CASE REPORT

Atypical Presentation of Multiple Myeloma: from Heart Failure to Multiple Myeloma

Ainur Elliana Sohaimi[1], Nur Syazwani Jamhuri[1], Ismail Ibrahim[1], Hotimah Masdan Salim[2]

[1]Department of Internal Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Malaysia.

[2]Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Nahdlatul Ulama Surabaya, Indonesia

ARTICLE INFO

Article history:
Received : June 19, 2024
Received in revised form:
September 29, 2024
Accepted:
October 20, 2024

Keywords:
Multiple myeloma, cardiac amyloidosis, systemic amyloidosis, heart failure, AL amyloidosis

*Correspondent Author:
diahayuaguspadita@unib.ac.id

ABSTRACT

Multiple myeloma (MM) is a hematological malignancy commonly associated with bone pain, hypercalcemia, and renal failure. However, its presentation can occasionally mimic other medical conditions, which may delay diagnosis. This case report describes a patient who was initially diagnosed and treated for heart failure but was later found to have MM, highlighting the importance of considering MM in the differential diagnosis of heart failure.

A 56-year-old lady presented with recurrent episodes of shortness of breath, orthopnea, paroxysmal nocturnal dypsnea and bilateral lower limb swelling which she had been treated for decompensated heart failure with optimal therapy. She denied any family history of cardiovascular disease personal history of underlying medical condition and was a non-smoker. This patient was diagnosed with multiple myeloma and probability of concomitant cardiac amyloidosis and commenced on bortezomib, thalidomide and dexamethasone (VTD) regime and standard optimal therapy of heart failure but her condition deteriorated. After a few days of starting chemotherapy, patient demised despite all the resuscitative effort. Multiple myeloma is common hematological malignancy with its distinct clinical features of "CRAB", however, more attention and alertness should also be exercised by clinicians as to be able to diagnose it early.

Medical and Health Science Journal

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy (after Non Hodgkin Lymphoma), accounts for incidence of 10%.[1] Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the proliferation of malignant plasma cells within the bone marrow and the presence of a monoclonal protein in the blood or urine. Commonly presenting symptoms of MM include bone pain, renal impairment, hypercalcemia, and anemia, which form part of the CRAB criteria used to diagnose the disease.[2] However, MM can occasionally present in less typical ways, complicating its diagnosis and management. MM is an immunoglobulin-producing tumour of plasma cells. It is uncommon for MM to present initially as progressive heart failure, with common presentations include anaemia, recurrent infections, bone lesions, and renal failure. On the other hand, amyloidosis is a

systemic infiltrative disease characterized by the extracellular deposition of amyloid proteins at various organs; cardiac, renal, and skin among others. AL amyloidosis (ALA) is a sub-type that is commonly related to monoclonal gammopathy of unknown significant (MGUS), multiple myeloma and Waldenström macroglobulinemia. The development of ALA estimated to be 10-15% in MM patients.[3,4] The abnormal plasma cells from the above plasma cell disorders secret large number of light chains, which then gets deposited to organs, forming amyloid proteins.

Heart failure is a rare presentation of MM and is not typically associated with the initial diagnosis of this plasma cell dyscrasia. Cardiac involvement in MM usually occurs due to secondary amyloidosis (AL amyloidosis) where amyloid fibrils deposit in the cardiac tissue, leading to restrictive cardiomyopathy and heart failure.[5] Recognizing this link is crucial as it significantly influences both prognosis and treatment choices.

Whilst cardiac amyloidosis is the commonest cause of restrictive cardiomyopathy; delay in diagnosis is common with delay in treatment initiation. This can be overcome with a high degree of suspicion based on the clinical history and laboratory investigations. Management of cardiac amyloidosis with multiple myeloma requires a multidisciplinary team. Once heart failure occurs, the median survival is less than six months in untreated patients and is the most common cause of death. This case report details the diagnostic challenge of a patient who initially presented with signs and symptoms suggestive of heart failure, which on thorough investigation, was attributed to undiagnosed multiple myeloma complicated by cardiac amyloidosis. The atypical presentation emphasizes the need for a high index of suspicion and comprehensive diagnostic approach in patients with unexplained heart failure, particularly in the absence of common cardiac pathology risk factors.

