Management of AL Amyloidosis at a South African State Hospital

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INTRODUCTION:

Amyloidosis is an uncommon cause of intrinsic renal disease. However, the most common renal presentation is nephrotic syndrome. Renal manifestations of systemic amyloidosis are most frequently seen either in the setting of chronic inflammation (AA amyloidosis), or plasma cell dyscrasias (AL amyloidosis). Without treatment, amyloidosis is associated significant morbidity and mortality. Those patients with kidney disease tend to progress rapidly to end-stage renal disease (ESRD) if untreated.

CASE REPORT:

- A 60-year-old Caucasian male presented to his general practitioner in September 2022 with pedal oedema. In addition, he reported a metallic taste in his mouth, experienced nausea, loss of appetite and weight loss of 12kg over the preceding 6 months. He also reported episodic back pain, dizziness, and syncopal episodes.

The patient has a significant smoking history of 45 pack years.

He was commenced on furosemide 40mg twice daily to relieve the oedema. It was also found that patient had nephrotic range proteinuria, 5g/day and in discussion with a nephrologist was commenced on a trial of corticosteroids. This was weaned off and stopped.
He was subsequently referred to the nephrologist for a renal biopsy. The full blood count (FBC) revealed a polycythaemia, with haemoglobin value of 18.1g/dL and haematocrit 0.526 L/L. He had a white cell count of WCC 19.35 X 10^9/L and a platelet count of 346 X 10^9/L.
His biochemistry results at presentation

Sodium	139 mmol/L
Potassium	5.1 mmol/L
Bicarbonate	27 mmol/L
Urea	5.1 mmol/L
Creatinine	96 mmol/L
Corrected calcium	2.29 mmol/L
Albumin	19g/L
LDH	487 U/L
Iron	14
Transferrin	1.66
% Saturation	34
Ferritin	619
Vitamin B12 and folate	Normal

The patient underwent a venesection and a renal biopsy was performed.

Renal biopsy
Amyloid deposition in the glomeruli, salmon pink in colour on Congo Red stains. Not enough tissue/ funds to submit for immunofluorescence.

Unfortunately, the patient could not afford the cost of further private health care and was referred to a state facility for further investigations and medical care.
The results of the investigations performed is shown below:

Bone marrow aspirate and trephine
Aspirate
Active trilineage haematopoiesis with serial maturation in different cell lineages.
Trephine
Plasma cells early seen with interstitial distribution. Small area of monomorphic, small mature cells resembling a lymphoid aggregate. No amyloid deposition. Plasma cells not increased - 3% of nucleated cells.

Flow cytometry on bone marrow aspirate
1.71% clonal plasma cells with lambda light chain restriction identified. In keeping with plasma cell dyscrasia.

Skeletal survey	Degenerative changes no lytic lesions

Positron Emission Tomography : 5 May 2023
Physiological distribution of tracer in the brain, heart, liver, spleen, bone marrow and kidneys. Head and Neck: No pathological uptake seen in the brain, head and neck. Thorax: No pathological uptake seen in the lungs and mediastinum. Abdomen and Pelvis: No pathological uptake seen. Musculoskeletal: No pathological uptake seen in the bones and soft tissue. PET/CT Conclusion There is no convincing of metabolically active disease.

Ultrasound of the kidneys and abdomen
Liver is enlarged in size (16.4 cm) with normal echopattern. No focal lesions or dilated intrahepatic ducts noted. Normal portal vein. The gallbladder is well distended. No calculi or wall thickening. The pancreas is normal. No focal lesions or pancreatic duct dilatation. The spleen is normal in size (10.4 cm) and echopattern and no focal lesions are noted. Both kidneys are normal in size (Rt: 11.6 cm, Lt: 11.6 cm) and echopattern with good corticomedullary differentiation. No evidence of hydronephrosis, hydroureter or perin ephric collections. No ascites.

Metabolic screening showed the patient to have dyslipidemia and a normal glucose tolerance test. Viral testing for HIV, hepatitis B and C screen as well as an antinuclear antibody screen was negative. The thyroid function test and Pro BNP were normal.

Serum protein electrophoresis	**3 April 2023**
Alpha-1-Globulins	2
Beta-1-Globulin	6
Beta-2-Globulin	2
Gamma Globulins	8
Paraprotein	2g/L (early gamma region)
Immune fixation	IgA Lambda. No immune paresis

Beta 2 microglobulin	2.7
Serum free light chains	Increased lambda light chains: 116. Lambda/kappa ratio low 0.1 (low)

17 May 2023 Protein/Creatinine Ratio	1.076 H

The Patient Was Referred to Our Centre in June 2023.

Patient reported paresthesia of both feet and legs.

