Case Report

The missing M band: Is it really Non Secretory Multiple Myeloma?

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Keywords

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Background: Non-secretory multiple myeloma (NSMM) is defined as clonal bone marrow plasma cells ≥10% or biopsy proven plasmacytoma, evidence of end-organ damage due to underlying plasma cell dyscrasia, namely hypercalcemia, renal insufficiency, anaemia, bone lesions and lack of serum and urinary monoclonal protein on electrophoresis and immunofixation. They represent 3-5% of multiple myeloma (MM). With the advent of serum free light chain (s FLC) measurement, most of NSMMs have been classified as Light chain Multiple myeloma (LCMM). Thus, the proportion of true NSMM, meaning MM that secretes no monoclonal protein (complete immunoglobulin, heavy or light chain) is close to 1-2% of all myelomas. There is a need to distinguish between the true non-secretory from the other forms of oligo-secretory (OSMM) and secretory form of myeloma like LCMM with use of advanced diagnostic tools such as s FLC assay as the former has a good prognosis.

Case Presentation: We discuss a case of a 65-years-old female who presented with chronic chest pain since one year. Cardiac and musculoskeletal involvement were ruled out. Monoclonal gammopathy was suspected in view of imaging abnormalities. Surprisingly, SPE and IFE reported absence of M band. A provisional diagnosis of NSMM was made based on biopsy features. However, diagnosis of NSMM was later changed to LCMM in view of a positive sFLC ratio.

Conclusions: It is well-known that the sequence of diagnostic investigations plays a crucial role in the timely diagnosis and management of patients. However, in this case it was a faulty sequence of ordering investigations which prolonged the hospital stay and delayed therapeutic intervention for the patient concerned. Serum Protein Electrophoresis (SPE), Immunofixation electrophoresis (IFE) and sFLC are simple blood-based tests which can help diagnose a majority of cases of monoclonal gammopathies. They need to be included as first line tests in our approach to evaluating a suspected case of monoclonal gammopathy.

Introduction

Multiple Myeloma (MM) is the second most common hematological malignancy in the United States of America (USA), with ~30,000 new cases/year accounting for 10% of all hematologic cancers and 1% of malignant diseases in USA [1]. It is a neoplasm of the bone marrow's well differentiated plasma cells (PCs), which usually contribute towards humoral response. MM is characterised by clonal proliferation of plasma cells of the bone marrow, and presence of CRAB features (hypercalcemia, renal involvement, anaemia, bone pain,) as well as three defined components. These three include: clonal bone marrow plasma cells ≥60 %, Serum free light chain (SFLC)ratio ≥100 (when involved FLC level is ≥100 mg/L) and greater than one focal lesion on magnetic resonance imaging (MRI) [2,3]. In India, MM accounted for 1.19% of all cancers in females and 1.36% in males during 2012-2014[4]. However, the age of onset is almost a decade earlier than the Western countries [4].

MM is characterised by the unchecked production of clonal immunoglobulin (Ig) from the plasma cells. They may be complete (heavy and light chain) or incomplete immunoglobulins (Igs) (either heavy chain or light chain). The invasive neoplastic plasma cell growth in the bone and bone marrow and the production of aberrant immunoglobulin leads to manifestations which include osteolytic lesions manifesting as bone pain, increased serum calcium, anaemias, cytopenias, neuropathy and renal injury [5]. Presence of the clonal aberrant immunoglobulin in the blood or urine is quantified to diagnose and monitor plasma cell dyscrasias using tests like serum and urine protein electrophoresis (SPEP and UPEP), serum and urine immunofixation (IFE), total immunoglobulin quantification and the serum free light chain assay [6]. Monoclonal component (MC) or protein (MP) can be detected in serum and urine as [7]:

a. a complete immunoglobulin molecule made of heavy and light chains bound together;
b. increased concentrations of complete Immunoglobulin molecule along with raised levels of light chains not bound to heavy chain (free light chains [FLCs]);
c. mainly FLC with low levels or absence of complete Immunoglobulin: LCMM
d. a fourth entity characterised by the presence of only free heavy chain with no bound light chain (very rare): heavy chain disease and
e. a fifth subclass characterised by MC not detectable either in the serum or the urine by SPE/IFE: the non-secretory variant of multiple myeloma.

