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Case Report

Diagnosing Non–Producers Non–Secretory Myeloma

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ABSTRACT

Multiple myelomas (MM) is the proliferation of malignant plasma cells in the bone marrow, which is characterized by the production of monoclonal immunoglobulins that are secreted in the blood and urine. However, in 1 – 5% of cases, the protein is undetectable and defined as non–secretory type of myeloma. A 36–year–old female presented with complaints of weakness in both legs so she could not walk. She also felt pain in the head, back, and thighs since one year before. Physical examination showed anemic conjunctiva, gibus as high as T4, hypoesthesia as high as T6 segment, increased physiological reflexes, and positive pathological reflexes on the right and left. She had anemia (Hb 10.2 g / dL), decreased kidney function (eGFR: 30 mL/min/1.73m^2) and multiple lytic lesions in the calvaria, ribs, superior–inferior pubic ramus, and left humeral os in the 1/3 proximal to 1/3 distal. A thoracolumbar MRI shows an extradural solid mass. Protein electrophoresis examination and Bence Jonce protein were negative, no hypercalcemia was obtained, and bone marrow aspiration showed myelodysplasia syndrome. Nonsecretory multiple myeloma were established by histopathology examination of extradural solid masses showing plasmacytoma. Non–secretory MM was defined into two groups, non–producers and multiple non–secretory myeloma patients who produce tumor proteins but cannot be excreted. This patients was categorized as non–producers non–secretory MM because she did not show a protein that can be measured in blood nor urine, but has significant plasma cells in tissue biopsy. The absence of paraprotein in the blood does not rule out multiple myeloma. Suspicion of multiple myeloma needs to be increased in patients who have symptoms of CRAB (calcium, renal impairment, anemia, bone lytic).

Keywords: *Multiple Myeloma, Non–Secretory, Plasmacytoma, Calcium, Lytic Lesions*

INTRODUCTION

Multiple myeloma (MM) is a malignant proliferation of plasma cells in the bone marrow. MM is a bone marrow disorder that accounts for 10–15% of all blood cancers and one to two percent of all malignancies. In the UK, this disease has a prevalence of 6.6 per 100,000. About 10–40% of MM patients can manifest asymptomatic, while around 50–70% of patients will show symptoms of bone pain due to lytic lesions and pathological fractures.(1)

Multiple myelomas are characterized by the proliferation of malignant plasma cells in the bone marrow and are often associated

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with the production of monoclonal immunoglobulin (M component), which is secreted in the blood and urine. This protein is often detected by serum electrophoresis. Measurement of monoclonal immunoglobulins in the circulation has become the standard for diagnosis, prognosis, and management. However, in one to five percent of myeloma cases, there are some cases where the protein is not detected and these patients are ultimately known to have a type of nonsecretory myeloma.[2]

Nonsecretoric multiple myeloma was first discovered in 1958 by Serre, who suggested that there was a decrease in protein synthesis or an increase in the destruction of abnormal intracellular or extracellular immunoglobulin chains.[3] Immunoglobulin is synthesized but not secreted, which may be caused by a decrease in permeability or a change or absence of light chains. This can explain that the excretion of intermittent immunoglobulin was not detected on examination.[2,4–6]

The diagnosis in cases of multiple nonsecretory myeloma depends on bone marrow biopsy and the discovery of plasmocytes in other tissues. In patients with osteolytic lesions, suspicion should be raised so that the diagnosis of multiple nonsecretory type myeloma can be established, thereby reducing the possibility of late management and worsening complications.[1]

The purpose of this case report is to raise suspicion regarding the diagnosis of multiple non–secretory myelomas in a 36–year–old female patient who presents with multiple pathological fractures, lytic lesions, anemia and decreased kidney function.

CASE ILLUTRATION

A female with the initials SK, aged 36 years, came from poly neurology for MRS at RSUD DR. SAIFUL ANWAR MALANG with complaints of weakness in both legs, which was felt for 20 days before hospitalization. Weakness is felt gradually. At first, it feels light, then it gets heavier so the patient cannot move at all. About one week before being admitted to the hospital, the patient noticed a wound on the buttocks that felt tender and wet.

