



CASE REPORT

Anaplastic Multiple Myeloma: A Rare Case Report in Surabaya, Indonesia

Fransiska Jaya Pranata¹, Paulus Budiono Notopuro^{2*}

¹Clinical Pathology Specialization Program, Department of Clinical Pathology, Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

²Department of Clinical Pathology, Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

ARTICLE INFO	ABSTRACT
Received: Sep 16, 2024	<p>Anaplastic multiple myeloma (AMM) is a relatively uncommon and severe type of multiple myeloma (MM), making up about 2.6% of cases. AMM progresses quickly, is resistant to standard treatments, and has a poor prognosis. Treatment typically involves aggressive chemotherapy and novel therapies, but managing AMM remains challenging. A 54-year-old man presented with significant weight loss (15-20 kg over four months), loss of appetite, and general weakness. Physical examination revealed hepatomegaly. The results of blood testing revealed a very low platelet count ($5 \times 10^3/\mu\text{L}$), a low white blood cell count ($1.22 \times 10^3/\mu\text{L}$), and a low haemoglobin level (8.9 g/dL). Bone marrow aspiration showed granulopoiesis and megakaryopoiesis hyperplasia, erythropoiesis hypoplasia, and 43% plasma cells, confirming an AMM diagnosis. Blood chemistry indicated low albumin (1.52 g/dL); elevated direct bilirubin (3.00 mg/dL), total bilirubin (3.50 mg/dL), creatinine (2.7 mg/dL), and urea (53.7 mg/dL); normal calcium (9.8 mg/dL), and prolonged coagulation times (PT: 22.1 s, APTT: 92.8 s). Protein electrophoresis showed increased gamma globulin, supporting multiple myeloma. Treatment included bortezomib, ceftriaxone, tranexamic acid, vitamin K, and platelet transfusions. However, after four days, the patient's health worsened, and he passed away. AMM's aggressive behavior and poor response to standard treatment pose unique challenges for diagnosis and management. Genetic mutations like TP53 and BRAF, along with chromosomal abnormalities (e.g., CKS1B amplification, t (4;14), 17p deletion), may play a role. The diagnosis follows International Myeloma Working Group criteria, often showing myeloma-defining events (MDE), including monoclonal protein in serum and CRAB features (anemia, high calcium levels, bone damage, and kidney failure). Recognizing AMM's morphological plasma cell variants is crucial for accurate diagnosis and prognosis. AMM is a challenging subtype of multiple myeloma due to its rapid progression and resistance to treatment. Improved early detection and therapeutic strategies are needed to enhance patient outcomes.</p>
Accepted: Nov 13, 2024	
Keywords	
Anaplastic	
Multiple Myeloma	
Variant	
Diagnosis	
*Corresponding Author:	
paulus-b-n@fk.unair.ac.id	

INTRODUCTION

Anaplastic multiple myeloma (AMM), known for its poor prognosis, is an uncommon and severe type of multiple myeloma (MM) (Alencar et al., 2023; Bahmanyar et al., 2013; Ichikawa et al., 2018). The term "anaplastic myeloma" describes a plasma cell cancer where immature, irregularly-shaped

plasma cells undergo severe transformation and spread beyond the bone marrow, with large, undifferentiated cells in the mix (Ammannagari et al., 2016; Bahmanyar et al., 2013).

In 1983, Foucar et al. first described anaplastic myeloma, detailing two cases involving extramedullary disease with substantial tumor masses in the retroperitoneal and intra-abdominal regions. At the start of the disease, AMM may appear by itself, or it can change over time from conventional plasma cell myeloma, with this shift typically occurring one to four years post-MM diagnosis (Wu et al., 2022). In some cases, AMM manifests as numerous tumors outside the bone marrow, and its pleomorphic, multinucleated cell pattern can confuse it with a multinucleated carcinoma (Huang et al., 2020; Ichikawa et al., 2018). Previous reports have mentioned a different form of multiple myeloma, where plasma cell nuclei appear multilobulated, convoluted, or cleaved (Fujimi et al., 2017). The prognosis for this variant is usually poor, and it is often resistant to chemotherapy; patients survive only 3 to 5 months after diagnosis (Alencar et al., 2023; Fujimi et al., 2017).

