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A Patient's Journey with Immunoglobulin Light Chain (Al) Amyloidosis

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Abstract: A 64-year-old man presented with progressively worsening difficulty in breathing and was subsequently diagnosed with immunoglobulin light chain (AL) amyloidosis. However, he was keen to seek a second opinion, causing a delay in initiating definitive treatment. His clinical manifestations included heart failure, chronic diarrhoea, symmetric lower extremity peripheral neuropathy, and autonomic neuropathy (postural hypotension). As he was non-transplant eligible and had financial constraints, he was initially treated with conventional chemotherapy [two cycles of cyclophosphamide + thalidomide + dexamethasone, followed by seven cycles of melphalan + prednisolone (MP)]. Throughout his disease course, he experienced chronic diarrhoea and profound oedema of lower limbs. He had to relocate to his son's residence in Kuala Lumpur to enable frequent and regular hospital visits. He had impaired health-related quality of life (HRQoL); however, he had excellent family support. After nine cycles of conventional chemotherapy, the optimal response was not achieved. Bortezomib was added to MP therapy [bortezomib + melphalan + prednisolone (VMP) regimen]. Following three cycles of VMP, he achieved complete haematologic response (CR), resulting in symptomatic improvement and his eventual return to his hometown. He continued the same treatment regimen to control the disease. His hospital admissions decreased, and his HRQoL improved, although no organ response was noted. Three years later, he developed decompensated cardiac failure and passed away. His overall survival was five years and two months. This case report highlights that achieving CR leads to prolonged overall survival and improved long-term clinical outcomes, including HRQoL.

Keywords: AL amyloidosis, clinical outcomes, complete haematologic response, survival outcome.

1. Introduction

Immunoglobulin light chain amyloidosis (also known as amyloid light chain amyloidosis, AL amyloidosis, or systemic light chain amyloidosis) is a monoclonal plasma cell proliferative disorder that is rare and associated with a poor prognosis, particularly when cardiac involvement is present (Palladini & Merlini, 2016).

In AL amyloidosis, there is uncontrolled proliferation of monoclonal plasma cells that secrete excessive amounts of abnormal immunoglobulin light chains. These misfolded light chains aggregate to form insoluble amyloid fibrils that subsequently deposit extracellularly within various tissues, ultimately impairing organ function, and in advanced cases, resulting in organ failure. Common sites of involvement include the heart (~75%), kidneys (~65%), liver (~15%), soft tissues (~15%), peripheral nerves/ autonomic nervous system (~10%), and gastrointestinal tract (~5%) (Palladini & Merlini, 2016). The clinical presentation and disease severity are heterogeneous and largely depend on the organs involved and the extent of amyloid deposition.

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We report a case of AL amyloidosis to emphasize that (1) the holistic management approach is essential for optimising clinical outcomes and improving health-related quality of life (HRQoL) in this debilitating and incurable disease, and (2) the depth of haematgic response significantly affects clinical outcomes and overall survival.

2. Case Report

In September 2017, a 64-year-old man, with hypertension and dyslipidaemia, presented with progressively worsening difficulty in breathing. He subsequently underwent percutaneous coronary intervention (PCI) to left anterior descending artery. During evaluation at that time, he was diagnosed with AL amyloidosis. However, the patient was keen to seek a second opinion, causing a delay in initiating definitive treatment. He lived in another district and traveled to Kuala Lumpur for a second opinion.

In December 2017, the patient presented with a five-month history of bilateral leg swelling and worsening shortness of breath. His clinical manifestations included New York Heart Association (NYHA) class III heart failure, chronic diarrhoea, symmetric lower extremity peripheral neuropathy, and autonomic neuropathy (postural hypotension).

Echocardiography revealed global biventricular hypertrophy, interatrial septal thickening, and ejection fraction of 50%.

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Cardiac magnetic resonance imaging (MRI) findings were consistent with infiltrative cardiomyopathy, strongly suggestive of cardiac amyloidosis (diffuse enhancement of right ventricle, left ventricle and interatrial septum post-gadolinium, thickened interatrial septum, pericardial effusion, and right pleural effusion).

Chest X-ray (CXR) revealed right-sided pleural effusion (Figure 1). Computed tomography scan (CT) of thorax demonstrated pericardial effusion and pleural effusion (more on the right) (Figure 1).

Additional investigations were performed, and the results are shown in Table 1.