About 1 year earlier, patients began experiencing frequent headaches, thigh, and lower back pain. Pain such as being pricked, does not spread and disappears when the patient consumes the drug he bought himself at the stall (the name of the drug is unknown). No history of previous falls. However, because the pain did not subside, the patient had a massage by a neighbor. Because of the back pain, the patient controls poly neurology. Weight loss is around 12 kg for one year. Complaints of fever are sometimes felt and disappear without the consumption of drugs. The patient is a housewife. He has three children. There is no family history of having the same disease or other cancers.

Physical examination showed a stable vital sign with a VAS pain scale of 5/10, anemic conjunctiva, a pressure ulcer in the sacrum region with a diameter of 5 cm and a gibus as high as T4. On neurological examination, hypoesthesia was found to be below the T6 segment, with increased physiological reflexes, and positive pathological reflexes (Babinski, Chaddock, Oppenheim, Gonda) on the right and left.

Laboratory tests are summarized in Table 1, with the results of normocytic normochromic anemia, decreased kidney function, and hypoalbuminemia (Table 1).

Table 1. Laboratory Results

Laboratory Categories	Normal Value	Test Result
Leukocytes (/µL)	3500 – 10000	10190
Hemoglobin (g/dl)	11 – 16.5	10.9
MCV	80 – 97	82.3
MCH	26.5 – 33.5	27
HCT (%)	35–50	37.2
Platelets (/µL)	146000 – 390000	517000
Eo/Ba/Neu/Ly/Mo	0.4 / 0.1 / 51 – 67 / 25 – 33 / 2 – 5	2.6 / 0.2 / 72 / 16 / 9.2
Sodium (mmol/L)	136 – 145	135
Potassium (mmol/L)	3.5 – 5	4.41
RBS (g/dl)		96
SGOT (U/L)	11 – 41	29
SGPT (U/L)	10 – 41	32
Albumin (gr/dL)	3.5 – 5	2.76
Calcium (mg/dL)	7.6 – 11.0	9.5
Phosphorus (mg/dL)	2.7 – 4.5	3.1
Ureum (mg/dL)	10 – 50	81.8
Creatinine (mg/dL)	0.7 – 1.5	2.69
eGFR	30 mL/min/1.73m^2	

**. MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; HCT, Hematocrite Test ; RBS, random blood glucose test; SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase.*

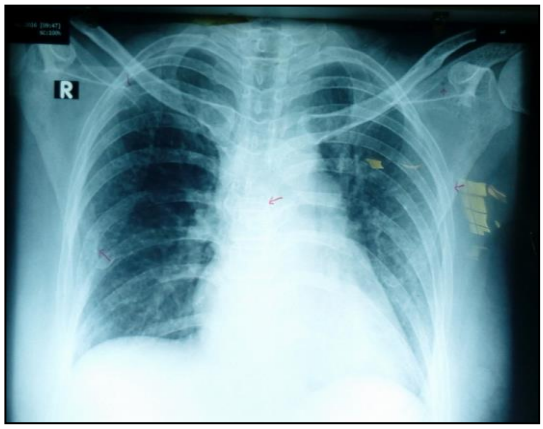

Figure 1. Chest X–ray Photo of Ms. SK, shows lytic lesions on the left scapula, pathological fractures in the right 4 and 7 ribs on the posterior side, pathological fractures in the left 3rd rib arch, and compression of the thoracic 7

Chest X–ray shows lytic lesions on the left scapula, pathological fractures in the right 4 and 7 ribs on the posterior side, pathological fractures in the left 3rd rib arch, and compression of the thoracic 7. In the lung picture, infiltrate in the bilateral lower lung field is obtained, with suspicion toward pneumonic metastases (Figure 1).

The bone survey was conducted and obtained the results of multiple lytic lesions in the calvaria, especially in the right–left frontoparietal region, as well as lytic lesions in the mandibular os. On the AP pelvic radiograph, lytic lesions appear on the superior inferior pubic ramus and osx femur 1/3 proximal. Lytic lesions were also seen on the left humeral os at 1/3 proximal to 1/3 distal (Figure 2).