The incidence of NSMM ranges from 3% to 5% of the total MM cases [8]. However, with technological advancements, FLCs can be detected by the serum FLC assay. Many previously classified NSMMs are now reclassified as oligo -secretors, producing FLC solely minus the heavy chain. Hence, actual proportion of true NSMM i.e MM secreting neither monoclonal heavy nor light chains is only 1–2% of all MMs [9,10]. The International Myeloma Working Group presently defines NSMM as MM devoid of MP detection by serum or urine immunofixation, which may include light-chain MM. This definition needs review since LCMM indeed actively secretes a component of the immunoglobulin monoclonal FLCs capable of detection by the SFLC assay [2,3,5,11,12]. This case highlights the diagnostic challenges faced in identification of NSMM and the importance of sFLC test in differentiating NSMM from LCMM.

Case history

A 65-years-old female presented to the hospital with complaints of chest pain that had lasted for one year. A cardiac consultation revealed no abnormality.

Investigations

A spine MRI done during early 2021 revealed the presence of numerous ill-defined lesions, replacement of the normal marrow and altered marrow signal intensity involving multiple thoracic and lumbar vertebral bodies. Spine MRI was done again six months later which revealed numerous ill-defined mixed lytic-sclerotic lesions in multiple thoracic and lumbar vertebrae. The MRI results suggested haematological malignancy most likely MM or metastasis. Compared to the earlier MRI scan there was a reduction in the height of multiple vertebral bodies in the second MRI and few of the vertebral bodies were partially collapsed. A heterogenous lesion measuring 1.8 x 1.9 cm in size was seen in left iliac blade and biopsy of the same was suggested. A Computed Tomography (CT) guided biopsy from left iliac blade revealed features suggestive of plasma cell dyscrasia (Figure 1 shows detailed radiological findings). A bone marrow aspirate revealed 26% plasma cells. She was then referred to the radiotherapy unit for further treatment. Serum protein electrophoresis and immunofixation using gel-based methodology (Sebia Diagnostics, France) failed to reveal the M band (Figure 2). A 24- hour urine specimen immunofixation (Sebia Diagnostics, France) using gel based methodology also did not reveal any M band. The fluorescent in situ hybridisation (FISH) for multiple myeloma panel performed on peripheral blood after CD 138+cells collection was positive for chromosomal translocation t(11;14) (CCND1/IGH).The serum sample value for β2 microglobulin was raised at 3.66mg/l. Immunohistochemistry(IHC) marker CD138 was diffuse and strongly positive in tumour cells on biopsy. Kappa restriction was positive while tumor cells were negative for lambda light chain. sFLC assay by nephelometry (ATTELICA NEPH 630, Siemens) revealed an increased kappa light chain concentration of 57.5mg/l and lambda light chain concentration of 8.85mg/l. Kappa / lambda ratio was elevated at 6.49. Table 1 shows details of laboratory investigations done on fully automated clinical chemistry analyser (Beckman Coulter, USA) and five part hematology analyser (Transasia) which revealed anaemia, borderline hypercalcemia with normal urea, creatinine and normal A:G ratio with low protein and albumin levels. In view of discrepancy between bone marrow biopsy findings and immunohistochemistry results vis-à-vis SPE and IFE findings,a SFLC was finally done which revealed an elevated κ/λ ratio. Immunoglobulin quantification of IgD could

not be performed due to unavailability of facility for the same in house. Unavailability of anti- sera to IgE and IgD during serum and urine immunofixation as well as IHC posed a limitation in ruling out IgD and IgE multiple myeloma. However, Serum IgE quantification by nephelometry revealed values below detection limits. We then made a provisional diagnosis of Light chain multiple myeloma with osteolytic lesions of the vertebra and anaemia as Myeloma defining events (MDE) without significant hypercalcemia and renal involvement. The elevated β2 microglobulin indicated a poor prognosis. Presence of chromosomal translocation (t 11;14) was noted in our case as has been observed in many previous studies on MM.

