Case Report

Systemic Amyloidosis: A Big Masquerade of Clinical Symptoms with Catastrophic Consequences

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ABSTRACT

A case of a 52-year-old woman presented with non-specific symptoms: generalised weakness, loss of appetite and left leg pain of about a week duration. She later developed nephrotic syndrome, cardiomegaly with arrhythmias, adrenal insufficiency, cutaneous amyloid, with consolidation on chest X-ray and hepatomegaly. She had a renal biopsy that revealed renal amyloidosis. She was treated with thalidomide, bortezomib, methylprednisolone, ranitidine and allopurinol without significant improvement. Amyloidosis is a rare disease that requires a high index of suspicion. She may have responded if she had been diagnosed early, and hence, early diagnosis is a key in successful management.

Key words: Amyloidosis, chronic kidney disease, nephrotic syndrome

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INTRODUCTION

Amyloidosis is a rare group of heterogeneous disorders caused by deposition of amyloid fibrils, which are composed of mis-folded, indissoluble proteins in one or more organs.[1,2] The clinical presentation is protean, and thus, the diagnosis may be missed if there is no high index of suspicion. The definitive diagnosis is through histology, and there is paucity of data from this environment. An autopsy report of 4235 autopsies in UCH Ibadan between 1970 and 1979 showed only eight cases (0.2%).[3]

We presented a case of a 52-year-old woman with systemic amyloidosis affecting the kidneys, adrenal gland and the myocardium with a challenge in definitive diagnosis.

CASE REPORT

Mrs BJ, 52-year-old patient presented with a week history of generalised weakness, loss of appetite and a 5-day history of left leg pain.

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The weakness was progressive and generalised, which limited her daily activities. There was associated loss of appetite with progressive weight loss, but there was no history of cough or drenching night sweats.

There was a history of vomiting twice daily containing recently ingested meals. The pain on the left leg was compressing in nature, progressive and limited her daily activity, and she was not able to walk for more than 6 m before taken a rest. There was no history of trauma or fall, leg was not swollen and there was no difficulty in breathing.

She had nocturia and passage of frothy urine though no history of haematuria, facial swelling or features of uraemia.

She was neither hypertensive nor diabetic and had no family history of such.

Examination revealed that she was a middle-aged woman who was not pale, anicteric and had no peripheral lymphadenopathy or pitting pedal oedema.

Cardiovascular system revealed a pulse rate of 96 bpm, regular, normal volume and a blood pressure of 120/70 mmHg, and the jugular venous pulse was not elevated. The apex beat was

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not displaced and the heart sounds were normal. Chest was clinically clear; abdomen and central nervous system were essentially normal.

Musculoskeletal system examination revealed tenderness in the left gluteal region with no swelling or differential warmth.

On urinalysis, appearance was turbid, glucose was negative, protein was ++, blood was + and ketone bodies were +.

An assessment of dermatomyositis to exclude connective tissue disease was made.

Results of investigations: Urinalysis showed 2 + proteinuria, specific gravity 1.025, pH - 5.0 and others were negative. Urine microscopy, culture and sensitivity showed pus cells 0–2 per high power field, but culture yielded no growth.

Creatinine clearance was 84 mL/min; 24-h urinary protein excretion was 4.4 g. The erythrocyte sedimentation rate was 30 mm/h.

Fasting blood sugar and total cholesterol were 100 mg/dL and 263 mg/dL, respectively.

The full blood count showed relative lymphocytosis. The total white cell count (WBC) was 6.68 × 10^9/L, packed cell volume (PCV) - 38%, neutrophil - 32.4%, lymphocyte - 60%, monocyte - 6.7%, eosinophil - 0.2%, basophil - 0.7%, red blood cell - 4.62 × 10^{12}/L and the platelets - 80.22 × 10^9/L.

Abdominal scan showed normal renal parenchyma echotexture. The corticomedullary differentiation was preserved. Right kidney measured 9.8 cm × 4.6 cm; left kidney measured10.7 cm × 4.8 cm. Liver size measuring 14.4 cm had regular outlines with preserved parenchyma echotexture. The gallbladder, spleen and the pancreas were essentially normal.

The electrolyte, urea, and creatinine results are shown in Table I.

The patient was treated with intravenous antibiotics and analgesics. Her clinical state improved, apart from the occasional mild left gluteal pain which improved with physiotherapy. She was subsequently discharged after 5 days on admission.

She re-presented 6 weeks later at a private facility with body weakness, poor appetite and severe left leg pain. She was stabilised and then referred back to us for further management. Further history revealed positive history of cold intolerance; she had attained menopause 8 years earlier. Her blood pressure was 90/50 mmHg. An assessment of multiple organ neoplasia was entertained.

