has a varying presentation ranging from low grade bodyache, backpain, pathological fractures, repeated infections to other non-specific complaints. About 10-40% are asymptomatic¹. Our patient had anaemia not corrected by repeated transfusions, repeated respiratory infections, generalized lymphadenopathy and hepatosplenomegaly with normal serum calcium levels and normal renal parameters.

An occasional patient presenting with plasma cell leukaemia has been described. The authors postulate that these cases may be more aggressive as immature plasma cells do not have the capacity to synthesize or secrete complete immunoglobulins. Hepatomegaly was seen infrequently as compared to plasma cell leukaemia and no patients had splenomegaly or peripheral lymphadenopathy at the time of diagnosis. They also used fluorescein-conjugated antisera against immunoglobulins to demonstrate free kappa chains in the cytoplasm of the plasma cells as was seen in our case. They described two categories of patients- one group of patients with positive immunofluorescence in plasma cells (secretory, non-excretory MM) and the other group with negative immunofluorescence (true nonsecretory MM)^{4,5,6}.

The clinical features of 13 patients with non-secretory multiple myeloma (NSMM) from a series of 172 consecutive multiple myelomas were studied. The non-secretors survived longer than the secretors, median 46 months versus 21 months (p -value < 0.01). Non-secretory myeloma was associated with a higher incidence of neurological presentation, lesser incidence of lytic bone lesions, a lower percentage of plasma cells in the marrow and a lower incidence of hypogammaglobulinaemia. The superior survival of

non-secretors was thus thought to be due to earlier presentation possibly as a result of a tendency to form symptomatic local tumours. A retrospective immunoperoxidase staining of the archived tissue was performed in nine cases. Monoclonal immunoglobulin was detected in eight cases. Thus, immunoperoxidase staining helps in establishing the diagnosis of non-secretory multiple myeloma⁷.

Non-secretory multiple myeloma is an aggressive disease as illustrated by a case-report where the patient had 4 relapses after multiple therapeutic regimens including conventional chemotherapy, high dose chemotherapy with autologous stem cell transplantation and the more potent, novel anti-myeloma agents. The last relapse was a nodular infiltration of liver following which the patient expired⁸.

Non-secretory multiple myeloma was first described in 1958 by Serre¹. It has since been postulated that either there is a reduced production or reduced secretion of immunoglobulins. In such cases intra-cytoplasmic immunoglobulins are detected by immunohistochemistry as was seen in our case where the kappa chain positive plasma cells were seen¹.

The morphology of plasma cells are characterized by a perinuclear halo and rough endoplasmic reticulum and a clear Golgi apparatus on electron microscopy. A case report of NSMM with azurophilic granules in the cytoplasm had been reported, which were identified as phagocytic vacuoles on electron microscopy. Immunohistochemical staining showed positivity for myeloma cells, B-cell associated markers, myeloid and stem cell markers. Such cases may present a diagnostic dilemma where electron microscopy may demonstrate the characteristic morphology⁹.

A case of NSMM presenting with pancytopenia had been reported. This patient had plasma cell infiltration of the bone-marrow. The plasma cells were multinucleated and showed erythrophagocytosis and phagocytosis of granulocytes. The patient lacked lytic lesions. The plasma cells were aberrantly positive for CD117 and CD13 and lacked expression of CD56 and were positive for kappa chains. The patient improved on dexamethasone therapy though haemophagocytosis persisted¹⁰.

A case report of NSMM showed plasma cells with distended rough endoplasmic reticulum containing cytoplasmic colloid. On immunoperoxidase staining, the cells showed IgA heavy and kappa light chain positivity. This distension of the endoplasmic reticulum may suggest either active synthesis or block in their excretion¹¹.

Also, the conventional methods of detection of immunoglobulins and light chains are not sensitive enough to detect these chains. The newer serum immunoglobulin-free light chain assay (FLC) detects the light chains not detectable by the earlier assays. Patients with non-secretory multiple myeloma have less involvement of the kidney as free chains are not excreted in the urine. Few reports claim a better survival for patients with NSMM because of lower

incidence of involvement of the kidney, but prognosis is guarded in such cases as the diagnosis is delayed because of the absence of M protein in the serum or the urine¹.