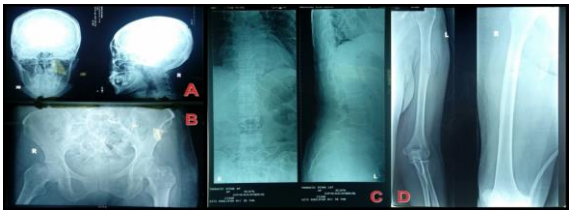

Figure 2. Bone survey, Ms SK, 36 years old. A: Multiple lytic lesions in the calvaria, especially in the right–left frontoparietal region, and lytic lesions in the mandibular os. B: Lytic lesions appear on the superior inferior pubic ramus and osx femur 1/3 proximal. C: Visible thoracic compression fracture 6 with a picture of the pancake vertebrae and thoracic anterior compression 12. D: Moreover seen lytic lesions on the left humeral os at 1/3 proximal to 1/3 distal

A thoracolumbar MRI showed an extra-dural solid mass involving the T5–T7 spinous process, T5–T7 lamina, T5–T7 inferior articular facies, T5–T7 intradural mass, T5–T6 dominant left forus and anterior– media column T6 level; with collapse of the T6 vertebrae and changes in the bone marrow of the thoracic vertebrae, probably due to metastases that cause severe calcaneal stenosis as high as T5–T6 and spinal cord edema at T5–T7 levels (Figure 3).

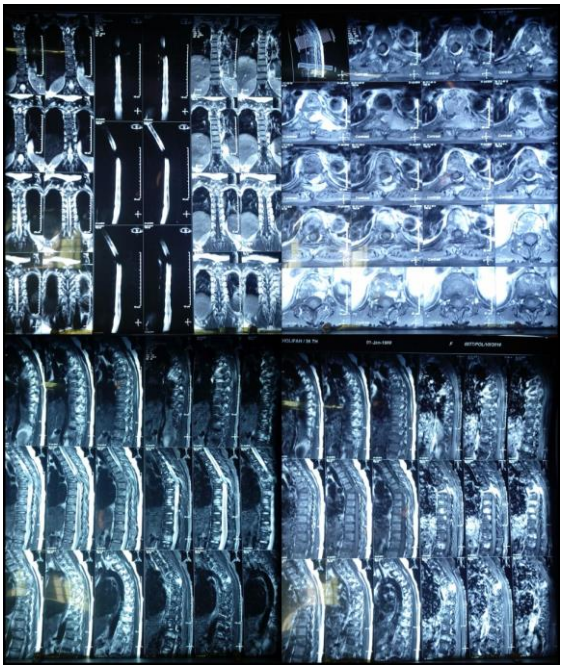

Figure 3. MRI Torakolumbal Ms. SK 36 years old, showed an extradural solid mass involving the T5–T7 spinous process, T5–T7 lamina, T5–T7 inferior articular facies, T5–T7 intra-dural mass, T5–T6 dominant left forus and anterior– media column T6 level; with col-lapse of the T6 vertebrae and changes in the bone marrow of the thoracic vertebrae, probably due to metastases that cause se-vere calcaneal stenosis as high as T5–T6 and spinal cord edema at T5–T7 levels.

Electrophoresis protein showed normal results (albumin: 3.01 gr / dL; α1 Globulin 0.20 gr / dL; α2 Globulin 0.89 gr / dL; β globulin: 0.9 gr / dL; ɣ globulin: 0.77 gr / dL; total protein: 5.85 gr / dL) (Figure 4), no Bence Jones protein in urine.