Table I: Baseline - Electrolyte, urea, creatinine

E, U, Cr	December 13, 2017	December 14, 2017
Na (mmol/L)	133	137
K (mmol/L)	3.4	4.1
Cl (mmol/L)	100	101
HCO_3 (mmol/L)	21	20
Urea (mg/dL)	10	12
Cr (mg/dL)	1.0	0.7

She was admitted and the investigations done included: electrolyte, urea and creatinine, urinalysis, Adrenocorticotrophic hormone (ACTH) assay, thyroid function test and lumbosacral X-ray. The serum cortisol was found to be 187.36 pmol/L (240–618 pmol/L) and ACTH assay was found to be 2.5 pmol/L (1.6–13.9 pmol/L), confirming the diagnosis of hypoadrenalism. Random blood sugar was 158 mg/dL.

She was commenced on hydrocortisone 200 mg stat, then 100 mg 12 hourly × 48 h, tablet prednisolone 10 mg twice daily tablet fludrocortisone 0.1 mg daily, tablet rosuvastatin 10 mg nocte.

The patient improved on these medications and was followed up at the endocrinology clinic.

Despite the improvement in general body weakness, she developed bilateral leg swelling and tenderness in the limbs.

She subsequently travelled to the United Kingdom where she had series of investigations. Her report showed serum amyloid P component scan, large total body amyloid load in the liver, spleen, kidneys and bones with obscured adrenal glands.

Renal biopsy was performed which revealed tubules and interstitium with abundant protein re-absorption droplets in the proximal tubular epithelium. No evidence of acute tubular injury was noted.

Vessels showed foci of amyloid deposits in the hilar arterioles.

Immunochemistry showed amyloid B intense positive amyloid deposits in the glomeruli and occasional vessel wall. Amyloid A was negative. C1q was strongly positive stain at sites of amyloid.

IgG, IgG4, IgA and C3 were negative.

IgM-Nonspecific positive mesangium.

Figure 1: Two-dimensional echocardiogram of the patient

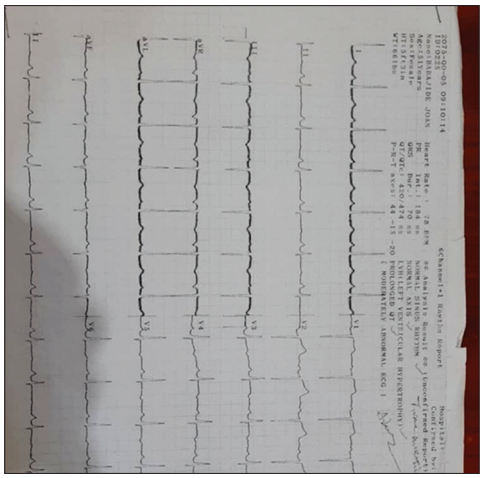

Figure 2: Electrocardiogram of the patient

The patient was then transferred to Amyloid Centre in the UK, where she was commenced on: intravenous bortezomib 2 mg on days 1, 4, 8, 11. Methylprednisolone 500 mg in 500 mls of 0.9% saline. tablet thalidomide 100 mg daily, ranitidine 150 mg twice daily and allopurinol 100 mg daily. There was no significant improvement in clinical state despite this treatment. At this point, she opted to return to Nigeria.

She presented a week after, with general body weakness, breathlessness and leg pain. Her: electrolyte, urea and creatinine were as follows: Na - 131 mmol/L, K - 3.7 mmol/L, Cl - 97 mmol/L, HCO_3-26 mmol/L, urea - 87 mg/dL and Cr - 2.0 mg/dL. Abdominopelvic scan showed increased renal parenchyma echotexture greater than the spleen. The corticomedullary differentiation and the central sinus echoes were lost. Right kidney measured 11.2 cm × 5.3 cm; left kidney measured 10.7 cm × 5.8 cm. The liver was enlarged and measured 18.3 cm. It had regular outlines with preserved parenchyma echotexture. No intrahepatic mass lesions or duct dilatation were noted. Bilateral pleural effusion was observed with internal echoes and ascites. Spleen was 10.8 cm and the pancreas was normal.

Chest X-ray revealed homogenous opacification of the mid and lower zones on the right and lower zone only on the left. The cardiac/diaphragmatic silhouettes and both costophrenic sulci were obliterated.

Bilateral hilar opacity with some hilar air bronchograms was seen.

The cardiac size could not be assessed. Normal bony thorax was noted.

An impression of bilateral pleural effusion with hilar consolidation was made.

She continued her chemotherapy, fluid restriction, frusemide and antibiotics. A pulmonologist opted to manage the pleural effusion conservatively, and she was subsequently discharged.