AMM is estimated to occur in approximately 2.6% of plasma cell myeloma cases (Huang et al., 2020; Wu et al., 2022). AMM affects all ethnic groups and both sexes. AMM is far more common in younger patients, with a median age of 57 years, than traditional multiple myeloma, with a median age of 69 years (Çiftçiler et al., 2023). The rarity of the disease means that AMM cases are few and far between, and there is no standard way to handle its management yet (Çiftçiler et al., 2023; Huang et al., 2020).

CASE

A 54-year-old male was admitted to the emergency department with the main complaints of general weakness, nausea (without vomiting), and a lack of appetite for eating and drinking over the past week. After one week of hospitalization, the patient complained of restlessness, shortness of breath, and intermittent gum bleeding. He had previously reported stomach pain for six months as part of his medical history but was only given stomach medication, which did not alleviate the symptoms. He eventually sought further treatment and was diagnosed with a blood condition. Gum bleeding complaints had been infrequent over the last three months, and he had experienced weight loss of around 15-20 kg in four months. His vital signs were all stable, his temperature was normal, and physical examination demonstrated hepatomegaly but no lymphadenopathy or splenomegaly. Laboratory data showed thrombocytopenia (platelet count $5 \times 10^3/\mu\text{L}$), leukopenia (white blood cell count $1.22 \times 10^3/\mu\text{L}$), hematocrit 26.4%, and anemia (hemoglobin 8.9 g/dL). Upon examining the peripheral smear, there was no rouleaux formation and the red blood cells appeared normal in both color and size. A subsequent bone marrow aspiration was performed, revealing hypercellularity with an increased myeloid-to-erythroid ratio (7:1) and decreased erythropoiesis activity. Myelopoiesis activity increased to 50%, and plasma cells were observed in a proportion of 43%, including immature, mature, myeloma cells, atypical plasma cells resembling high-grade lymphoma, abnormal megakaryoblasts, and immature plasma cells with Snapper-Schneid granules (Figure 1). Megakaryocytes were also easily observed. The bone marrow conclusion was anaplastic multiple myeloma.

Clinical chemistry results showed low albumin (1.52 g/dL); elevated direct bilirubin (3.00 mg/dL), total bilirubin (3.50 mg/dL), creatinine (2.7 mg/dL), and urea (53.7 mg/dL); and normal calcium (9.8 mg/dL), but no abnormalities in other electrolytes or serum transaminase levels. Coagulation tests revealed elevated PT (22.1 s) and APTT (92.8 s). Protein electrophoresis detected decreased albumin, alpha 1, alpha 2, and beta globulin fractions, while the gamma globulin fraction increased, indicating monoclonal gammopathy consistent with multiple myeloma (Figure 2).

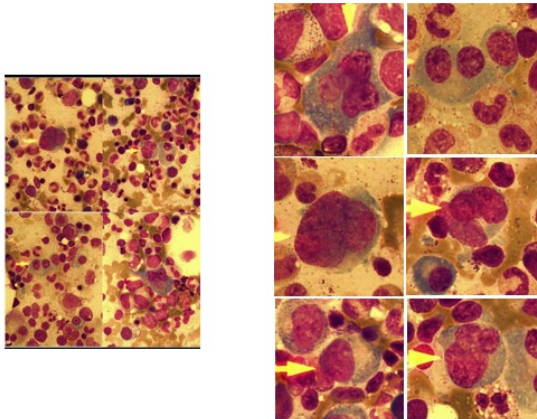


Figure 1. Bone Marrow Aspiration

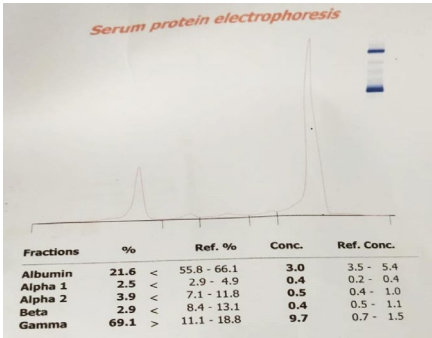


Figure 2. Protein Serum Electrophoresis

A thorax AP X-ray examination showed a reticular pattern in both lungs, which could indicate interstitial lung edema or interstitial pneumonia (Figure 3). Skull AP/Lateral X-ray examination was within normal limits (Figure 4). Electrocardiography showed ST elevation in V2-3. Echocardiology results suggested a VSD peri-membrane bidirectional shunt, normal LV EF of 81%, moderate aortic regurgitation (AR) with RCC & LCC noncoaptation, and visible vegetation attached to the aortic (AO) valve measuring 25 mm, covering the left ventricular outflow tract (LVOT) with moderate aortic stenosis (AS). Conclusion: Infective endocarditis was observed with vegetation attached to the aortic valve, causing LVOT obstruction, moderate AR, and a suspected subaortic VSD bidirectional shunt.

