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CASE REPORT

A Case of Paraproteinaemia with Systemic Amyloidosis: A Progression or Merely a Coincidence?

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ABSTRACT

Paraprotein is commonly associated with plasma cell myeloma. However, certain diseases may also be associated with paraprotein. We present an unusual case of a 55-year-old woman with systemic amyloidosis and concomitant monoclonal gammopathy of undetermined significance (MGUS). The patient presented with symptoms of acute onset of cardiac failure with discordant findings between echocardiogram and magnetic resonance imaging of the heart, suggesting infiltrative cardiomyopathy and hypertrophic cardiomyopathy. She was otherwise free of any myeloma-defining events. Radio-imaging showed a constellation of findings suggestive of systemic amyloidosis. The presence of paraprotein was not pathognomonic of plasma cell myeloma. A low concentration of paraprotein may be associated with systemic amyloidosis.

KEYWORDS: Paraprotein, amyloidosis, MGUS, cardiomyopathy

INTRODUCTION

A paraprotein is a monoclonal immunoglobulin arising from the clonal proliferation of mature B cells. There are various causes of paraproteinaemia, with MGUS being the most prevalent cause. MGUS is a premalignant condition that may progress into plasma cell myeloma, lymphoproliferative disease (LPD) or even amyloidosis [1]. Diagnosing MGUS is difficult because of the absence of symptoms. It is most often diagnosed incidentally during investigations for some other pathologies [2]. The risk of progression towards more incurable diseases like plasma cell myeloma, LPD and amyloidosis also depends on the type of MGUS, either IgM or non-IgM MGUS [3]. The value of screening for MGUS, however, remains questionable [4].

To our knowledge, this is the first case of MGUS with systemic amyloidosis reported in Malaysia. Here, we present a case of a 55-year-old woman with acute onset heart failure secondary to infiltrative cardiomyopathy with paraproteinaemia, who was finally diagnosed as MGUS with systemic amyloidosis.

CASE PRESENTATION

A 55-year-old woman with a history of childhood polio and dyslipidaemia had presented to a private healthcare centre after having symptoms of heart failure for three months. She underwent an echocardiogram and magnetic resonance imaging of the heart and the findings suggested of infiltrative cardiomyopathy and hypertrophic cardiomyopathy, respectively. The treating physician suspected cardiac amyloidosis as the cause for the symptoms of cardiac failure and ordered for rectal and abdominal fat biopsy and serum protein

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electrophoresis (SPE). Surprisingly, the rectal biopsy was positive for amyloidosis. The discordant cardiac imaging reports, presence of amyloidosis on rectal submucosal polyp biopsy, and the paraprotein in the SPE caused a referral of this patient to our centre for confirmation of the diagnosis of either multiple myeloma or systemic amyloidosis or both. On examination, she was cachectic, with signs of heart failure.

Blood investigations revealed normal haemoglobin concentration with normochromic normocytic red cell morphology, normal renal profile, and normocalcaemia. Positron Emission Tomography - Computed Tomography (PET-CT) reported a constellation of findings suggestive of systemic amyloidosis without any lytic bony lesion. Bone marrow aspiration (BMA) and trephine biopsy were done. BMA showed the presence of four percent of plasma cells. Trephine biopsy revealed proliferation of plasma cells with lambda light chain (LC) restriction indicative of plasma cell neoplasm and positive for Congo red stain suggestive of amyloidosis (Figure 1). Serum and urine protein electrophoresis (SPE) and immunofixation electrophoresis (IFE) revealed the presence of a low concentration of IgG Lambda paraprotein quantitated at 2.2 g/L with a background of immunoparesis and lambda LC paraprotein in the urine quantitated at 116 mg/L (Figure 2). The serum-free light chain (sFLC) assay revealed a very high lambda light chain (LC) concentration of 257.4 mg/L. The assay also showed an involved: uninvolved sFLC ratio of <100, which was not supportive of diagnosing plasma cell myeloma. After considering the history, physical examination, laboratory and imaging findings, the final diagnosis was MGUS with systemic amyloidosis. Chemotherapy with Velcade, Cyclophosphamide, and Dexamethasone regime was commenced for cardiomyopathy. Unfortunately, she received only one cycle of chemotherapy before she succumbed to death at home in her sleep.