A month after, she was brought to emergency treatment room on account of severe leg pain, generalised body swelling of 2 weeks and loss of consciousness 18 h before presentation. She was said to have lapsed into unconsciousness 18 h before presentation. No prior history of headache, irrational behaviour or seizures was noted. No history of unilateral limb weakness was noted. Examination at this time revealed a comatose middle-aged woman, with a Glasgow coma score of 6/15. Neck was supple, pupils were of normal size and reacted to light, muscle tone was normal globally, there was no differential weakness and reflexes were normal globally.

An assessment of renal amyloidosis with adrenal insufficiency was made.

Her investigations revealed Hb: 8.7 g/dL, PCV: 23.9%, WBC: 5.5×10^3, neutrophils: 88.2% and lymphocyte: 10.4%.

She was transfused with two pints of blood, antibiotics changed and her clinical condition remarkably improved in terms of the level of consciousness but was observed to have petechial haemorrhages around the neck and chest which was reviewed by a dermatologist, and an assessment of vasculitis secondary to cutaneous amyloid was made.

The cardiology team were invited on account of low pulse volume and missed beat. The electrocardiography showed low voltage on all leads. Echocardiogram was requested to confirm cardiac involvement.

Two-dimensional echocardiogram [Figure 1] revealed marked thickening of interventricular septum 1.9 cm (normal 0.6–1.2 cm), posterior wall thickness 1.7 cm and speckle appearance of interventricular septum. Left atrial area was 24.5 cm (normal <20 cm) and right atrial area was 18.7 cm (normal <20.5 cm). The ejection fraction was 58%.

Restrictive diastolic dysfunction with pericardial effusion but not in tamponade; consequently, an assessment of amyloid heart disease was made.

Electrocardiogram [Figure 2] showed low voltage complexes in the limb and augmented leads. Left ventricular hypertrophy and prolonged QT interval.

She recommenced her chemotherapy: intravenous bortezomib 2 mg, on days: 1, 4, 8, 11; methylprednisolone 500 mg in 500 ml of 0.9% saline; tablet thalidomide 100 mg daily; tablet ranitidine 150 mg twice daily and allopurinol 100 mg thrice daily.

After day 4, of the first cycle of chemotherapy, she was noticed to be deteriorating and was transferred to the intensive care unit.

Patient condition continued to deteriorate despite all medications and intervention given, and she subsequently died after 31 days of admission.

DISCUSSION

The word *amylon* was first used in 1834 by the German Botanist Mathias Schleiden[1] to describe the waxy starch in

plants. Rudolph Virchow then coined the word 'amyloid' in 1854 to describe tissue deposits that stained like cellulose when exposed to iodine.[1]

Amyloidosis is a protein mis-folding in which soluble proteins aggregate as insoluble amyloid fibrils. These structures cause functional and structural organ damage respectively. [1,4]

Approximately, sixty heterogeneous amyloidogenic proteins have been identified, 27 of these associated with known human disease. [2] The unifying feature of these proteins is their tendency to form β-pleated sheets aligned in the parallel fashion. These sheets then form rigid, non-branching fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress, in affected organs such as the heart, liver, kidney and gastrointestinal tract, [4] as in this case. Our index patient had amyloidosis affecting kidneys, heart, adrenal gland, lungs and the liver.

The common types of systemic disease are light chain (AL), inflammation (AA), dialysis (Aβ2M), hereditary and old age (ATTR).[4]

There are three major forms of amyloidosis.[5]

1. Primary amyloidosis, which is the most common form, it occurs *de novo* and most often affects the heart, lungs, skin, tongue, nerves and intestine as in this case
2. Secondary or acquired amyloidosis, which is associated with chronic diseases such as tuberculosis, rheumatoid arthritis or osteomyelitis. It most often affects the kidneys, spleen, liver and intestine. If the underlying disease is treated, this form of amyloidosis will resolve. There was no evidence of any of these in this patient
3. Hereditary amyloidosis, which runs in families. This type often affects the nervous and digestive system.

Our patient had primary AL amyloidosis with no known hereditary component.

In the eight cases of multisystem, amyloid reported in 4235 autopsies (0.2%) at UCH Ibadan between 1970 and 1979. Seven cases showed the organ distribution associated with secondary amyloid, involving kidney, spleen and the liver. Five cases were associated with tuberculosis, and in two, there was no identifiable cause.[3] There appears to be a low incidence of amyloidosis in Africans, despite the occurrence of a large number of potential amyloidogenic stimuli, indicating the importance of individual host reactivity and failure of amyloid degradation in the causation of amyloidosis.

The presentation is protean and can be easily missed as in this case which leads to late diagnosis.

