CASE REPORT

A young patient with recurrent respiratory tract infection and anasarca

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koshussain@dha.gov.ac**SUMMARY**

A young man with a history of recurrent respiratory tract infections for the past 8 years presented with generalised anasarca. He was found to have advanced renal disease (stage 4) and a profound proteinuria of 82.9 g/day. Further workup revealed the presence of advanced bronchiectatic changes in the lungs. Rectal biopsy showed the characteristic pattern of amyloid deposition. A diagnosis of systemic amyloidosis secondary to bronchiectasis was made. To the best of our knowledge no other cases of bronchiectasis-associated renal amyloid disease with such marked proteinuria have been reported in the literature. Our patient had a relatively short duration between the onset of his symptoms related to underlying bronchiectasis and his clinical presentation of renal amyloidosis. He had an aggressive course of disease and unfortunately died at a very young age.

BACKGROUND

To the best of our knowledge no other cases of bronchiectasis-associated renal amyloid disease with such marked proteinuria have been reported in the literature. Our patient had a relatively short duration between the onset of his symptoms related to underlying bronchiectasis and his clinical presentation of renal amyloidosis. He had an aggressive course of disease and unfortunately died at a very young age.

CASE PRESENTATION

A 26-year-old Pakistani man presented with a 2-week history of fatigue, productive cough, progressive dyspnoea and generalised body swelling. There was no associated fever, haemoptysis, night sweats and weight loss or pleuritic chest pain. He was dyspnoeic with less than the usual level of daily activity (New York Heart Association NYHA class III) with mild orthopnoea. Two weeks previously he had noticed that he was developing periorbital puffiness on waking up, which gradually progressed to generalised body swelling.

The patient's medical history was remarkable for recurrent episodes of fever and productive cough for the past 8 years for which he had received multiple courses of oral antibiotics from his general practitioner. However, he could not recall which antibiotics he had actually received. He was never admitted to a hospital, nor was he investigated for his recurrent respiratory symptoms. He had undergone a set of routine laboratory investigations 3 years previously, which included a renal function test. He was told that the results were normal. He

did not have a history of chronic diarrhoea, steatorrhoea, diabetes, joint pain or rash. There was no occupational exposure to any toxin, no history of tuberculosis and no significant childhood illness. Other family members were healthy. He was a non-smoker and denied alcohol consumption.

On examination his blood pressure was 90/55 mm Hg, heart rate was 120 bpm, respiratory rate was 30 breaths/min, oxygen saturation was 95% in room air and he was afebrile. He appeared ill and in respiratory distress. He had digital clubbing but no other skin changes. Examination of the cardiovascular system revealed elevated jugular venous pressure and a gallop rhythm. Bilateral coarse inspiratory and expiratory crepitation was noted on chest auscultation. He also had bilateral pedal oedema up to the knees with ascites and bilateral hydroceles.

INVESTIGATIONS

His routine laboratory parameters are shown in table 1 and renal parameters are shown in table 2.

Chest X-ray showed bilateral blunting of costophrenic angles with multiple cystic air spaces and tram-track lines. The cardiothoracic ratio was normal. These changes were suggestive of bronchiectatic changes (figure 1). Chest CT confirmed the same findings (figure 2). It showed multiple bilateral segmental air-filled cystic structures, some of which showed air-fluid levels. The routine cultures were negative for any particular organism.

An ECG showed low-voltage complexes. An echocardiogram revealed a moderately dilated right ventricle with impaired right ventricular function and mild pericardial effusion. There was mild thickening of the intraventricular septum (12 mm). The ejection fraction was 55% and pulmonary artery pressure was 40 mm Hg. However, no 'granular sparkling' was observed. These findings were attributable to the long-standing involvement of the respiratory system.

An abdominal ultrasound scan revealed normal-sized liver, spleen and kidneys. The right kidney measured 10.9 cm while the left kidney measured 11.1 cm. However, both kidneys had increased echogenicity of the renal cortex with poor corticomedullary differentiation (figure 3).

Doppler of the lower limbs did not show any evidence of deep venous thrombosis. An ultrasound scan of the thyroid gland did not show thyromegaly.

The serum electrophoresis result was as follows: low albumin, highly increased α 2 globulins and decreased γ globulins.

In summary, our patient had sepsis secondary to bronchiectasis exacerbation with new-onset

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Table 1 Routine laboratory parameters at the time of admission

Laboratory parameter	Patient's result
WBC	18.5×10 ³ /μL (75% neutrophils)
Hb	8.9 g/dL (normocytic normochromic)
Platelet	788×10 ³ /μL
PT	15.3 s (11–14)
APTT	70 s (28–41)
D-dimer	1.1 mg/L (<0.5)
Pro-BNP	8548 pg/mL
ESR	117 mm/h
CRP	64 mg/dL
PCT	1.02 pg/mL
Blood culture	Negative
Liver function test	Liver enzymes: normal Albumin: 0.8 gm/dL (3.4–4.8) Globulin: 2.0 gm/dL
Lipid profile	Total cholesterol 212 mg/dL LDL 148 mg/dL HDL 38 mg/dL TG 162 mg/dL
Thyroid function test	TSH 7.26 uIU/mL (0.3–4.2) T3 1.9 pmol/L (2.8–7.1) T4 6.7 pmol/L (11.0–22.0) Anti-thyroglobulin, TPO: negative
HIV, HBsAg, HCV	Negative
Fasting glucose	90 mg/dL
Post prandial glucose	Persistently <140 mg/dL
HBA1c	5.3%

APTT, activated partial thromboplastin time; BNP, pro-brain natriuretic peptide; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HBA1c, glycosylated haemoglobin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PT, prothrombin time; TG, triglycerides; TPO, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; WBC, white blood cells.