Case Report

A 56-year-old lady presented with recurrent episodes of shortness of breath, orthopnea, paroxysmal nocturnal dypsnea and bilateral lower limb swelling which she had been treated for decompensated heart failure with optimal therapy. She denied any family history of cardiovascular disease personal history of underlying medical condition and was a non-smoker.

Laboratory tests showed anemia with hemoglobin (Hb) of 7.5 g/dl, elevated total protein of 96 g/L, renal impairment (creatinine clearance to 31 ml /min/1.73m2) and normocalcemia of 2.45mmol/L. Cardiac parameters revealed elevated troponin I of 67.9 and pro brain natriuretic peptide (pro BNP) of 4505 . Electrocardiogram (ECG) recorded sinus rhythm, with absence of low voltage QRS complex, and echocardiography showed evidenced of heart failure preserved ejection fraction (Left ventricular ejection fraction 50-60% with grade 3 diastolic dysfunction) with an additional finding of ‘granular sparkling’ appearance on myocardium. There was presence of moderate rouleux formation peripheral blood film. Bone marrow aspiration and trephine biopsy analysis showed 44% mature plasma cell infiltration, CD 138+, CD38+, with aberrant expression of CD56.

This patient was diagnosed with multiple myeloma and probability of concomitant cardiac amyloidosis and commenced on bortezomib, thalidomide and dexamethasone (VTD) regime and standard optimal therapy of heart failure but her

condition deteriorated. After a few days of starting chemotherapy, patient demised despite all the resuscitative effort.