Figure 1: Radiological findings A) lateral skull radiograph showing multiple punched out lytic lesions of variable sizes in the calvarium as well the mandible B) frontal knee radiograph showing lytic lesions in both femur and tibia C) Sagittal reformatted CT thoracic spine image showing diffuse osteopenia and lytic lesions of the entire visible spine as well as the sternum, wedging and collapse of multiple vertebrae is evident D) CT guided bone biopsy procedure from a lesion of the left ilium E) Sagittal T1W image of the lumabosacral spine, F) Sagittal whole spine T2W image, and G) Sagittal post contrast fat-suppressed T1W image showing replacement of the vertebral marrow with poorly defined lesions, some of them showing enhancement, and the multi-level vertebral collapse H) Sagittal T2W, and I) Sagittal post contrast fat suppressed T1W images six-months after the first MRI, showing further progression of the disease, with extensive marrow replacement, enhancement and vertebral collapse.

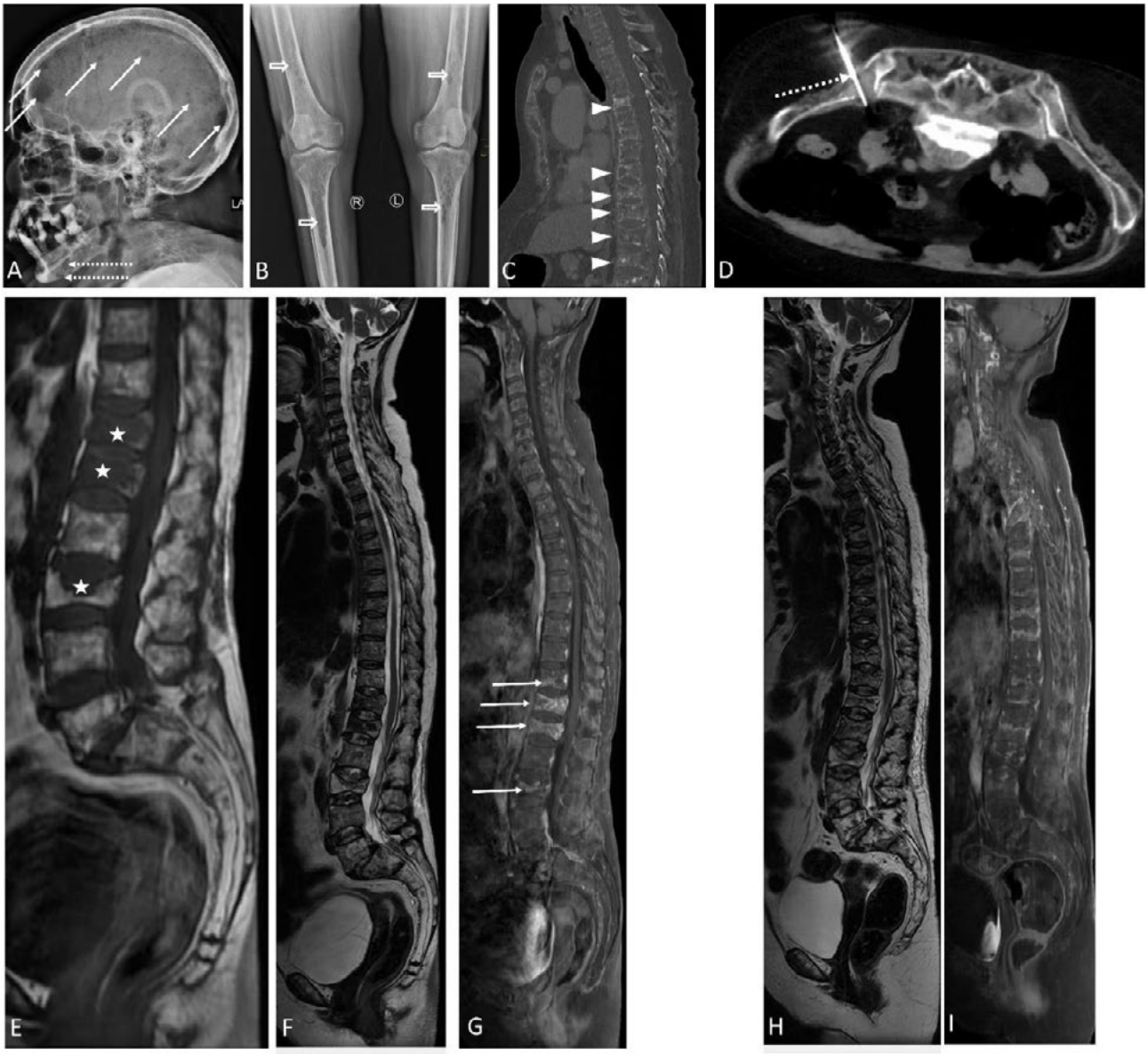
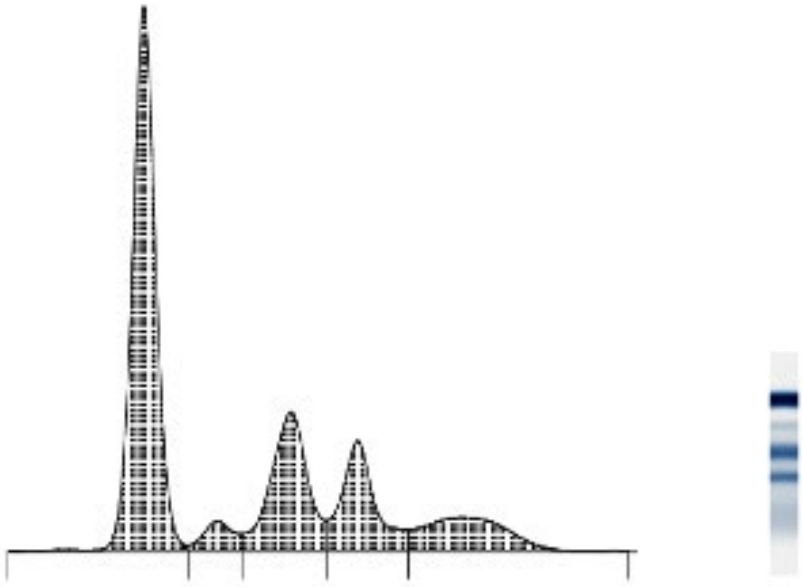