Table 2 Renal function tests at the time of admission

Laboratory parameters	Patient's results
Urea	64 mg/dL (12–40)
Creatinine	3.0 mg/dL
Creatinine clearance	15 mL/min
Sodium	131 mmol/L (136–145)
Potassium	3.1 mmol/L (3.3–4.8)
Calcium	6.7 mmol/L (8.6–10.2)
Phosphate	6.3 mmol/L (2.7–4.5)
Urine routine	Hyaline and granular casts RBC 0–5 WBC 4–6 Protein by dipstick 3+ Glucose 3+
Urine culture	Negative
Protein random urine	684.9 mg/dL
24 h urine protein	82.9 gm/day
Albumin/creatinine ratio	36095.5 mg/g (<20)
Autoimmune antibodies	Rheumatoid factor, ANF, anti-DNA, c-ANCA, p-ANCA, ENA profile: negative
Complement	C3 0.54 (low) C4 0.30 (normal)

ANF, antinuclear factor; c-ANCA, cytoplasmic-antineutrophil cytoplasmic antibody; ENA, extractable nuclear antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; RBC, red blood cells; WBC, white blood cells.

Figure 1 A chest X-ray showing bilateral bronchiectatic changes.

nephrotic syndrome and advanced renal failure. Even after resolution of sepsis, his renal parameters did not improve and he continued to have marked proteinuria and remained hypotensive. He also had laboratory features of hypothyroidism and right-sided heart dysfunction.

As the clinical and laboratory signs were suggestive of pathology with a multiorgan involvement in addition to bronchiectasis, suspicion was raised for secondary amyloidosis. A rectal biopsy was arranged. The biopsy result showed apple-green birefringence when viewed under polarised light after staining with Congo red (figure 4). The patient was diagnosed with systemic amyloidosis secondary to bronchiectasis with renal, thyroid and possibly cardiac involvement. The patient was offered a kidney biopsy, but declined it as he preferred to travel to his home country for further workup.

DIFFERENTIAL DIAGNOSIS

- ▶ Renal failure as a result of recurrent courses of antimicrobial agents
- ▶ Renal failure from sepsis
- ▶ Infectious glomerulonephritis
- ▶ Minimal change disease
- ▶ Systemic amyloidosis secondary to bronchiectasis
- ▶ Amyloid-associated cardiomyopathy causing low blood pressure and thus renal failure.

Figure 2 High-resolution CT scan revealed the presence of multiple bilateral cystic structures with air-fluid levels, which was suggestive of bronchiectasis exacerbation.

Figure 3 An ultrasound scan of the right kidney (measuring 10.9 cm) with poor corticomedullary differentiation.

TREATMENT

Our patient was initially admitted to the intensive care unit due to hypotension and respiratory distress. He was started on inotropes and a broad spectrum antibiotic due to presumed sepsis. His general condition improved and the raised inflammatory markers gradually returned to normal levels after a week. However, his blood pressure continued to remain in the lower range. In spite of aggressive albumin infusion, his serum albumin level never rose above 1.5 gm/dL. He continued to have profound proteinuria and severe oedema that was refractory to diuretics and colloid administration.

OUTCOME AND FOLLOW-UP

He was kept in hospital for 2 weeks. The need for renal replacement therapy was explained to the patient; however, he opted to return to his home country for further management. At discharge he was clinically stable. Unfortunately he died after 2 months in his home country. We could not confirm the cause of death.

DISCUSSION

Amyloidosis is a heterogeneous group of disorders that result from extracellular deposition of insoluble fibrillar proteins that leads to organ dysfunction and subsequently organ failure.¹

Figure 4 Rectal biopsy showed apple-green birefringence when viewed under polarised light after staining with Congo red.

Amyloidosis is classified based on whether there is a localised or systemic involvement. It can be primary, secondary or inherited.

Amyloid A (AA) amyloidosis is a type of secondary systemic amyloidosis that is due to chronic inflammatory, infectious or neoplastic conditions. Serum amyloid A protein, an acute phase reactant, is the precursor protein found in this subtype.² In the developed countries, the most common cause of secondary amyloidosis is rheumatological conditions.^{3 4} However, in the developing parts of the world, it is not uncommon to still encounter infectious aetiologies as the underlying causes in patients with AA amyloidosis.