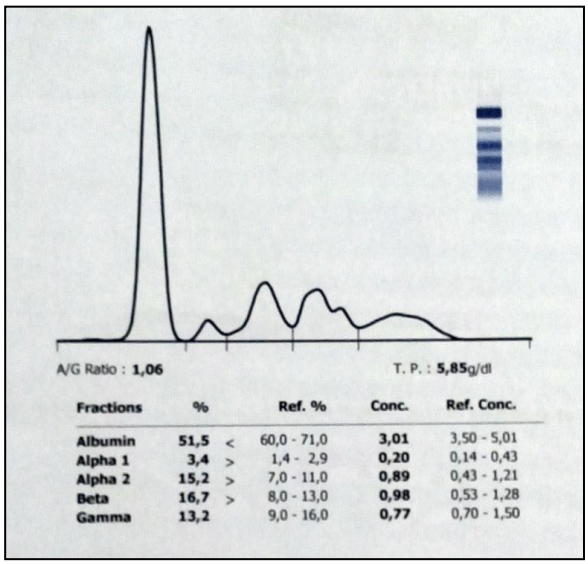

Figure 4. Protein electrophoresis showed normal results, no Bence Jones protein in urine.

PA results from the core biopsy examination showed a picture of plasmacytoma (multiple myeloma). The patient was diagnosed as non–secretory multiple myeloma, was transferred to the internal leader, and given the chemotherapy melphalan–prednisone–ibandronate regimen for 12 cycles per 28 days.