Figure 2: Serum protein electrophoresis reveals absence of M band.



Serum protein electrophoresis

Fractions	%		Ref. %	Conc.	Ref. Conc.
Albumin	**50.3**	<	59.8 - 72.4	**3.5**	
Alpha 1	**3.6**	>	1.0 - 3.2	**0.2**	
Alpha 2	**20.3**	>	7.4 - 12.6	**1.4**	
Beta	**14.5**	>	7.5 - 12.9	**1.0**	
Gamma	**11.3**		8.0 - 15.8	**0.8**	

Table 1: Routine and special laboratory investigations.

Parameters	Result	Unit	Reference Range
Serum urea	5.81	mmol/l	2.1-7.1
Serum creatinine	42.44	µmol/l	40-66
Serum uric acid	0.277	mmol/l	0.15-0.35
Serum calcium	2.58	mmol/l	2.15-2.57
Serum phosphorus	0.946	mmol/l	0.81-1.45
Sodium	138.37	meq/l	136-145
Potassium	4.10	meq/l	3.5-5.1
Chloride	103.42	meq/l	98-107
Total bilirubin	12.48	µmol/l	0-34
Indirect bilirubin	7.87	µmol/l	0.0-30.6
Direct bilirubin	4.62	µmol/l	0.0-3.4
Alanine Amino Transferase(ALT)	25	U/L	<34
Aspartate Aminotransferase (AST)	30.1	U/L	<31
Alkaline phosphatase(ALP)	118.6	U/L	33-96
Total Protein	4.50	gm/dl	6.4-8.3
Albumin	2.79	gm/dl	3.5-5.5
Globulin	1.71	gm/dl	2.0-3.5
A:G ratio	1.63	---	1.5-2.5
Hemoglobin	10.9	gm/dl	12-15.8
White Blood Cells	7.81	$10^3/\mu L$	3.54-9.06
Platelet	153	$10^3/\mu L$	165-415
Beta 2 microglobulin	3.66	mg/l	1.09-2.53
SPE findings	M band absent	--	--
IFE findings	No MP detected	--	--
SFLC(Kappa)	57.5	mg/l	6.7-22.4
SFLC (Lambda)	8.85	mg/l	8.3-27
κ/λ ratio	6.49	---	0.31-1.56
Urine IFE	No MP detected	--	--
Bone marrow biopsy	Plasma cells 26%	--	--

Diagnosis and Management

Our patient presented to the hospital's radiology wing for an MRI of the spine due to progressive increase in pain in chest wall. She was initially diagnosed as a case of MM stage II based on laboratory and radiological findings and chemotherapy started. She was put on VTD (bortezomib, thalidomide, and dexamethasone) regimen.