The presenting features of non-secretory myeloma are similar to those in patients with a detectable M-protein, except for the absence of renal function impairment. The response to therapy and survival of patients with non-secretory myeloma are similar to those of patients with measurable M-protein¹² though there are case reports of NSMM with hypercalcemic acute renal failure¹³.

Intact and fragmented intracellular immunoglobulin and kappa chain in the plasma cells in a case of non-secretory myeloma have been demonstrated by polyacrylamide gel electrophoresis before the introduction of FLC assay¹⁴. Another method which was tried was by immunoelectrophoresis. These methods have been replaced by the introduction of the FLC assay¹⁵.

The serum free light-chain (FLC) assay (Freelite™, The Binding Site Limited, Birmingham, U.K.) is a nephelometric assay that can be performed on automated chemistry analysers and allows quantification of free kappa (κ) and lambda (λ) chains (i.e., light chains that are not bound to intact immunoglobulin) secreted by plasma cells. An abnormal kappa/lambda FLC ratio indicates an excess of one light chain type versus the other, and is interpreted as a surrogate for clonal expansion of plasma cells. The assay is used to monitor patients with oligo-secretory or non-secretory myeloma and primary amyloidosis^{16,17}.

Asymptomatic myeloma with a high risk of progression to symptomatic disease is identified by the presence of extensive bone marrow (BM) infiltration, abnormal free light chain (FLC) ratio and serum monoclonal (M)-protein >3 gr/dl whereas the type of heavy (IgG vs IgA) or light chain or immunoparesis of the uninvolved immunoglobulins were not. Abnormal marrow signal of magnetic resonance imaging of the spine was associated with a significant risk of progression (median 15 months, $p=0.001$). Extensive BM infiltration $>60\%$ (hazard ratio, HR: 13.7, $p<0.001$) and FLC ratio >100 (HR: 9, $p=0.003$) independently identified a 'very high-risk' group¹⁸.

The quantitative assay for free light chains (FLCs) is a recently introduced commercial test reported to be sensitive and specific for detecting FLC diseases such as primary systemic amyloidosis (AL), light chain deposition disease (LCDD), non-secretory multiple myeloma (NSMM), and light chain multiple myeloma. The authors performed the FLC assay and found the results to be consistent with published data¹⁹.

Serum free light chains (FLC) are present in the serum and urine of many patients with monoclonal gammopathies and is useful in the management of light chain MM, non-secretory MM and AL amyloidosis. It cannot be recommended for monitoring intact immunoglobulin multiple myeloma^{20,21}.

The serum immunoglobulin-free light chain (FLC) assay measures levels of free kappa and lambda immunoglobulin light chains. There are three major indications for the FLC assay in the evaluation and management of multiple myeloma and related plasma cell disorders (PCD). In the context of screening, the serum FLC assay in combination with serum protein electrophoresis (PEL) and immunofixation yields high sensitivity, and negates the need for 24-h urine studies for diagnoses other than light chain amyloidosis (AL). Second, the baseline FLC measurement is of major prognostic value in virtually every PCD. Third, the FLC assay allows for quantitative monitoring of patients with oligosecretory PCD, including AL, oligosecretory myeloma and nearly two-thirds of patients who had previously been diagnosed to have non-secretory myeloma. In AL patients, serial FLC measurements outperformed PEL and immunofixation. In oligosecretory myeloma patients, serial FLC measurements reduce the need for frequent bone marrow biopsies. In contrast, there is no data supporting the use of FLC assay in place of 24-h urine PEL for monitoring or for serial measurements in PCD with measurable disease by serum or urine PEL. This paper provides consensus guidelines for the use of this important assay, in the diagnosis and management of clonal PCD^{22,23,24}.