CLINICAL EXAMINATION FINDINGS:

Performance status: ECOG2
Initial blood pressure 137/92 mmHg and pulse rate of 101. A postural drop in blood pressure was noted at 1 minute - BP 116/74 mmHg and at 3 minutes-110/73 mmHg .
He was afebrile. Respiratory rate: 14/min
General examination findings: Livedo reticularis. Bilateral moderate pedal oedema.
No lymphadenopathy
Oral cavity: Macroglossia. Dental caries noted.
Cardiovascular system: Normal heart sounds. No murmurs. No bruits
Chest: Hyperinflated. No crackles or wheezes
Abdomen: Soft; normal bowel sounds. No hepatosplenomegaly
Calves: Soft
Central nervous system: No abnormalities

MANAGEMENT:

Commenced CyBorD Regimen on 11 July 2023 with prophylactic acyclovir.
- Bortezomib mg SC once per day on days 1, 8, 15, 22
- Dexamethasone 40mg PO once per day on days 1, 8, 15, 22
- Cyclophosphamide 650mg PO once per day on days 1, 8, 15, 22

After 2.5 cycles of CyBorD, the patient reports feeling better.

The table below illustrates the response to therapy biochemically.

	10 October 2023
Alpha-1-Globulins	2
Beta-1-Globulin	4
Beta-2-Globulin	2
Gamma Globulins	4
Paraprotein	< 1 (early gamma)
Protein/Creatinine Ratio	0.891

Following 4 cycles of CyBorD, we plan to proceed to autologous stem cell harvest with etoposide and G-CSF. Thereafter Mel-200 and stem cell re-infusion.

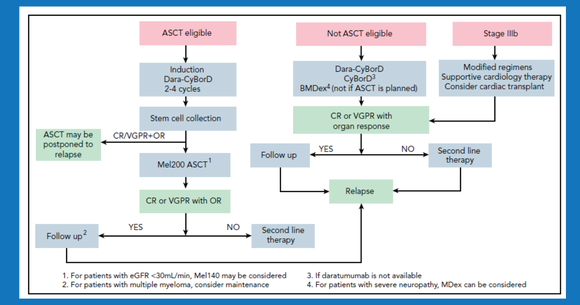
DISCUSSION:

Amyloidosis may affect different organs and clinical manifestations are deceitful and often recognized at an irreversible stage[1]. This case highlights the importance of creating awareness amongst primary health care practitioners to facilitate early referrals for further investigations prior to the onset of advanced end organ damage. The table below entitled “Presymptomatic hints, symptoms, and signs leading to the diagnosis of AL amyloidosis” is a useful reference, to help guide clinicians.[1]

Presymptomatic	Symptomatic		
	Organ involved	**Symptoms**	**Signs**
Increased markers of possible amyloid organ involvement: • Heart: NT-proBNP • Kidney: Albuminuria • Liver: Alkaline phosphatase Monitored during follow-up of MGUS patients and particularly in those with abnormal FLC ratio, and LC propensity to form amyloid (glycosylated κ-LCs, use of LC genes IGLV6-57, IGLV2-14, IGLV1-44, and LCs identified by machine learning algorithm)	Heart	Reduced exercise tolerance Dyspnea at rest or exertion Fatigue Syncope Angina	Lower extremity edema Pleural effusions Jugular vein distension Arrhythmia Thickened ventricular walls and low voltages on ECG
	Kidney	Loss of appetite Fatigue and weakness	Lower extremity edema Anasarca
	Soft tissues	Jaw or buttock claudication Carpal tunnel (often bilateral) Dysarthria	Periorbital (upper body) purpura Macroglossia Nail dystrophy Shoulder pad Arthropathy Myopathy
	Peripheral nervous system including autonomic nervous system	Length dependent sensory-motor neuropathy Lipothymia Taste alterations Early satiety	Orthostatic hypotension Intestinal dysmotility Erectile dysfunction Voiding dysfunction
	Liver	Right upper quadrant tendemess Jaundice Early satiety	Hepatomegaly Weight loss
	Gastrointestinal tract	Abdominal discomfort	Malabsorption Gastrointestinal bleeding Diarrhea Weight loss

Palladini G, Merlini G. How I treat AL Amyloidosis. Blood 2022. 139(19)

Treatment should be tailored according to the organ involved and clonal characteristics. The combination of daratumumab and bortezomib combination is considered the standard-of-care for newly diagnosed patients with AL amyloidosis.[1] (see algorithm below). This combination has the capability of inducing rapid and deep responses, however in the resource constrained health care settings, the use of this combination may not be possible.



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CyBorD followed autologous stem cell transplant remains a viable option in transplant eligible patients with AL amyloidosis in the South African context.

CONCLUSION :

Amyloidosis is an uncommon cause of kidney disease and typically presents with nephrotic syndrome. It is therefore important for health care practitioners to consider this as a potential cause of nephrotic syndrome once the more common causes have been reliably excluded.

REFERENCES :

1. Palladini G, Merlini G. How I treat AL Amyloidosis. Blood 2022. 139(19)