There was a significant delay in the final diagnosis; more so as the patient's workup began with radiological tests followed by SPE, immunofixation and FISH. The bone marrow biopsy and IHC were done at a much later stage. SFLC was done much later due to its unavailability at the hospital. She is now regularly on follow up treatment receiving chemotherapy cycles in our hospital.

Discussion

NSMM is defined as clonal plasma cells in the bone marrow to the extent of ≥10% or plasmacytoma proven on biopsy with evidence of end-organ involvement due to the underlying plasma cell neoplasm. Manifestations include raised serum calcium, renal impairment, anaemia, skeletal lesions and undetectable serum and urinary MP on electrophoresis and immunofixation [13].

NSMM patients are categorised into different groups. True NSMM consists of non-producers of immunoglobulin chains with a defect in immunoglobulin synthesis leading to undetectable protein in the blood or urine despite significant plasmacytosis in the bone marrow. The s FLC assay will not detect any MP and hence no measurable disease can be identified in such patients [13]. In the second category of NSMM patients,

neoplastic plasma cells produce non-functional MC with defects in secretion. It is believed that true NSMMs arise from a loss of heavy chain secretion first followed by the loss of light chain secretion [14,15]. LCMM patients produce only light chain component of immunoglobulin. They are hypothesised to have never displayed a legitimate heavy chain recombination. Non-functional IgH recombinations at the DNA level indicative of abnormalities in the IgH gene re-arrangements during B-cell maturation allows secretion of only light chains in the abnormal plasma cells [16]. A study in 2002 observed that 11 amongst 14 NSMM patients had a t(11 ; 14)(q13;q32) rearrangement, probably giving the cells a more "lymphoplasmacytic morphology" with a decreased secreting capacity [17]. All these are suggestive that the progression of NSMM cells may be sequentially from fully secretory MM to MM devoid of heavy chain production and then ultimately the light chain.

A group of patients with impaired secretion producing only low levels of light chains also exists. Such patients are classified as oligo-secretory "free light only" myeloma as their protein secretion is not as high as classical myeloma, but still measurable using sFLC assay. Oligo-secretory multiple myeloma is often characterized by serum MP concentration less than1.0 g/dL, urinary protein less than 200 mg/day and sFLC values less than 100 mg/L [12].

The identification of NSMM poses a significant challenge to physicians and laboratory specialists. A combination of biochemical, pathological and radiological investigations is required to identify non- secretory MM including SPEP, UPEP, and sFLC assay and an imaging survey apart from the routine tests. Bone marrow aspiration and biopsy of the suspected lesion for plasma cell morphology and count is suggested in all patients with suspected NSMM. Flow cytometry may sort CD138-enriched cells for FISH testing to identify associated translocations. Samples should also be stained for intracellular immunoglobulin if there is a suspicion of true NSMM. The diagnosis of NSMM requires the presence of MM-mediated end-organ damage (CRAB). Patients with LCMM may have only detectable serum/urine free light chain but they should not be classified as NSMM. The group of true NSMM has disease manifestations with no serum/urine MC, or presence of free light chain. A skeletal survey is recommended in such patients by use of positron emission tomography (PET)/CT scan. Bone survey and marrow plasmacytosis, assess disease extension at presentation and the level of response to treatment. PET/CT imaging can help identify sites of bone involvement and differentiate between active and dormant lesions at treatment completion and during follow-up.

The inability to use serum and urine immunoglobulin tests by clinicians as dependable markers for tumour load assessment presents a dilemma for clinical decision making in NSMM. Serially performed bone marrow studies permit direct assessment of tumour burden and are the gold standard. However, the cost, time, and patient discomfort involved with frequent bone marrow aspirations and biopsies are practically unconvincing and hence the preference for imaging studies. Conventional X-rays don't correlate with tumor response. Advanced imaging modality such as PET/CT offers an advantage over MRI for monitoring response to treatment. Current treatment modality for NSMM is the same as other variants of MM. However as chromosomal translocation t(11 ; 14) is more frequently found in NSMM, there may be a change in treatment modality in near future. As NSMM variant is less frequent and difficulties are encountered in monitoring response to treatment, very less data is available either in the form of retrospective or prospective studies on NSMM [18].