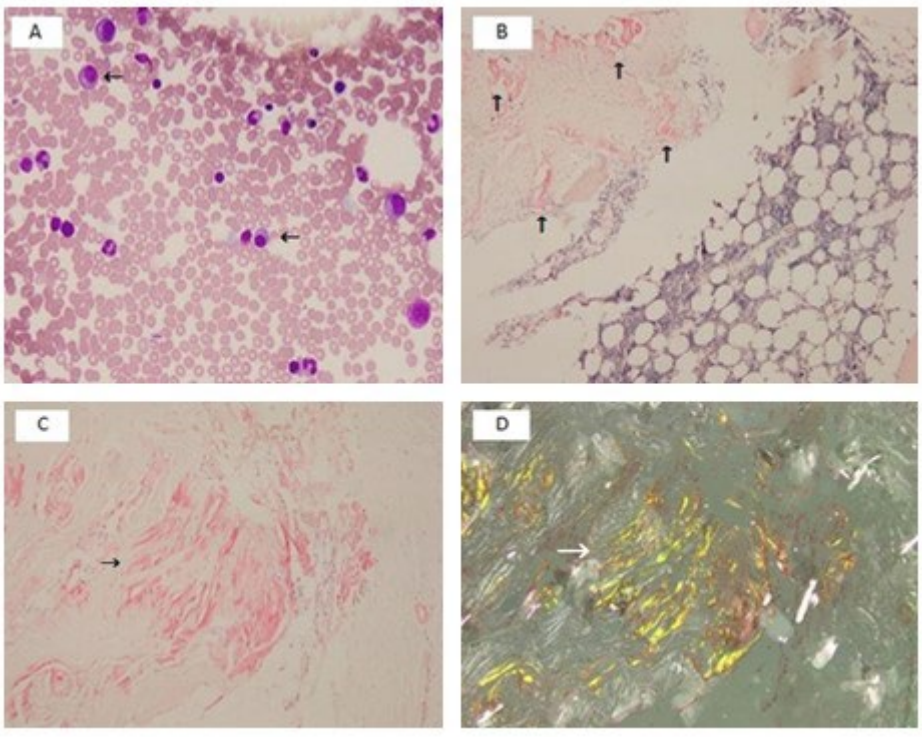

Figure 1 (A) BMA showed minimal plasma cells (←) in the background of reactive marrow (X100, May-Grunwald Giemsa stain). (B) Trephine biopsy showing scattered areas of extracellular pinkish amorphous amyloid-like materials (↑) (X40, Haematoxylin & Eosin stain). (C) Trephine biopsy showing extracellular pinkish amorphous amyloid-like materials (→) under light microscopy (X200, Congo red stain). (D) Trephine biopsy showing apple-green birefringence (white arrow) under polarised light microscopy (X200, Congo Red stain).

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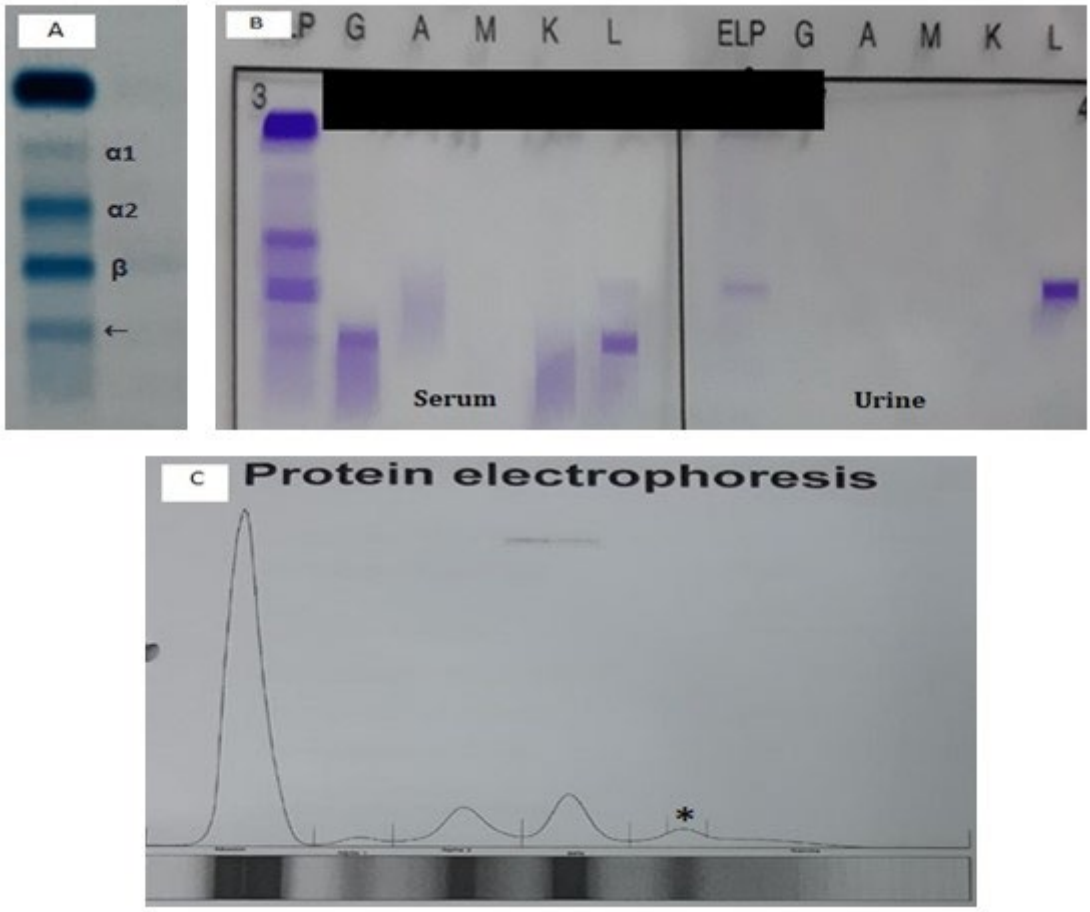

Figure 2 (A) Serum protein electrophoresis using agarose gel showing the presence of a distinct band of paraprotein in the gamma region (←). (B) Immunofixation gel confirmed the paraprotein in the serum to be of IgG lambda with lambda light chain paraproteinuria in the urine. (C) Densitometry of the serum protein electrophoresis shows a low paraprotein concentration present within the gamma globulin region (*).