Close to 90% of patients will have fatigue, weight loss and oedema. [5] As in this patient, oedema may have multiple causes, including hypoalbuminaemia and right heart failure. [5]

Cardiac involvement has been reported in up to 30%–50% of symptomatic heart failure in 25%–30%[5,6] of cases.

Features of adrenocortical insufficiency may be masked by those of renal failure such as anorexia, nausea, vomiting, weight loss, hyperkalaemia and metabolic acidosis.[7] The renal function was essentially preserved until late in the course of the illness. Amyloid-related adrenal dysfunction is an insidious process which may remain subclinical for a long time although amyloid deposits are frequently found in the adrenal glands of patients with reactive systemic amyloidosis at autopsy.[7,8] Clinical diagnosis of adrenal insufficiency has been reported to be uncommon.[9] In three studies, only one of 48,[9] two of 124[6] and one of 19[10] patients with renal amyloid were thought to have features suggesting hypoadrenalism. However, the use of synacthen stimulation test for the assessment of adrenal function[11,12] has clearly shown that adrenal insufficiency may be more common in these patients. Two groups of researchers reported diminished adrenocortical reserve in approximately 50% of patients with renal amyloidosis.[13,14] Another group has reported similar findings in patients with familial amyloid polyneuropathy.[15]

In the last few years, immunomodulatory drugs such as thalidomide and lenalidomide and the proteasome inhibitor bortezomib have dramatically changed the outcome of treatment for multiple myeloma and are increasingly being applied to amyloidosis as was used in this patient.[16,17] These medications are helpful if commenced early; however, this patient was diagnosed late and this may be responsible for the poor outcome.

Bortezomib alone has been reported to show overall response rate of 50%, with better response with the addition of dexamethasone (54%–80%)[16-18] In this patient, methyl prednisolone 500 mg was given, but the response was poor most likely because the diagnosis was made very late. In those judged eligible, the most effective treatment for amyloidosis may be autologous heamatopoietic stem cell transplantation.[18]

In conclusion, systemic amyloidosis is rare and the presentation is protean leading to late diagnosis. There is a need for a high index of suspicion for such rare conditions, particularly when symptoms appear strange and diagnosis unclear. Histological staining facilities should be made available.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, *et al*. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010;17:101-4.
2. Kyle RA. Amyloidosis: A convoluted story. Br J Haematol 2001;114:529-38.
3. MacIver AG, Thomas SM. Protein AA amyloidosis in Nigeria. J Trop Med Hyg 1982;85:209-12.
4. Merlini G, Balloti V. Molecular mechanism of amyloidosis. N Eng J Med 2003;349:583-96.
5. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, *et al*. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998;91:141-57.
6. Browning MJ, Banks RA, Tribe CR, Hollingworth P, Kingswood C, Mackenzie JC, *et al*. Ten years' experience of an amyloid clinic – A clinicopathological survey. Q J Med 1985;54:213-27.
7. Heller EL, Camarata SJ. Addison's disease from amyloidosis of adrenal glands. Arch Pathol 1950;49:601-4.
8. Brandt K, Cathcart ES, Cohen AS. A clinical analysis of the course and prognosis of forty-two patients. Am J Med 1968;44:955-69.
9. Triger DR, Joekes AM. Renal amyloidosis, a fourteen years follow up. Q J Med 1973;165:15-40.
10. Ogg CS, Cameron JS, Williams DG, Turner DR. Presentation and cause of primary amyloidosis of the kidney. Clin Nephrol 1981;15:9-13.
11. May EM, Carey RM. Rapid adrenocorticotropic hormone test in practice. Am J Med 1985;79:679-83.
12. Clayton RN. Diagnosis of adrenal insufficiency. Br Med J 1989;298:271-2.
13. Danby P, Harris KP, Williams B, Feehally J, Walls J. Adrenal dysfunction in patients with renal amyloid. Q J Med 1990;76:915-22.
14. Arik N, Tasdemir I, Karaaslan Y, Yasavul U, Turgan C, Caglar S. Subclinical adrenocortical insufficiency in renal amyloidosis. Nephron 1990;56:246-8.
15. Olofsson BO, Grankvist K, Boman K, Forsberg K, Lafvas I, Lithner F. Assessment of thyroid and adrenal function in patients with familial amyloidotic polyneuropathy. J Intern Med 1989;225:337-41.
16. Palladini G, Perfetti V, Perlini S, Obici L, Lavatelli F, Caccialanza R, *et al*. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105:2949-51.
17. Reece DE, Sanchorawala V, Hegenbart U, Merlini G, Palladini G, Fermand JP, *et al*. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: Results of a phase 1 dose-escalation study. Blood 2009;114:1489-97.
18. Wechalekar AS, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Efficacy of bartozemib in systemic AL amyloidosis with relapse/refractory clonal disease. Heamatologica 2008;93:295-8.