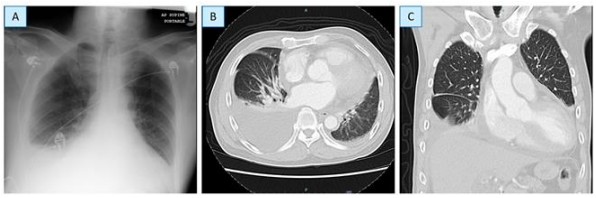

Figure 1. (A) Chest X-ray showing right-sided pleural effusion. (B&C) Computed tomography scan of thorax demonstrating pericardial effusion and pleural effusion.

Investigations excluded hypercalcemia, renal function impairment, lytic bone lesions, and extramedullary involvement.

In December 2017, the diagnosis of systemic AL amyloidosis was established based on the following:

Table 1. Results of investigations performed in our patient

Investigations	Results
Rectal biopsy	Chronic proctitis with amyloidosis Microscopic examination showed amorphous eosinophilic acellular material. Positive Congo red stain
Bone marrow aspirate and trephine biopsy examination	Clonal plasma cells (14%)
Serum protein electrophoresis, Serum immunofixation electrophoresis, Urine protein electrophoresis, Urine immunofixation electrophoresis	Paraproteinaemia (8.9 g/L, IgG lambda) No detectable paraprotein in the urine
Serum free light chain (FLC) assay	kappa (κ) FLC — normal (12.7 mg/L) lambda (λ) FLC — elevated (227 mg/L) kappa : lambda ratio — abnormal (0.06)
Full blood count	Normochromic normocytic anaemia (Hb 11.2 g/dL) White cell count — normal Platelet count — normal
Serum troponin I level	Elevated (65.9 pg/mL)

(1) amyloid-related systemic syndrome, including involvement of the heart, peripheral nerves, autonomic nervous system, and gastrointestinal tract;

(2) positive Congo red stain in rectal biopsy indicating the presence of amyloid;

(3) monoclonal plasma cell proliferative disorder, evidenced by clonal plasma cells in bone marrow, paraproteinaemia, and abnormal serum free light chain (FLC) ratio.

He was a small business owner but could not work due to illness. His son works in a restaurant. He had financial constraints, resulting in limited access to certain medications (bortezomib).

Since he was non-transplant eligible, he received conventional chemotherapy [two cycles of cyclophosphamide + thalidomide + dexamethasone, followed by seven cycles of melphalan + prednisolone (MP)].

Throughout his journey with immunoglobulin light chain (AL) amyloidosis, he experienced chronic diarrhoea and profound oedema of the legs. He needed to relocate to his son's house in Kuala Lumpur to enable frequent and regular hospital visits. His health-related quality of life (HRQoL) was impaired; however, he had excellent family social support.

After nine cycles of conventional chemotherapy, an optimal response was not achieved.

With support from the patient assistance programme, bortezomib was added to MP therapy [bortezomib + melphalan + prednisolone (VMP) regimen].

In March 2019, after three cycles of VMP, he achieved complete haematologic response (CR) (negative serum and urine immunofixation; normal FLC ratio), resulting in symptomatic improvement that allowed him to return to his hometown.

He continued the same treatment regimen to control the disease. His hospital admissions decreased, although no organ response was detected. His HRQoL improved.

Three years later, in January 2023, he succumbed to decompensated cardiac failure.

3. Discussion

Our patient achieved CR but no organ response, with an overall survival of five years and two months. Adding bortezomib to conventional chemotherapy enabled rapid and deep complete haematologic response, resulting in prolonged overall survival and improvement in HRQoL.

3.1 Haematologic Response and Survival Outcome

Response to therapy in AL amyloidosis can be assessed by evaluating haematologic response and organ responses.

Haematologic response is assessed by measuring levels of monoclonal proteins, FLCs, FLC ratio, and the difference between involved and uninvolved FLCs (dFLC). Criteria for complete haematologic response (CR) include normalisation of FLC levels and ratio (when FLC ratio is not within the reference range, the uninvolved FLC concentration must be greater than the involved FLC concentration), and negative serum and urine immunofixation (for monoclonal protein) (Palladini et al., 2020).

In AL amyloidosis, the CR rate was lower with conventional chemotherapy (melphalan plus dexamethasone) compared to bortezomib-based therapy (bortezomib, melphalan and dexamethasone) (Wechalekar et al., 2023).

In AL amyloidosis, bortezomib-based therapy has demonstrated superior CR rate compared with conventional chemotherapy: 8% (4/53) in the bortezomib, melphalan and dexamethasone (BMDex) group versus 4% (2/56) in the melphalan and dexamethasone (MDex) group ($p = 0.012$) (Kastritis et al., 2020).

