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Pathological Fracture of Multiple Myeloma with CRAB Criteria: A Case Report

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ABSTRACT

Multiple myeloma (MM) is a malignancy of plasma cells, often preceded by an asymptomatic condition known as the precursor state of monoclonal gammopathy of undetermined significance (MGUS). The diagnosis of multiple myeloma is typically confirmed using the CRAB criteria, which include hypercalcemia, renal impairment characterized by elevated serum urea and creatinine levels, anemia, and bone abnormalities. We report a rare case of multiple myeloma in a 63-year-old male patient who presented with pain in his left hand following a fall against a wall. Clinical and radiological examinations revealed findings consistent with multiple myeloma, with a differential diagnosis including metabolic bone disease and metastatic bone disease.

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CASE REPORTS

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Key Messages:

- This study highlights the importance of the CRAB criteria as an effective and practical diagnostic tool for multiple myeloma, especially in areas with limited laboratory facilities.
- The application of CRAB criteria allows for faster diagnosis and management, potentially improving patients' quality of life. The use of this criterion is not only clinically relevant but also efficient and economical, making it an appropriate choice for healthcare settings with limited resources.
- Additionally, this study enhances clinicians' understanding of the importance of a systematic approach in diagnosing multiple myeloma, reinforcing awareness of the applicability of CRAB criteria in various clinical conditions.

Introduction

Multiple myeloma (MM) is a heterogeneous disease characterized by clonal plasma cell neoplasms, with survival durations ranging from a few months to more than 10 years. Although rare in Indonesia, the incidence of multiple myeloma is increasing annually (1). A notable rise in the global incidence of multiple myeloma (MM). It predicts a 1.7% annual increase in age-standardized incidence rates, projecting these rates to reach 0.045 cases per 100,000 individuals by 2030 (2). Multiple myeloma (MM) is a complex and heterogeneous hematologic malignancy characterized by the uncontrolled proliferation of plasma cells in the bone marrow, with recent advances in molecular genetics revealing various genetic and epigenetic alterations, including mutations in tumor suppressor genes like TP53, chromosomal translocations, and changes in the bone marrow microenvironment that contribute to its pathogenesis (3). Multiple myeloma is associated with high morbidity and mortality, leading to end-organ damage such as renal impairment, hypercalcemia, lytic bone lesions, and anemia (4,5). Myeloma arises from the asymptomatic proliferation of monoclonal plasma cells originating from post-germinal center B cells. Gradual genetic and microenvironmental changes transform these cells into a malignant neoplasm. This process typically begins with monoclonal gammopathy of undetermined clinical significance (MGUS), which can progress to smoldering myeloma and, eventually, symptomatic myeloma (6). Multiple

myeloma accounts for approximately 1% of all cancers and about 10% of all hematologic malignancies. It is slightly more common in men than women and is twice as prevalent among African Americans compared to Caucasians, with a median age of diagnosis around 65 years (7).

The revised diagnostic criteria by the International Myeloma Working Group (IMWG) require evidence of 10% or more clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma, along with one or more myeloma-defining events (MDE). MDE includes CRAB features (hypercalcemia, renal failure, anemia, or lytic bone lesions) and three specific biomarkers: ≥60% clonal plasma cells, a serum free light chain (FLC) ratio ≥100 (with involved FLC level ≥100 mg/L), and more than one focal lesion on MRI (7). Each biomarker has approximately an 80% risk of progression to symptomatic organ damage (7). This study aims to describe a case of multiple myeloma in an adult male with complete CRAB features.

Case Description

A 63-year-old man was admitted to Banten Regional General Hospital on September 16, 2024. The patient presented with complaints of pain in his left hand that began one week prior. Initially, he fell and hit a wall, resulting in persistent pain in his left hand. The pain had no aggravating or mitigating factors and caused difficulty in moving his left hand, prompting him to support it with a cloth. The patient also reported swelling and redness in the left arm and shoulder area, for which he applied warm compresses continuously. Before the fall, the patient had experienced generalized joint pain (elbow, knee, and thigh joints) accompanied by low-grade fever for approximately one month. The pain was persistent, causing him to become immobile and reliant on assistance for daily activities. Additional complaints included generalized weakness, decreased appetite, significant weight loss (approximately 15 kg), nausea, and vomiting after eating. The patient also experienced black-colored vomitus, bloody stools, oliguria (urinating twice daily with a small volume), painful urination with gritty particles, and swelling in both hands and feet. The patient had no prior similar symptoms and denied a history of diabetes, lung disease, or uncontrolled hypertension. There was no family history of similar conditions. However, the patient had been a heavy smoker (more than one pack per day since his teenage years), consumed coffee daily, and had a poor dietary and hydration history. He worked as a construction laborer, often working 8 hours per day.