Transthoracic Echo

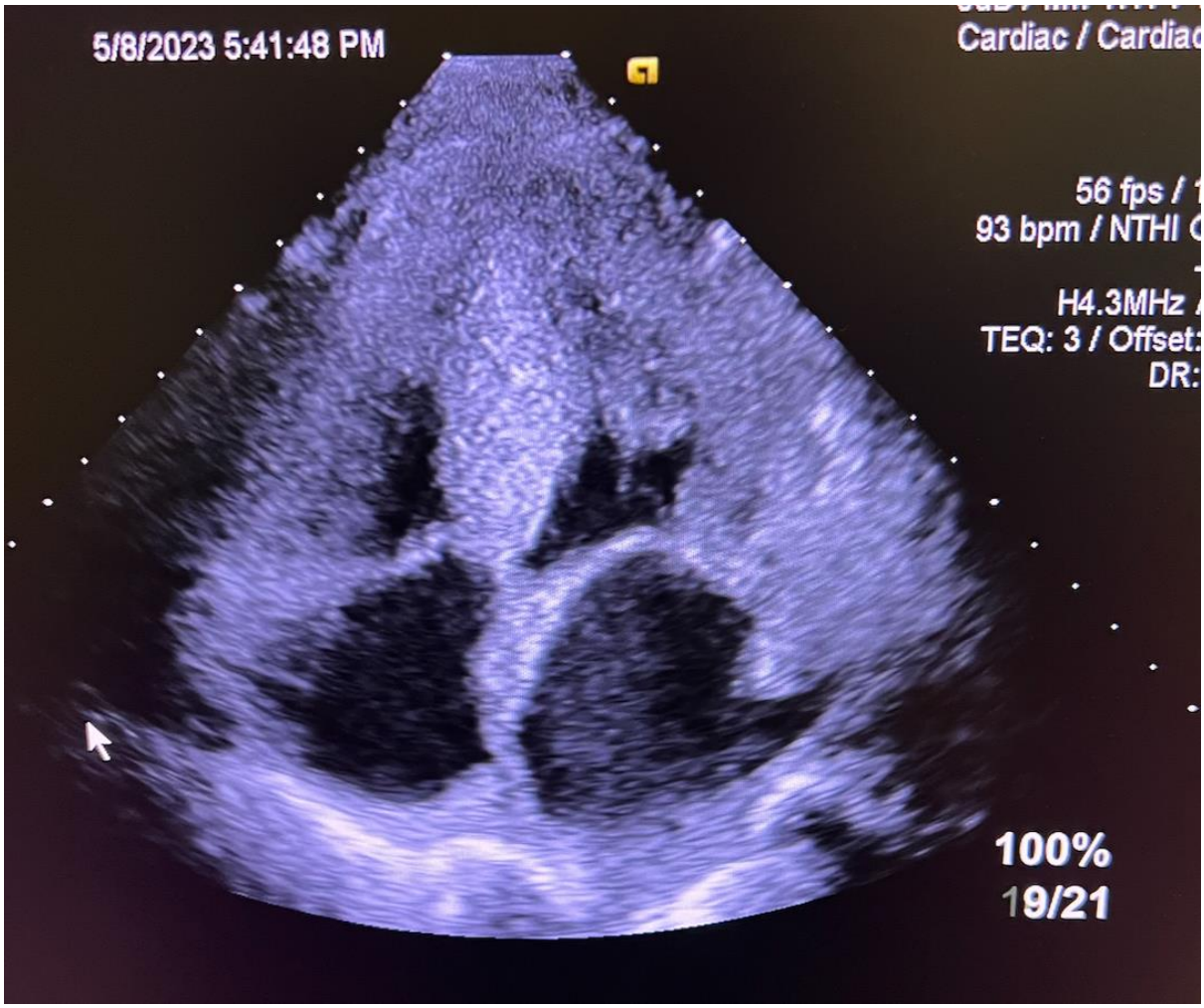

Figure 1 Patient transthoracic echo showing evidence starry sky appearance which suggestive of cardiac amyloidosis.

Bone Marrow Biopsy

HPE - Biopsy				
HPE				
Specimen # HPE				P230001280
Request details				HPE - Diagnostic Biopsy
Topography				
Request status				Request validated & printed
Summary report				Trephine biopsy: Consistent with Plasma cell Myeloma.

Figure 2 Result of patient bone marrow biopsy consistent with plasma cell myeloma

Discussion

This case illustrated an active multiple myeloma in a patient presenting with recurrence episode of decompensated heart failure. MM is part of plasma cell neoplasm with presence of monoclonal gammopathy. On the other hand, amyloidosis is a rare disorder characterized by extracellular deposition of light chain protein, called amyloids. ALA is the most common type of systemic amyloidosis. Approximately 10-15% of MM patients will develop ALA due to abnormal plasma cells produce light chain proteins which then deposited to become amyloid.[3,4] MM diagnosis can be made with either presence of clonal plasma cell proliferation in bone marrow >10%, or evidence of bony or extramedullary plasmacytoma, and any of the following myeloma-defining events (serum involve: uninvolved free light chain > 100, ≥ 1 focal bony lesions on imaging with size ≥ 5mm) or "CRAB" features (hypercalcemia, renal impairment, anemia and osteolytic bone lesions).[6] These classic symptoms are often clear indicators that prompt further diagnostic investigation into possible MM. However, when MM presents atypically, as in the case of heart failure without these traditional signs, the diagnosis can be markedly delayed, complicating and potentially worsening patient outcomes (Rajkumar et al., 2016).[2] In this case, due to the rarity of its presentation with further supported by investigation findings, the likelihood of cardiac amyloidosis as co-existing condition is entertained. Cardiac involvement in MM is primarily due to amyloid deposition, which results in restrictive cardiomyopathy—a condition often misdiagnosed due to its non-specific clinical presentation.[2,8]

Cardiac amyloidosis may manifest with progressive heart failure, with presence of "red flag" signs and symptoms (skin bruises, macroglossia, carpal tunnel syndrome, heart failure) are essential to raise suspicion of concomitant presence of MM.[5,8,9] In cardiac amyloidosis, disproportionately high N-terminal pro-B-type natriuretic peptide (NT-pro BNP), persistently raise troponin, low QRS complex on ECG, in addition to certain objective criteria on cardiac imaging helps to evoke cardiac amyloidosis. Diagnosis can be made either with the need for invasive (tissue biopsy for histopathological examination) or non-invasive (echocardiogram, cardiac magnetic resonance imaging, serum and urine electrophoresis, serum free light chain).[10] This depends on types of amyloid deposition though no impact on overall treatment management. More than 98% of cardiac amyloidosis consists of either light chain deposition, AL or transthyretin (ATTR). Biopsy proven AL deposition for AL cardiac amyloidosis is mandatory where else, non-invasive investigations are adequate for diagnosis in relation to ATTR.[11] Early diagnosis of MM, particularly in cases with atypical presentations such as unexplained heart failure, requires a high index of suspicion and may necessitate an integrated approach involving hematological, biochemical, and imaging studies. In cases like this, serum and urine electrophoresis, coupled with bone marrow biopsy, can be pivotal in uncovering the underlying MM.[12]

Illustrated by this case, given the atypical presentation with progressive heart failure without clinical improvement despite adequate optimal therapy, a second look of other probable diagnosis need to be considered. Diagnosis of MM is made by the evidence seen from initial investigations;

rouleaux formation on peripheral blood film, raised total protein, anemia and renal impairment. This is further supported by presence of 44% mature plasma cell infiltration in bone marrow.