DISCUSSION

Paraproteins is characterised by a homogenous electrophoretic migration on agarose media. The clonality is confirmed using IFE [2]. Trace amounts of paraprotein may be detectable in the premalignant state, low tumour burden, oligosecretory plasma cell dyscrasia, whereas the concentration may reach over 100 g/L in large tumour burden gammopathies [3]. MGUS is a premalignant condition associated with plasma cell dyscrasias associated with trace amount of paraprotein in serum. Diagnosing MGUS is challenging due to the lack of symptoms [1].

Amyloidosis is a heterogeneous group of disorders characterised by extracellular deposition of misfolded insoluble proteinaceous material with cross beta-pleated sheet structure [5]. Amyloidosis can be localised or systemic and can occur without plasma cell dyscrasia in a minority of cases. Systemic amyloidosis is characterised by amyloid deposition at multiple sites and visceral organs, leading to organ dysfunction [6], similar to that in this patient. Systemic amyloidosis can be divided into three subtypes. The amyloid fibril precursor proteins specific to each type are primary systemic amyloidosis (AL), secondary systemic amyloidosis (AA), and heredofamilial amyloidosis like transthyretin, AA, beta 2-microglobulin, apolipoprotein A-I, gelsolin [7]. Of all three subtypes, only primary systemic amyloidosis commonly occurs with plasma cell dyscrasia [8]. However, Ashley, Elise & Ross (2007) showed that only 15 per cent of 494 cases of

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primary systemic amyloidosis were associated with MGUS.

Systemic amyloidosis has a poor prognosis, with a median survival of 13 to 43 months for primary systemic amyloidosis. The adverse predictive outcomes include primary systemic amyloidosis, congestive heart failure, increased septal thickness, urinary light chains, hepatomegaly, and significant weight loss [8].

In this patient, paraprotein detection was confirmed as MGUS based on International Myeloma Working Group (IMWG) diagnostic criteria [9]. MGUS is most commonly observed as an incidental finding during investigation of other diseases compared to systemic amyloidosis, where the patient usually presents with significant organ-related symptoms [6]. The non-IgM MGUS seen on the patient's serum IFE is usually associated with a risk of progression into multiple myeloma and rarely an increased risk of progressing to plasmacytoma and AL amyloidosis [4]. A combination of serum and urine IFE and measurement of sFLC are required to detect subtle monoclonal protein underlying AL amyloidosis [3, 10]

Furthermore, in the absence of cardiac biopsy, systemic amyloidosis is diagnosed based on infiltrative cardiomyopathy on cardiac echocardiography and demonstration of amyloid deposition in trephine biopsy. Diagnosis of amyloidosis must be followed with amyloid typing, allowing clinicians to select appropriate therapy. This step is crucial, as amyloid therapy is type-specific and varies from liver transplant to chemotherapy and hematopoietic stem cell transplantation [6, 11]. Various lab tools available for amyloid typing include immunofluorescence, immunohistochemistry, immunoelectron microscopy and proteomic study [6]. The proteomics method of mass spectrophotometry analysis of amyloidotic material is the gold standard for fibril typing amyloidosis [12]. However, amyloid typing was not available at our centre, and it is one of the limitations in this case report.

An atypical course of MGUS progression to amyloidosis of the lung and non-amyloid eosinophilic deposition in the brain has been reported before [13].

Another study demonstrated that all patients with AL amyloidosis have paraprotein detected before clinical presentation, with an increase in the concentration of the paraprotein years before the diagnosis of amyloidosis was made [14]. Despite the modest but persistent lifetime risk of progression to incurable cancer, screening for MGUS is still not feasible [4]. In this case, the patient was concomitantly diagnosed with systemic amyloidosis and MGUS.

CONCLUSION

In conclusion, based on the amyloid disposition in this patient, clinical manifestation, the IMWG criteria for MGUS, and no evidence on amyloid typing, it is justifiable to assume that our patient has double pathology rather than a progression of one disease state to another. Although the median survival is claimed to be short for those with cardiac amyloidosis, it is essential to hasten amyloid typing to provide better options for the subsequent management of such a case. Publication of more similar cases is encouraged as there is a need for more information, which will be of benefit to practitioners.

Conflict of Interest

Authors declare none.

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Authors' contribution

Literature search and manuscript were prepared by IAB. AI and NY together with BMAT. IAB and DNN interpreted the serum electrophoresis. The manuscript was edited by AI, NY, DNN and MMM. All authors approved the final version of the manuscript submitted for publication and take responsibility for the statements in the article.

Informed Consent

Informed consent was obtained from the patient.

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