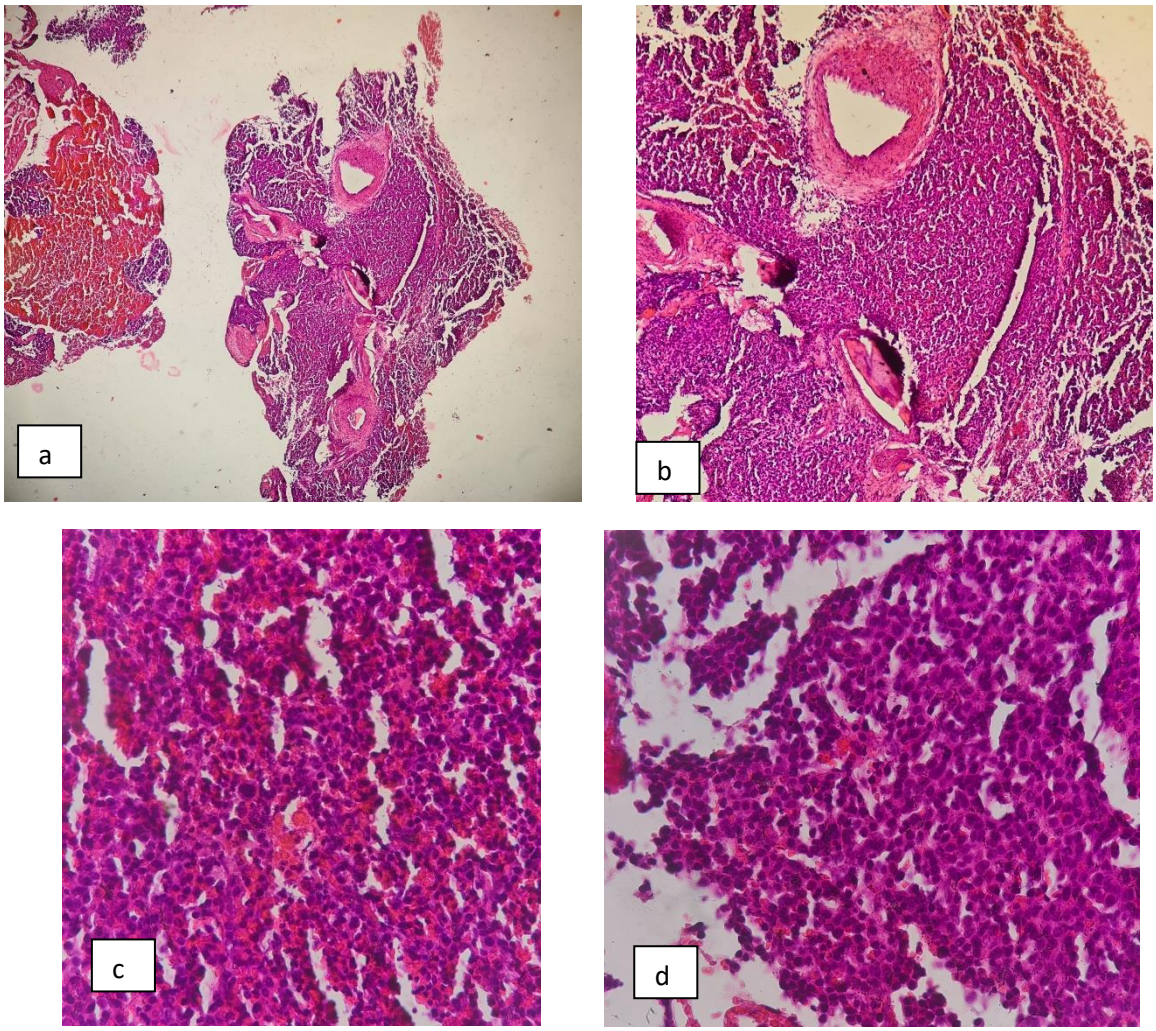

Figure 5. Tumor cells are round in shape, have eccentric nuclei and monotone eosinophilic cytoplasm - favoring plasmacytoma. a. 4X magnification; b. 10x magnification; c. 40x magnification; d. 100x magnification

DISCUSSIONS

Multiple myeloma is a disorder characterized by the presence of plasma clonal cells in the bone marrow, which results in damage to organs, such as in the hematological system, kidney, or bone complications. Myeloma can be preceded by the premalignant phase, where clonal plasma cells already exist but there is no evidence of end–organ damage (this is known as "monoclonal gammopathy of unknown significance" (MGUS) or "smoldering myeloma").[2,7,8]

The hallmark of most cases of multiple myeloma is the continuous production of some form of immunoglobulin, both in the form of complete antibodies and a separate component of monoclonal antibodies.[6,8] This protein is often detected by serum protein electrophoresis. Measurement of monoclonal immunoglobulins in circulation has become the standard for diagnosis, prognosis, and

management. However, in one to five percent of myeloma cases, there are some cases where the protein is not detected and these patients are ultimately known to have a type of non–secretory myeloma.[1]

Table 2. Symptoms and signs of multiple myeloma.[4]

Bone Problem	• General pain in the back, pelvis, and head. • Bone weakness, commonly osteoporosis. • Bone fracture, which is sometimes triggered by small collisions.
Cytopenia	• Anemia: causes symptoms of fatigue, shortness of breath, dizziness. • Leukopenia: causes frequent infections. • Thrombocytopenia: bruising with major bleeding.
Hypercalcemia	• Frequent thirst and polyuria. • Dehydration conditions. • Kidney disorders even with kidney failure. • Constipation • Abdominal pain • Decreased appetite. • Confusion (drowsy or confusion)
Central nerve disorders	• Severe back pain. • Thickness in the lower extremities. • Muscle weakness in the lower limb.
Hyperviscosity	• Decreased awareness: confusion, dizziness, stroke.
Symptoms of light chain amyloidosis (light chain)	• Heart problems: arrhythmias, heart failure. • Hepatosplenomegaly. • Macroglossia • Discoloration of the skin: caused by a tendency to bleed raccoon eyes. • Diarrhea • Carpal tunnel syndrome

Multiple myelomas need to be considered in patients over the age of 40 with anemia whose cause is unclear, kidney disorders and bone lesions. Only less than patients with multiple myeloma aged <40 years. Patients have shown complaints and symptoms in multiple myeloma patients related to tumor mass, size, plasma cell kinetic, growth and physiochemicals, immunologic and humoral effects produced by plasma cells (Table 2). The patient has complained of bone pain for 1 year and is getting heavier until both legs are weak and unable to walk. Chronic inflammatory complaints were obtained in the form of weight loss of about 12 kg in 1 year and the fever that disappeared. Bone pain (bone pain) is generally caused by compression fractures at the site of osteopenia or due to bone lytic lesions, usually the backbone. Osteoclast activating factors (OAF) such as IL1–β, lymphotoxins, and tumor necrosis factor (TNF) are responsible for typical osteolysis and osteoporosis. These factors also inhibit osteoblastic activity. Because of these abnormalities, there are microfractures that cause bone pain, hypercalcemia, and hypercalciuria.[10]