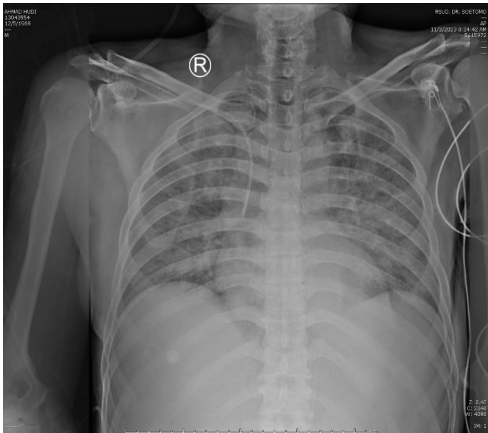


Figure 3. Thorax AP

The patient was administered Bortezomib (Fonkozumib) 3.5 mg as therapy for multiple myeloma, along with ceftriaxone injection (1x2 g), inpepsa (3x1), tranexamic acid (3x1), vitamin K (3x1), and thrombocyte concentrate transfusion. Four days after the bone marrow aspiration, the patient's condition deteriorated, with fever and blood pressure dropping to 98/70. The patient was given dopamine at 5 mcg/kg/min and vascon at 75 ng/kg/min; however, the patient subsequently passed away.



Figure 4. Skull AP/Lateral

DISCUSSION

Anaplastic multiple myeloma is a relatively uncommon and severe type of multiple myeloma that presents unique challenges in diagnosis, treatment, and prognosis (Lückerath et al., 2013). It is characterized by a high level of proliferation, the occurrence of anaplastic plasma cells that have unusual morphology, and a higher risk of organ involvement and progression compared to other types of multiple myeloma (Raman Ramalingam et al., 2022). To date, there is limited research specifically focused on anaplastic multiple myeloma due to its rarity, making it difficult to establish standardized treatment guidelines and recommendations (Tang et al., 2021; Sulasa et al., 2024). The pathogenesis of anaplastic multiple myeloma is not well understood. However, it is believed that environmental changes and genetic mutations in the bone marrow are seen as important factors in its development. Genetic mutations in certain genes, such as TP53 and BRAF, have been identified in several AMM cases (Ammannagari et al., 2016). Other studies suggest AMM is often seen with a higher frequency of CKS1B amplification, t (4;14), and 17p (p53) deletion, with one study demonstrating that compared to regular MM, AMM had a much higher rate of CKS1B amplification (91% vs. 34%), which could lead to genetic instability and a worse prognosis, making the disease more aggressive (Shaughnessy, 2005; Zhan et al., 2007; Jam et al., 2011).

The updated diagnostic criteria from the International Myeloma Working Group say that, in order to diagnose MM, there needs to be at least one MDE present and either a plasmacytoma from a biopsy or 10% monoclonal plasma cells from a bone marrow aspiration. MDE is defined as the presence of CRAB features (which include bone lytic lesions, anemia, kidney failure, and/or hypercalcemia) along with three key biological markers: at least one lesion visible on MRI, a serum-free light chain (FLC) ratio greater than 100 (and FLC levels above 100 mg/L), and more than 60% clonal plasma cells in the bone marrow. All of these biological markers have been linked to an 80% likelihood of developing symptomatic target organ damage (Gunawan & Notopuro, 2019; Morrison et al., 2019; Rajkumar, 2020).