Our case had diffuse homogenous deposition in the liver prompting suspicion of amyloidosis which was disproved on further biopsy of the abdominal fat which was negative for amyloid. There are few reports of NSMM being associated with amyloidosis. An attempt has been made to explain the lack of monoclonal immunoglobulins in the serum and urine, although extensive organ amyloidosis of AL type (kappa-light chains) has been found. The immunoglobulins get degraded on excretion or pathologic immunoglobulins are secreted as amyloid proteins which polymerize into amyloid fibrils^{25,26}.

Patients with multiple myeloma and NSMM are prone to having infections due to decreased levels of polyclonal serum immunoglobulins. *Pneumococcal*, *Haemophilus influenzae B*, and *Pneumocystis carinii* infections are seen commonly with myeloma²⁷. Infections are the main cause of morbidity and mortality in multiple myeloma due to impaired humoral immunity. Infections of the urinary tract with *Escherichia coli*, *Pseudomonas*, *Proteus* and *Klebsiella* are common. These infections result in sepsis and the resultant sepsis can be fatal in nearly 20% of patients²⁸.

An increased reactivation of *Herpes simplex* and *Herpes zoster* infections in patients treated with novel anti-myeloma drugs like bortezomib has been seen. Stem cell transplantation, which is being used for treatment of multiple myeloma is associated with an increased risk of infection with *Clostridium difficile*, cytomegalovirus and opportunistic moulds²⁹. After diagnosis, gram negative bacilli and *Staphylococcus aureus* infection increases markedly and are responsible for $>90\%$ deaths from infection³⁰.

Conclusion

A high degree of suspicion for a haematological malignancy is warranted in a case of recurrent anaemia despite blood transfusions, repeated infections, generalised lymphadenopathy and hepatosplenomegaly. A bone-marrow examination with immunohistochemistry is helpful in such cases to establish haematological malignancy, which can be supported by ancillary tests like serum protein electrophoresis with immunofixation, Free-Light Chain assay and X-ray for lytic lesions in bone, where indicated.

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Answer to : Diagnose the condition

ECG shows Normal sinus rhythm; Tall peaked P waves were seen more evident in lead V2 and II. QRS is broad and splintered suggesting an intraventricular conduction defect. The patient was diagnosed to have Ebsteins anomaly on Echocardiogram.

Ebsteins anomaly: It is a congenital anomaly of the right heart, where the septal tricuspid leaflet is apically displaced and right atrium is large due to atrialisation of right ventricle. ECG is seldom normal even in mild anomaly. A confident diagnosis can be made on the ECG per se. These tall P waves are characteristically described as Himalayan P waves, occurring due to right atrial conduction disturbance. Prolongation of QRS is due to prolonged activation of the atrialised RV, which leads to Bizzare second QRS attached to first normal QRS. Other common ECG findings of the condition include, prolonged PR, atrial flutter/fibrillation, type B WPW pattern.

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"Whey" to Relief in Type II Diabetes

Post-prandial glucose surge is considered to be responsible for most of the type II diabetes complications such as, cardiovascular disease, retinopathy, renal damage and dementia. A study conducted in Tel Aviv University has found a new solution to these post meal glucose surges: consumption of "Whey" protein concentrate (Daniela Jakubowicz et al. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load in type 2 diabetes: a randomised clinical trial. *Diabetologia*, 2014; 57 (9): 1807 DOI: 10.1007/s00125-014-3305-x). Whey is the watery portion of curdled milk. In the study, whey protein concentrate was administered 30 minutes before a high glycaemic breakfast. Blood glucose, insulin and intact Glucagon-like Protein 1 (GLP-1) levels were estimated at half hourly intervals for 3 hours following the breakfast. The study found that glucose levels were 28% lower, and insulin/GLP-1 levels higher, in whey protein treated individuals than in controls. Whey protein acts by stimulating the release of GLP-1 which in turn increases the levels of insulin. Whey protein concentrate promises to be a novel solution to a difficult problem.

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