Local pain can also be caused by tumor pressure on the spinal cord and nerves exiting the spinal cord.[10] This can be explained by radiological examination in the form of a thoracolumbar X–ray showing a thoracic compression fracture 6 with a picture of the vertebrae pancake and anterior thoracic compression 12 and MRI showing an extradural solid mass involving the T5–T7 spinous process, T5 –T7 laminae, inferior articular facies T5–T7, intradural T5–T7, left dominant T5–T6 neural foramen and T6 anterior–media column.

Kidney disorders also occur in these patients with urea levels of 81.8 mg / dL and creatinine 2.69 mg / dL (eGFR: 30 mL / min / 1.73m^2). In multiple myeloma patients, nephropathy occurs when there is an increased capacity for heavy chain absorption. Other causes are hypercalcemia, which can cause accumulation in the renal tubules and one of the causes of intersectional nephritis.[11] Another cause of decreased kidney function in MM patients is the use of painkillers used to

treat pain.[10,11] Whereas this patient often takes pain medication for about 1 year.

There was no Bence Jones protein was found in the urine. The Bence–Jones protein was described in 1962 as a free, monoclonal light chain, synthesized by clones of a single B cell. Normal plasma cells produce a slight excess of light chains, but neoplasms of B cells can produce excess light chains that are much larger. After the tubular reabsorption mechanism becomes saturated, the Bence Jones protein will be excreted in the urine, as is the case in 75% of cases of multiple myeloma.[12,13]

Hypercalcemia generally occurs in 13% of multiple myeloma patients.[12] Hypercalcemia is the most frequent metabolic complication in patients with multiple myeloma, and excessive osteolysis is a major contributor in its pathogenesis. Hypercalcemia can range in presentation from mild to life–threatening and occurs in about one–third of multiple myeloma patients.[9] The pathogenesis of hypercalcemia is an increase in osteoclastic bone resorption caused by cytokines secreted locally by myeloma cells (receptor activator of nuclear factor–κB ligand [RANKL], macrophage inflammatory protein [MIP] –1α, and tumor necrosis factors [TNFs] or over–expression of other surrounding cells, bone resorption will cause calcium efflux to extracellular fluid, but the pathogenesis of hypercalcemia in multiple myeloma is more complex than this mechanism because not all patients with multiple myeloma show significant hypercalcemia conditions course of the disease.[11]

Anatomic pathology results from myeloma tissue (taken from core biopsy) show a picture of multiple myeloma (plasmacytoma).[9] Based on these results, the patient Ms. SK, 36 years of age meet the criteria of the Revised International Myeloma Working Group, namely plasmacytoma in tissue biopsy with signs of organ damage related to plasma proliferative disease based on the distribution of monoclonal immunoglobulins, multiple myeloma in these patients are classified as non–secretory.[8]

There are several groups of non–secretory multiple myeloma. Patients who are nonproducers. Patients have defects in immunoglobulin systems and are unable to synthesize or secrete proteins even though the features of plasma cell disorders have been present.[9] The patient does not show a protein that can be measured in blood or urine, but which still has significant plasma cells in the bone marrow and there is evidence of end–organ damage.[8,9]

Multiple non–secretory myeloma patients who produce tumor proteins but cannot be excreted. This condition has been proven in vitro that there is a single amino acid substitution in the light chain that has the potential to block outward secretion of cells, and there is some evidence of mutations in the immunoglobulin gene that can explain the decrease in secretion in patients with multiple nonsecretoric myeloma.[9]

CONCLUSION

The absence of paraprotein in the blood does not rule out multiple myeloma. Suspicion of multiple myeloma needs to be increased in patients who have symptoms of CRAB (calcium, renal impairment, anemia, bone, lytic) so that patients with non–secretory multiple myeloma immediately get appropriate management.

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