On physical examination, the patient appeared moderately ill. Vital signs were as follows: blood pressure 137/59 mmHg, temperature 36.5°C, SpO_2 95% on room air, pulse 81 beats/min (regular), and respiratory rate 22 breaths/min. Conjunctival pallor was noted, indicating anemia. Examination of the extremities revealed hyperemia on the left shoulder, a visible bony lump, restricted range of motion in the left hand, warm acral regions, capillary refill time >2 seconds, and non-pitting edema in the left hand and both feet. Supporting Examination of the extremities revealed inations on September 16, 2024, revealed hypercalcemia, anemia, elevated urea and creatinine levels, and a decreased glomerular filtration rate (Table 1). X-ray results showed multiple lytic lesions in the bilateral clavicles, scapulae, ulna, distal radius, left humerus, calvaria, mandibles, maxilla, and a suspected fracture in the proximal one-third of the left ulna.

Discussion

The following is a table 1 of the laboratory examination results.

Table 1. Laboratory examination results

Inspection	Results	Reference Value	Unit
Hematology			
Routine Blood (Hb, L , T, Ht)			
Hemoglobin	5.4	13.2 - 17.3	g/dL
Hematocrit	17	40 - 52	%
Leukocytes	6.5	3.8 - 10.6	$10^3/\mu L$
Platelets	148	150 - 440	$10^3/\mu L$
Erythrocytes	1.9	4.4 - 5.9	$10^6/\mu L$
Blood Glucose			
Random Blood Glucose	111	Normal: <200 Diabetes Mellitus: ≥200	mg/dL
Blood Calcium			
Calcium (Blood)	12.5	8.1 - 10.4	mg/dL

Function Kidney			
Estimate Rate Glomerular Filtration	34.00	≥ 90	mL/min/1.73 m^2
Urea (Blood)	62	15 - 40	mg/dL
Creatinine	2.74	0.80 - 1.30	mg/dL

The following is the image of the radiology examination results.

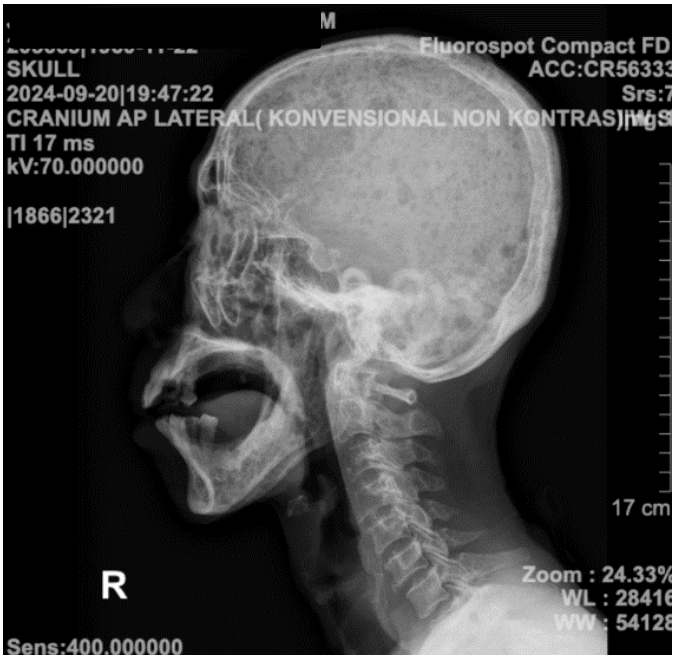

Figure 1. Cranium AP Lateral (Conventional non- contrast)