A high index of clinical suspicion is required to diagnose cardiac amyloidosis. In addition to MM, the progressive heart failure with elevated pro BNP and troponin levels, presence of grade 3 diastolic dysfunction and 'granular sparkling' appearance on myocardium from echocardiogram makes the constellation of signs and symptoms highly suggestive of cardiac amyloidosis. Further confirmation with myocardial biopsy or cardiac magnetic resonance imaging (MRI) are not feasible in the context of this case, due to the hemodynamic instability of involved patient.[13]

Prognosis for MM associated with amyloidosis is grim in comparison to MM or amyloidosis alone. Furthermore, the extend of cardiac involvement in amyloidosis alone impacts negatively on disease survival. The parameters include granular sparkling appearance, diastolic relaxation abnormalities on echocardiogram, elevated troponin and pro BNP level (≥8500pg/mL) among others. Besides these, bone marrow plasma clonal size and level of free light chain (FLC) at the time of diagnosis also carries weight on poorer prognosis.[5,14,15] A retrospective study looking at effects of ALA with MM on prognosis shows that, the presence cardiac amyloidosis related to shorter overall survival, and pro BNP level ≥ 700pg/mL is an individual poor prognostic factor. This study also noted higher pro BNP level among ALA with MM, then in ALA alone.[3,16,17] These findings are supported by another study which shows in ALA with MM population, besides having higher pro BNP level, it was also reported to have higher FLC and larger bone marrow plasma clonal size. Poorer survival noted in ALA with MM and pro BNP appears to be a significant independent factor that negatively impact overall survival (≥8500pg/mL).[9,18,19] In this case, once MM was diagnosed, targeted therapy for MM, along with supportive measures for heart failure, was initiated, which is crucial for improving quality of life and extending survival.[20]

In this case, though the diagnosis of co-existing cardiac amyloidosis with MM was likely but not certain, there were poor prognosis factors present that negatively impact the overall survival; granular sparkling appearance, diastolic relaxation abnormalities on echocardiogram, high pro BNP (4505 pg/mL) and troponin levels. Despite initiation of MM-related therapy and optimization of heart failure therapy, patient still succumbed to her illness.

Conclusion

Multiple myeloma is common hematological malignancy with its distinct clinical features of "CRAB", however, more attention and alertness should also be exercised by clinicians as to be able to diagnose it early. As MM and systemic AL amyloidosis tends to co-exist, high index of suspicion is necessary, especially when cardiac involvement is seen in myeloma patients at any point throughout the course of illness. Due to its poorer prognosis, delay in diagnosis will delay in delivering focus directed therapy which subsequently affects the survival.