The sensitivity of sFLC assays has been particularly useful in detection of M protein in patients previously described non-secretory as per electrophoresis findings. In a study of 28 patients with NSMM, it has been found that sFLC measurement at diagnosis for many NSMM patients has proved beneficial for them. It helps avoid diagnostic delays and is therefore recommended by the International Myeloma Working Group for patients with NSMM [19]. In another study involving 74 patients diagnosed with monoclonal gammopathy, sFLC assays were carried out using two different methods i.e Freelite assays and N latex FLC assay [20]. The data obtained in this study suggested the superiority of the polyclonal antibody reagent used in Freelite assay over the monoclonal antibody reagent used in N Latex FLC resulting in better clinical senstivity. The authors speculated that the Freelite assays could identify majority of the polymorphic monoclonal FLC but the N Latex FLC based on monoclonal antibodies with limited epitope specificity was unable to recognize all monoclonal FLC clones. More studies are needed in future to establish the rates of agreement between different sFLC assays available in the market. In patients with renal failure, reticuloendothelial pinocytosis is the main mechanism for sFLC clearance. This leads to increased half-life of sFLC and serum levels 20–30 times normal. The sFLC assay can become potentially unreliable as the differential ability to clear κ and λ LCs by the kidney is lost in such cases, leading to the change in sFLC ratio. About 500 mg/day of FLCs are produced normally with a κ/λ ratio of about 2:1. Due to dimeric nature of λ FLC, resulting in slower renal clearance compared with κ LCs leading to a κ/λ ratio in the serum of about 0.58 (range 0.26–1.75). FLCs have a serum half-life of 2–6 hours as they are rapidly filtered by the glomeruli followed by metabolism in the proximal tubules. When FLCs are produced in excess of the reabsorptive capacity of the tubules they can lead to accumulation of sFLC. A different normal range with κ/λ ratio increased to 0.37–3.1for patients with renal failure may result in an increased sensitivity of the assay. The treatment of renal myeloma aims to rapidly eliminate nephrotoxic light chains from the serum. Plasma exchange or high cut-off hemodialysis, is suggested as a supplement to dexamethasone ± bortezomib-based regimens in these settings. sFLC assays could also be helpful in these situations to monitor the effectiveness of the dialytic procedures intended to selectively remove the SFLC(21). Table 2 shows a comparative analysis of NSMM and LCMM. Authors have suggested an algorithm for workup of patients clinically suspected to be probable cases of monoclonal gammopathy (Figure 3).

Figure 3: Algorithm suggested for evaluation of suspected cases of Monoclonal Gammopathy.