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Clinical trials have demonstrated that failure to achieve CR correlates with poorer survival outcomes in AL amyloidosis (Kastritis et al., 2020; Wechalekar et al., 2023). This case report supports existing evidence indicating that achieving CR is associated with improved overall survival in AL amyloidosis.

3.2 Organ Response

Organ-specific responses in AL amyloidosis are evaluated by measuring specific organ biomarkers for organ involvement.

Organ response (heart) is assessed by measuring N-terminal pro-B-type natriuretic peptide (NT-proBNP). Criteria for organ response (heart) include NT-proBNP response (30% and >300 ng/L decrease over the starting value in patients with baseline NT-proBNP ≥650 ng/L) or NYHA class response (≥2 class decrease in subjects with baseline NYHA class III or IV) (Palladini et al., 2020; Comenzo et al., 2012).

Organ response (kidney) is assessed through quantification of proteinuria and estimation of glomerular filtration rate (eGFR). Criteria for organ response (kidney) include 30% decrease in proteinuria or drop of proteinuria below 0.5 g per 24 hours in the absence of renal progression (defined as ≥25% decrease in eGFR) (Palladini et al., 2020; Comenzo et al., 2012).

Criteria for organ response (liver) include 50% decrease in abnormal alkaline phosphatase value, decrease in liver size radiographically by at least 2 cm (Comenzo et al., 2012).

Criteria for organ response (peripheral nervous system) include improvement in electromyogram nerve conduction velocity (Comenzo et al., 2012).

Unlike haematologic responses, cardiac responses are less frequent and often delayed. Our patient's lack of cardiac improvement despite CR is consistent with the literature, where cardiac amyloidosis remains a major determinant of mortality (Palladini & Merlini, 2016).

3.3 Impact of Delay in Initiation of Treatment and Financial Constraints

The delay in diagnosis and initiation of definitive treatment is not uncommon in AL amyloidosis, thereby worsening prognosis. Early intervention remains critical to prevent irreversible organ damage.

Financial barriers restricting access to novel therapies (e.g., bortezomib, daratumumab) constitute a recurring issue in real-world settings.

3.4 Recent Advances and Future Directions

The addition of bortezomib to conventional chemotherapy resulted in CR, leading to favourable long-term clinical outcomes with prolonged overall survival (Kastritis et al., 2020).

In this era, a paradigm shift with emerging treatment, the addition of daratumumab to bortezomib-based therapy (daratumumab, bortezomib, cyclophosphamide and dexamethasone), resulted in deeper responses [53.3% (104/195) in the daratumumab group versus 18.1% (35/193) in the control group (bortezomib, cyclophosphamide and dexamethasone); $p < 0.001$] and delayed major organ deterioration in patients with newly diagnosed AL amyloidosis (ANDROMEDA trial) (Kastritis et al., 2021).

However, clinical trials with novel agents are urgently required to improve rapid, deep, and durable haematologic response rates and organ response rates, with the ultimate goal of achieving a cure in AL amyloidosis.

3.5 Implications for Clinical Practice

A comprehensive and timely diagnostic work-up, including tissue biopsy, bone marrow biopsy examination, serum and urine protein electrophoresis with immunofixation, and serum FLC assay, is essential for establishing early diagnosis of this rare and often underdiagnosed disorder. Early identification and prompt initiation of definitive treatment are crucial for improving clinical outcomes.

For patients with newly diagnosed AL amyloidosis, first-line therapies such as bortezomib-based or daratumumab-based regimens result in deeper responses and higher rates of CR.

Addressing socioeconomic barriers (e.g., through patient assistance programmes) may enhance access to novel therapies.

Multidisciplinary care involving cardiology, nephrology, neurology, and supportive care is essential for the holistic management of this systemic disorder.

Clinical trials evaluating anti-fibril therapies, such as monoclonal antibodies targeting amyloid deposits, may further improve haematologic responses, organ responses, and optimise clinical outcomes.

4. Conclusion

This case report highlights that achieving CR leads to prolonged overall survival and improved long-term clinical outcomes, including HRQoL. Achieving a rapid and durable complete haematologic response is essential for optimising outcomes and improving survival in AL amyloidosis. An integrated and holistic management strategy incorporating novel therapies is crucial to improve patients' HRQoL in addition to achieving rapid, deep, and durable haematologic response and organ responses, with the ultimate goal of achieving a cure in immunoglobulin light chain (AL) amyloidosis.

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