Conflicts of Interest

The author started there is no conflict of interest

References

1. Castaneda O, Baz R. Multiple Myeloma Genomics - A Concise Review. *Acta Med Acad*. 2019;48(1):57-67. doi:10.5644/ama2006-124.242
2. Rajkumar, S. V., Dimopoulos, M. A., Palumbo, A., Blade, J., Merlini, G., Mateos, M. V., Kumar, S., Hillengass, J., Kastritis, E., Richardson, P., Landgren, O., & Paiva, B. (2016). International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology*, 17(12), e538-e548.
3. 3Xu J, Wang M, Shen Y, et al. Effects of amyloid light-chain amyloidosis on clinical characteristics and prognosis in multiple myeloma: A single-center retrospective study. *Cancer Manag Res*. 2021;13:1343-1356. doi:10.2147/CMAR.S287922
4. 4Kirichenko YY, Ilgisonis IS, Nakhodnova ES, et al. Case Report: AL Amyloidosis Severe Restrictive Cardiomyopathy Associated With Multiple Myeloma—Diagnostic Difficulties. *Front Cardiovasc Med*. 2022;9(June):1-7. doi:10.3389/fcvm.2022.862409
5. Gertz, M. A. (2018). Amyloidosis and its renal manifestations. *Reviews in Clinical Gerontology*, 28(2), 100-112.
6. Gertz MA. Immunoglobulin light chain amyloidosis: 2020 update on diagnosis, prognosis, and treatment. *Am J Hematol*. 2020;95(7):848-860. doi:10.1002/ajh.25819
7. Kyle, R. A., & Rajkumar, S. V. (2009). Epidemiology of the plasma-cell disorders. *Best Practice & Research Clinical Haematology*, 22(6), 637-664
8. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: A position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072
9. 9Ríos-Tamayo R, Krsnik I, Gómez-Bueno M, et al. AL Amyloidosis and Multiple Myeloma: A Complex Scenario in Which Cardiac Involvement Remains the Key Prognostic Factor. *Life*. 2023;13(7):1-11. doi:10.3390/life13071518
10. Vergaro G, Castiglione V, Aimo A, et al. N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T hold diagnostic value in cardiac amyloidosis. *Eur J Heart Fail*. 2023;25(3):335-346. doi:10.1002/ejhf.2769
11. Shams P, Ahmed I. Cardiac Amyloidosis. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580521/
12. Dispenzieri, A., Gertz, M. A., Kyle, R. A., & Lacy, M. Q. (2012). Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *Journal of Clinical Oncology*, 22(18), 3751-3757.
13. Yilmaz, A., Bauersachs, J., Bengel, F., Büchel, R., Kindermann, I., Klingel, K., Knebel, F., Meder, B., Morbach, C., Nagel, E., Schulze-Bahr, E., Aus dem Siepen, F., & Frey, N. (2021). Diagnosis and treatment

of cardiac amyloidosis: position statement of the German Cardiac Society (DGK). *Clinical research in cardiology : official journal of the German Cardiac Society*, *110*(4), 479–506. https://doi.org/10.1007/s00392-020-01799-3

14. Wang, J., Yang, S., Liao, P., Zeng, L., Ling, W., Wan, L., Weng, J., & Zhong, L. (2022). Incidence and effect of secondary cardiac amyloidosis on outcomes of patients with t(11;14) multiple myeloma. *Frontiers in cardiovascular medicine*, *9*, 994384. https://doi.org/10.3389/fcvm.2022.994384
15. Lei, C., Zhu, X., Hsi, D.H. *et al.* Predictors of cardiac involvement and survival in patients with primary systemic light-chain amyloidosis: roles of the clinical, chemical, and 3-D speckle tracking echocardiography parameters. *BMC Cardiovasc Disord* **21**, 43 (2021). https://doi.org/10.1186/s12872-021-01856-3
16. Xu, J., Qiu, Z., Yan, M., Wang, B., Song, Z., Liu, H., Wang, M., & Cen, X. (2022). Prognostic Factors of AL-PCMM and AL-MM: A Single-Center Retrospective Study. *International journal of medical sciences*, *19*(3), 588–595. https://doi.org/10.7150/ijms.61712
17. Gustine, J. N., Staron, A., Mendelson, L., Joshi, T., Gopal, D. M., Siddiqi, O. K., Ruberg, F. L., & Sanchorawala, V. (2023). Predictors of treatment response and survival outcomes in patients with advanced cardiac AL amyloidosis. *Blood advances*, *7*(20), 6080–6091. https://doi.org/10.1182/bloodadvances.2023010324
18. Vaxman, I., Kumar, S. K., Buadi, F., Lacy, M. Q., Dingli, D., Hwa, Y., Fonder, A., Hobbs, M., Hayman, S., Kourelis, T., Warsame, R., Muchtar, E., Leung, N., Kapoor, P., Grogan, M., Go, R., Lin, Y., Gonsalves, W., Siddiqui, M., Kyle, R. A., … Dispenzieri, A. (2021). Outcomes among newly diagnosed AL amyloidosis patients with a very high NT-proBNP: implications for trial design. *Leukemia*, *35*(12), 3604–3607. https://doi.org/10.1038/s41375-021-01297-z
19. Yao, Y., Feng, L., Sun, Y. *et al.* Myocardial fibrosis combined with NT-proBNP improves the accuracy of survival prediction in ADHF patients. *BMC Cardiovasc Disord* **21**, 264 (2021). https://doi.org/10.1186/s12872-021-02083-6
20. Moreau, P., Attal, M., & Facon, T. (2017). Frontline therapy of multiple myeloma. *Blood*, 129(25), 3076-3084.