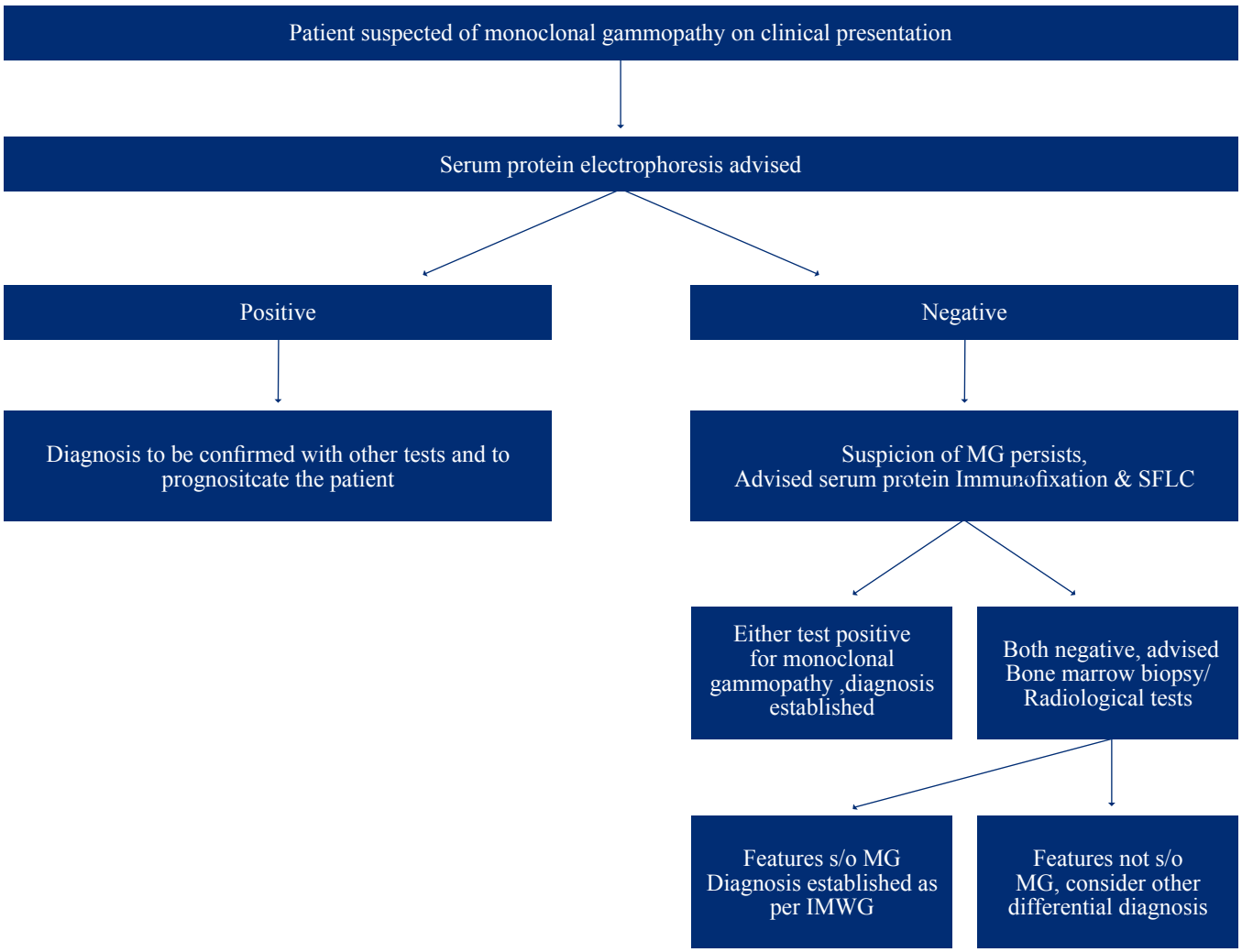


Table 2: A comparative analysis of NSMM and LCMM.

Non secretory multiple myeloma (NSMM)	Light Chain multiple myeloma (LCMM)
a) Accounts for upto 2-3% of all multiple myeloma cases	a) Accounts for up to 15% of all multiple myeloma cases
b) No M protein detectable in serum /urine protein electrophoresis and immunofixation	b) Clonal plasma cells are unable to produce heavy chains resulting in exclusive production of light chains
c) 85% of these will have M protein detectable in the cytoplasm of neoplastic plasma cells ,15% will have no immunoglobulin detectable in plasma cells	c) kappa or lambda light chain will be constituting the M protein
d) sFLC assays can be used to detect monoclonal protein in the absence of M protein by the above mentioned techniques	d) SPE and IFE may be able to detect the M protein depending on tumour load
e) sFLC assays will also fail to detect M protein	e) However cases which escape detection will be eventually detected by s FLC assays.
f) Better prognosis, Not at risk for developing myeloma kidney	f) Poorer prognosis, has more aggressive course, poses high risk for development of myeloma kidney.

Conclusion

Paraprotein absence on serum protein electrophoresis or serum immunofixation does not exclude a multiple myeloma diagnosis. sFLC assays can differentiate non-secretory/oligo-secretory type MM from light chain MM which may go undetected by SPE, Serum IF or Urine IF in case of less tumor burden. Additionally, a pre-treatment FLC assay should be performed because serial FLC values are helpful in monitoring treatment effects. For further differentiation of non-secretory /oligo-secretory from other cases of MM, a bone marrow aspiration/biopsy or osteolytic lesion biopsy is helpful. Moreover, we would suggest an algorithm involving initial workup of suspected multiple myeloma cases to include sFLC along with serum immunofixation.

Author disclosures

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Ethical considerations

Ethical clearance is waived off for case reports from our institute.

Consent for publication

Informed consent has been taken from husband of the patient concerned to go ahead with possible publication in a medical journal.

Competing interests

None.

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None.

Author's contributions

All authors fulfil the criteria for authorship as set out by the ICMJE and as recommended by the Committee on Publication Ethics (COPE).

Data availability

All data related to the case has been submitted along with the manuscript.

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