We have described the case of a young patient with bronchiectasis who presented with advanced renal failure, massive proteinuria of >80 g/day and other multisystem involvement. Although the right-sided cardiac involvement could be attributed to the chronic lung disease, nevertheless amyloid heart disease could not be definitely ruled out. Regarding the thyroid involvement, since the thyroid antibodies were negative, it was clinically suspected that the hypothyroidism was also due to amyloid infiltration of the thyroid gland. Systemic amyloidosis in this case would explain the persistent hypotension which could be due to autonomic neuropathy. Although a renal biopsy could not be performed, as advanced renal failure, nephrotic syndrome, normal kidney sizes and multiorgan involvement were present, renal amyloidosis remains the most probable differential diagnosis in this case.

Secondary AA amyloidosis occurs in the setting of a chronic inflammatory condition. In general, the duration between the symptomatic inflammatory state and the clinical onset of amyloidosis is frequently prolonged, lasting for more than two decades.⁵ The average age at presentation is generally in the fourth decade of life.⁴ However, progression of the disease can be very rapid. Our patient had a relatively short duration of respiratory symptoms and very rapid progression of his illness.

Although amyloid fibrils are deposited in many organs, the predominant manifestation of systemic AA amyloidosis is renal involvement.⁵ On the other hand, cardiac amyloidosis, amyloid goitre, coagulation derangements and autonomic neuropathy are relatively uncommon findings in this condition.^{5–8} Amyloid renal disease may manifest as nephrotic syndrome and/or renal failure.³ Another uncommon manifestation is acquired Fanconi syndrome due to deposition of amyloid in the proximal convoluting tubules.⁹ This might explain the presence of glycosuria in spite of a normal blood glucose level. Another interesting aspect of renal amyloidosis is that it is uncommon to find elevated blood pressure, even in the presence of severe renal failure. In fact its presence is indicative of vascular involvement in amyloidosis.¹⁰ Proteinuria in renal amyloidosis is known to range from subnephrotic to massive proteinuria that can be as high as 20–30 g/day.¹⁰ Our patient presumably had AA amyloidosis and presented with a massive proteinuria of >80 g/day, because of which he was grossly oedematous. To the best of our knowledge, no previous cases of secondary amyloidosis with such high levels of proteinuria have been reported in the literature. Massive proteinuria (>10 g/day) is commonly associated with disease states that have excessive amounts of relatively freely filtered plasma proteins, such as immunoglobulins in multiple myeloma. These proteins overcome the resorptive capacity of the renal tubules and so are leaked into the urine. Therefore cases with such marked proteinuria are more often associated with primary amyloid light-chain amyloidosis rather than secondary AA amyloidosis.¹¹

The rate of decline in renal function is correlated to serum albumin and 24 h urinary albumin.⁴ A cohort study by Lachmann *et al*⁵ identified older age, reduced serum albumin, and end-stage renal failure at baseline as markers of poor prognosis. Since renal function is closely correlated with survival in AA amyloidosis, there should be a high index of suspicion in the diagnosis of these cases with prompt referral to the nephrologist.

Unfortunately very little is known about the clinical course and optimal management in cases of advanced renal disease that occurs in bronchiectasis-associated amyloidosis, with experience being limited to scattered case series in the literature. In a small cohort study by Akçay *et al*,⁶ the mean age at diagnosis and the duration of symptomatic bronchiectasis were reported as 50.6 ± 13.5 years and 22.18 ± 12.02 years, respectively.

The marginally low level of complement (C3) in our patient is not typical of renal amyloidosis. However, the low levels can be explained by consumption of complement factors during activation of the complement system in sepsis.¹²

Treatment in cases of amyloidosis is generally directed towards stopping the excess production of the protein precursor and disruption of the already deposited amyloid proteins. In cases of AA amyloidosis, the primary aim of treatment is to control the underlying inflammatory state.^{5 13} In patients with underlying bronchiectasis, therapy may be directed towards the judicious use of antimicrobial agents, postural drainage and lung transplantation as a final resort.¹⁴ Turgut *et al*¹⁵ reported a case of AA amyloidosis secondary to bronchiectasis with severe proteinuria that was managed by bilateral renal artery embolisation to prevent the loss of albumin. Another option for patients with end-stage renal disease is renal transplantation, which has been shown to improve survival.^{16 17} Dember *et al*¹⁸ performed a multicentre, randomised, double blind, placebo-controlled trial to evaluated the use of eprodisate in patients with AA amyloidosis

with kidney involvement. They concluded that the risk of worsening renal function and the rate of decline in creatinine clearance was lower in patients who were treated with eprodisate. However, this medication had no significant effect on the risk of progression to end-stage renal disease or death.

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Learning points

- Amyloidosis is a rare complication of a chronic inflammatory state that can result in multiorgan dysfunction.
- A diagnosis of amyloid A amyloidosis should be considered in patients who present with proteinuric renal failure with a background of a chronic inflammatory state.
- Early diagnosis is essential because patients with advanced disease are generally unable to undergo intensive therapy.

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