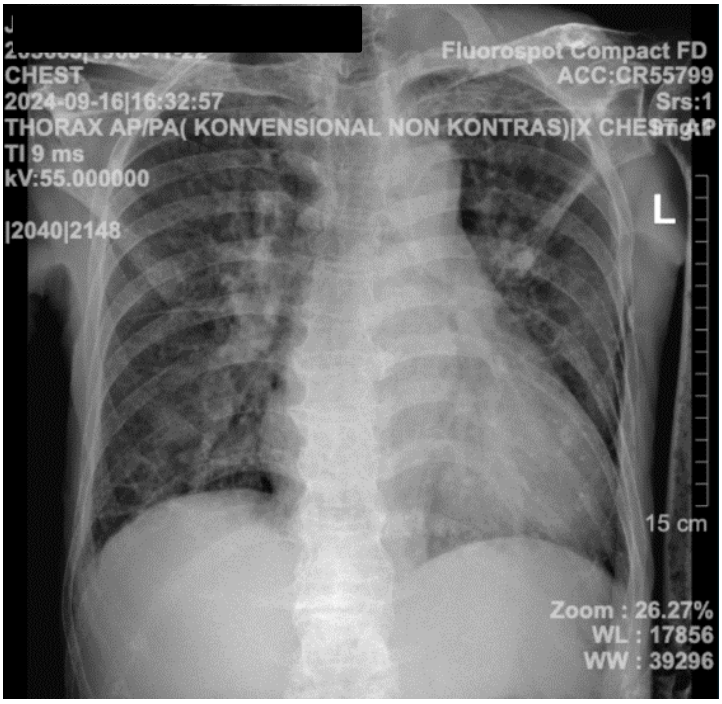

Figure 2. Thorax AP/PA (Conventional non -contrast)

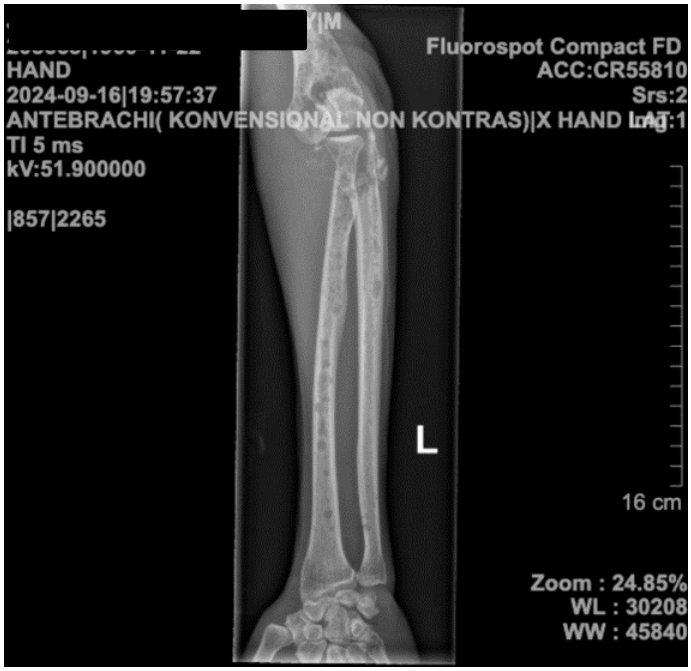

Figure 3. Antebrachium (Conventional non-contrast) and Humerus (Conventional non-contrast)

This case highlights a classic presentation of multiple myeloma (MM), a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells in the bone marrow. The patient's symptoms (progressive bone pain after a fall, generalized weakness, weight loss, and anemia) are consistent with the CRAB criteria for diagnosing MM, which include hypercalcemia, renal insufficiency, anemia, and bone lesions. His history revealed constitutional symptoms, including fever, weight loss, and fatigue, which are common in MM. Complaints of progressive bone pain, especially following minor trauma, suggest significant bone loss due to osteolytic activity (9).

Physical examination revealed anemia (pale conjunctiva), a pathological fracture (deformity and pain in the left arm), and extremity edema, which may be associated with hypoalbuminemia, hypocalcemia, or hyperviscosity syndrome. Laboratory findings showed normochromic, normocytic anemia (Hb 5.4 g/dL) and hypercalcemia (Ca 12.5 mg/dL), a hallmark of MM caused by excessive bone resorption. Renal insufficiency was evidenced by elevated creatinine (2.74 mg/dL) and a decreased glomerular filtration rate (34 mL/min/1.73 m^2). Radiological imaging identified multiple lytic lesions, a pathognomonic feature of MM (8,9).

The pathophysiology of MM involves the clonal expansion of neoplastic plasma cells in the bone marrow. These cells overproduce monoclonal immunoglobulins (paraproteins) or their fragments (light chains), which contributes to anemia, hypercalcemia, and renal dysfunction through mechanisms such as bone resorption and light chain deposition. Anemia in multiple myeloma (MM) results from bone marrow infiltration by malignant plasma cells, which suppress normal hematopoiesis and red blood cell production (4). Inflammatory cytokines like IL-6 further exacerbate this suppression, leading to normochromic, normocytic anemia, as seen in this patient with low hemoglobin (Hb 5.4 g/dL). Anemia contributes to the patient's weakness and fatigue, common symptoms of MM. Anemia arises from bone marrow infiltration by myeloma cells, which suppress erythropoiesis through inflammatory cytokines. Additionally, renal dysfunction contributes to a relative erythropoietin deficiency. Hypercalcemia occurs due to increased osteoclast activity driven by osteoclast-activating factors (RANKL, MIP-1α, IL-3, and IL-6) secreted by myeloma cells and bone marrow stromal cells (10).