Patients suspected of having MM must be tested for M proteins using different techniques, including serum FLC analysis, serum immunofixation (IFS), and serum protein electrophoresis (EFPS). When making the first diagnosis, FISH should be part of the bone marrow aspiration to check for del(17p), trisomies, t(14;20), t(6;14), t(14;16), t(4;14), and t(11;14). While traditional karyotyping is effective

for identifying hypoploidy and deletions on chromosome 13, FISH has limited utility for risk classification (Gunawan & Notopuro, 2019; Morrison et al., 2019).

Immunophenotyping is used to evaluate bone marrow subjectively and quantitatively. In a 2023 case report, Çiftçiler found that AMM patients had a CD45-negative bone marrow population that expressed CD38, CD117, and lambda but not CD138 or CD56 (Figure 2). These plasma cells did not exhibit CD19, CD20, CD22, or CD23 on their surfaces, although intracytoplasmic CD79a was present (Çiftçiler et al., 2023; Walker et al., 2018).

Bone marrow aspiration revealed Snapper-Schneid granules-5, which is an immature plasma cell of medium size featuring a large, round nucleus with chromatin clumped around the edges. Inside the cytoplasm, which is violaceous and abundant, there are several distinct azurophilic granules, which are known as Snapper-Schneid granules and correspond to enlarged lysosomes without peroxidase, as well as a big Golgi zone resembling sarcoplasm (d'Onofrio & Zini, 2014; Gupta et al., 2018; Wajs & Sawicki, 2013).

Recent studies have shown that anaplastic multiple myeloma shares similarities with other myeloid tumors, suggesting that myeloid-directed therapies may hold promise in improving outcomes for patients with anaplastic multiple myeloma. Additionally, whole genome sequencing has been utilized to gain insights into the genetic basis of anaplastic multiple myeloma, which may offer valuable insights into the disease and lead to the development of more targeted therapies.

Cytopathologists and clinicians need to be able to spot the morphological variants of neoplastic plasma cells to avoid diagnostic errors, as these forms of myeloma are associated with poor prognosis and are known to be aggressive (Beljan Perak et al., 2016).

CONCLUSION

Diagnosing MM can be tough due to its anaplastic morphology. The need for a multidisciplinary approach to detect hematological neoplasms is highlighted, and for AMM cases, prompt radiography, flow cytometry, and histological examination may assist in diagnosis.

CONFLICT OF INTEREST

The authors stated that there is no conflict of interest.

ACKNOWLEDGEMENT

We would like to thank the Dean of the Faculty of Medicine, Airlangga University, and the Director of Dr. Soetomo General Academic Hospital.

REFERENCES

- Alencar RN, GA Martinez, MG Cordeiro and E Velloso, 2023. Anaplastic multiple myeloma with amplification of the IGH-CCND1 gene fusion. *Hematol Transfus Cell Ther*, 45: 495-498.
- Ammannagari N, K Celotto, V Neppalli, K Lee and SA Holstein, 2016. Anaplastic Multiple Myeloma: An Aggressive Variant With a Poor Response to Novel Therapies. *Clinical Lymphoma, Myeloma & Leukemia*, 16: e129-e131.
- Bahmanyar M, X Qi and H Chang, 2013. Genomic aberrations in anaplastic multiple myeloma: high frequency of 1q21(CKS1B) amplifications. *Leukemia Research*, 37: 1726-1728.
- Beljan Perak R, I Karaman, D Sundov, J Jakelic Pitesa, A Novak and A Pavlovic, 2016. Anaplastic variant of plasma cell myeloma: a pitfall of morphological identification. *Acta Cytologica*, 60: 275-276.
- Çiftçiler R, M Erol, ŞN Güner and İ Reisli, 2023. Anaplastic Multiple Myeloma: A Report of a Rare Case with CD38 and CD117 Positivity. *Acta Oncol Tur.*, 56: 272-276.
- d'Onofrio G and G Zini. (2014). Plasma Cell Proliferative Disorders. In *Plasma Cell Proliferative Disorders* (pp. 681–726). <https://doi.org/10.1002/9781118442562.ch10>
- Fujimi A, Y Nagamachi, N Yamauchi and Y Kanisawa, 2017. Morphological Transformation of Myeloma Cells into Multilobated Plasma Cell Nuclei within 7 Days in a Case of Secondary Plasma Cell