Renal insufficiency in MM has multifactorial etiologies. As seen in this case, renal insufficiency is commonly caused by cast nephropathy, where light chains precipitate in the renal tubules, leading to obstruction and inflammation. Contributing factors include hypercalcemia, dehydration, hyperuricemia, and nephrotoxic drug use. The patient's elevated urea and creatinine levels, along with a decreased glomerular filtration rate (GFR of 34 mL/min/1.73 m^2), indicate significant renal involvement, which is a common and serious complication of MM. Early recognition and management of these complications are crucial, as they significantly impact the patient's prognosis and quality of life. Bone lesions in multiple myeloma (MM) occur due to increased osteoclast activity stimulated by myeloma cells, which release cytokines like RANKL and IL-6, the imbalance in osteoclast and osteoblast activity, with

increased bone resorption and inhibited new bone formation. These cytokines promote bone resorption, leading to lytic lesions, osteoporosis, and an increased risk of fractures. The patient's radiological findings of multiple lytic lesions across various bones, including the clavicles and humerus, are consistent with the bone damage typically seen in MM. This results in bone pain, particularly after minor trauma, as observed in this case (10,11). Comparing it with a case report by Annadatha et al. (2020) about a 57-year-old with multiple myeloma, both our patients presented with bone pain, anemia, and renal dysfunction, which are typical features of multiple myeloma (MM). Both had elevated serum calcium and renal failure, with the 57-year-old showing severe hypercalcemia (14 mg/dL) and the 63-year-old having slightly lower hypercalcemia (12.5 mg/dL). X-ray imaging in both cases revealed bone lesions, and both were treated with aggressive hydration, corticosteroids, and bisphosphonates. However, the 63-year-old patient had additional systemic symptoms, including nausea, vomiting, oliguria, and swelling, suggesting more widespread organ involvement compared to the 57-year-old, whose primary complications were hypercalcemia and renal failure (12).

The management of MM is multidisciplinary, aiming to control the disease, alleviate symptoms, and improve quality of life. Initial therapy typically involves a combination of immunomodulators (e.g., lenalidomide), proteasome inhibitors (e.g., bortezomib), and corticosteroids (e.g., dexamethasone), known as the RVd regimen. Eligible patients may undergo autologous stem cell transplantation. For patient's ineligible for transplantation due to age or comorbidities, as in this case, the DRd regimen (daratumumab-lenalidomide-dexamethasone) can be considered as a first-line therapy (13,14).

Management of MM complications includes the use of bisphosphonates (e.g., zoledronate) to treat hypercalcemia and prevent pathological fractures, as well as aggressive hydration and electrolyte correction for renal insufficiency. Severe renal impairment may necessitate hemodialysis. Thromboembolic prophylaxis with aspirin or low-dose anticoagulants is recommended due to the increased risk of thrombosis, particularly with immunomodulator use (13,14).

Monitoring the therapeutic response involves periodic evaluation of serum and urine M-protein levels, serum-free light chains, and bone marrow examinations. Assessment of minimal residual disease (MRD) through flow cytometry or next-generation sequencing is increasingly important for evaluating the depth of response and guiding therapeutic decisions (13).

Recent advances in MM therapy include immunotherapies such as monoclonal antibodies (e.g., daratumumab, isatuximab), bispecific antibodies (e.g., teclistamab), and CAR T-cell therapy. Other promising agents include nuclear export inhibitors (e.g., selinexor) and cereblon modulators (e.g., iberdomide). Genomic profiling is being developed to optimize treatment regimens based on individual patient mutations (14).

Conclusion

Based on the case description, the CRAB criteria approach in diagnosing multiple myeloma indicated that this patient meets the criteria for multiple myeloma. The CRAB criteria can be used as a guideline for diagnosing multiple myeloma, especially in areas with limited access to comprehensive laboratory testing. This approach enables a quick diagnosis, allowing prompt management of the condition.

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Conflicts of Interest: The authors declare no conflict of interest.

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