- Leukemia That Finally Transformed as Anaplastic Myeloma. *Case Rep Hematol*, 2017: 5758368.
- Gunawan H and PB Notopuro, 2019. Rapid progression of clavicular solitary plasmacytoma to multiple myeloma. *INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY*, 25: 246-249.
- Gupta A, P Tripathi and S Tyagi, 2018. Cytoplasmic azurophilic inclusion bodies in reactive plasmacytosis. *Blood Res*, 53: 265.
- Huang JX, FJ Meng, XQ Feng, X Lyu and X Wang, 2020. Clinical and histopathological analyses of anaplastic myeloma. *Chinese Medical Journal (Engl.)*, 133: 1614-1616.
- Ichikawa S, N Fukuhara, S Hatta, M Himuro, K Nasu, K Ono, Y Okitsu, M Kobayashi, Y Onishi, M Ri, R Ichinohasama and H Harigae, 2018. Anaplastic multiple myeloma: possible limitations of conventional chemotherapy for long-term remission. *Journal of Clinical and Experimental Hematopathology*, 58: 39-42.
- Lückerath K, C Lapa, A Spahmann, G Jörg, S Samnick, A Rosenwald, H Einsele, S Knop and AK Buck, 2013. Targeting paraprotein biosynthesis for non-invasive characterization of myeloma biology. *PloS One*, 8: e84840.
- Morrison T, RA Booth, K Hauff, P Berardi and A Visram, 2019. Laboratory assessment of multiple myeloma. *Advances in Clinical Chemistry*, 89: 1-58.
- Rajkumar SV, 2020. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *American Journal of Hematology*, 95: 548-567.
- Raman Ramalingam T, L Vaidhyanathan and P Pandurangan, 2022. Anaplastic plasma cell myeloma - A morphological dilemma. *Hematol Transfus Cell Ther*, 44: 132-133.
- Shaughnessy J, 2005. Amplification and overexpression of CKS1B at chromosome band 1q21 is associated with reduced levels of p27 Kip1 and an aggressive clinical course in multiple myeloma. *Hematology (Amsterdam, Netherlands)*, 10: 117-126.
- Tang W, Y Xu and B Xiang, 2021. Successful outcome of anaplastic multiple myeloma with lenalidomide, cyclophosphamide, and dexamethasone therapy. *Annals of Hematology*, 100: 3039-3040.
- Wajs J and W Sawicki, 2013. The morphology of myeloma cells changes with progression of the disease. *Contemp Oncol (Pozn)*, 17: 272-275.
- Walker BA, K Mavrommatis, CP Wardell, TC Ashby, M Bauer, FE Davies, A Rosenthal, H Wang, P Qu, A Hoering, M Samur, F Towfic, M Ortiz, E Flynt, Z Yu, Z Yang, D Rozelle, J Obenauer, M Trotter, D Auclair, J Keats, N Bolli, M Fulciniti, R Szalat, P Moreau, B Durie, AK Stewart, H Goldschmidt, MS Raab, H Einsele, P Sonneveld, J San Miguel, S Lonial, GH Jackson, KC Anderson, H Avet-Loiseau, N Munshi, A Thakurta and GJ Morgan, 2018. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood*, 132: 587-597.
- Wu J, E Chu, CC Chase, T Choi, C Gasparetto, K Young and Y Kang, 2022. Anaplastic Multiple Myeloma: Case Series and Literature Review. *Asploro J Biomed Clin Case Rep*, 5: 1-11.
- Zhan F, S Colla, X Wu, B Chen, JP Stewart, WM Kuehl, B Barlogie and JD Shaughnessy Jr, 2007. CKS1B, overexpressed in aggressive disease, regulates multiple myeloma growth and survival through SKP2-and p27Kip1-dependent and-independent mechanisms. *Blood, The Journal of the American Society of Hematology*, 109: 4995-5001.
- Jam, F. A., Sheikh, R. A., Iqbal, H., Zaidi, B. H., Anis, Y., & Muzaffar, M. (2011). Combined effects of perception of politics and political skill on employee job outcomes. *African Journal of Business Management*, 5(23), 9896-9904.
- Sulasa, T. J., & Kumar, R. (2024). Role of Modern Technology for Rehabilitation in Mitigation of Juvenile Recidivism: A Critical Appraisal. *Pakistan Journal of Life and Social Sciences*, 22(2), 101012-101018.