

Amyloidosis complicating cystic fibrosis

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Abstract

Two patients with cystic fibrosis developed acute onset nephrotic syndrome and died within three months of presentation. Examination of renal biopsy specimens indicated amyloid. The onset of proteinuria or a fall in baseline renal function should alert the physician to this rare complication.

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Secondary amyloidosis is a recognised but extremely rare complication of cystic fibrosis, only 21 cases having been reported in the world literature since the disease was first described in 1938. Renal involvement is a frequent and devastating feature of amyloidosis in these patients and portends a very poor prognosis.¹ Since the establishment of our unit in 1977 over 200 young adults have attended. We now report our first two patients with this complication.

Case 1

This male patient was diagnosed as having cystic fibrosis in 1973 at the age of 8. He had minimal symptoms throughout childhood and adolescence and first required hospitalisation in 1986 at the age of 21. He had established bronchiectasis complicated by recurrent right sided pneumothoraces and respiratory tract infections.

In September 1991 at the age of 26 he was admitted to hospital with pneumonia. Urinalysis showed +3 proteinuria of recent onset; a urinalysis performed three months previously had shown no protein. He had grade 3 clubbing and evidence of left upper lobe consolidation. There was no goitre, hepatosplenomegaly, or oedema. Spirometric measurements showed airflow obstruction with an FEV₁ of 0.89 l (21% predicted) and an FVC of 2.01 l (43% predicted).

The results of laboratory investigations showed an erythrocyte sedimentation rate of 113 mm in the first hour, urea 11.4 mmol/l, creatinine 204 µmol/l, and albumin 26 g/l. Urine microscopy was normal. The 24 hour urinary protein excretion was 10 g, serum cholesterol 5.8 mmol/l, and glomerular filtration rate 24 ml/min. Chest radiography confirmed the presence of left upper lobe consolidation. A multiresistant strain of *Pseudomonas cepacia* was cultured from the sputum. Abdominal ultrasonography showed

enlarged kidneys but the liver and spleen were of normal size. Examination of a renal biopsy specimen showed amyloid type AA on immunocytochemical staining (fig).

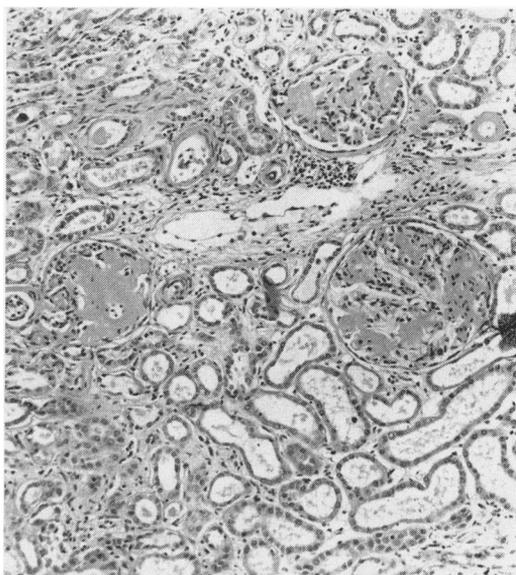
Renal and respiratory function deteriorated over the following weeks. Terminally he developed a right sided pneumothorax, pneumomediastinum and subcutaneous emphysema, and he died 41 days after admission. Post mortem examination showed considerable hepatosplenomegaly. There were extensive amyloid deposits in kidneys, spleen, liver, thyroid, adrenal glands, rectum, and lung.

Case 2

In December 1991 an 18 year old girl with cystic fibrosis was admitted for evaluation of a one month history of progressive ankle oedema. Cystic fibrosis had been diagnosed at the age of 6 when she presented with recurrent respiratory tract infections. She required frequent hospitalisation during childhood and adolescence with infective exacerbations of bronchiectasis and was treated for pulmonary tuberculosis at the age of 16.

On examination she was pale, cachectic, and tachypnoeic. Urinalysis showed recent onset +3 proteinuria which had not been present three months previously. She had gross clubbing. Wheezes and crackles were audible throughout both lung fields. There was pitting oedema of both lower extremities. No goitre or organomegaly was noted. Spirometric measurements showed an FEV₁ of 2.04 l (64% predicted) and an FVC of 2.67 l (74% predicted).

The results of laboratory studies were: haemoglobin 9 g/dl, erythrocyte sedimentation rate 142 mm in the first hour, creatinine 62 µmol/l, albumin 13 g/l, cholesterol 9.1 mmol/l, 24 hour urinary protein excretion



Section of kidney showing extensive deposition of amyloid in glomeruli and around vessels. Stain: haematoxylin and eosin.

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14.1 g, and glomerular filtration rate 66 ml/min. *Pseudomonas aeruginosa* grew from sputum cultures. Ultrasonography of the kidneys was normal. Examination of renal biopsy samples showed amyloid.

She was started on a low dose diuretic to control her oedema and discharged from hospital 10 days later. Her overall condition progressively deteriorated at home and she died two months later. Post mortem examination was not performed.

Discussion

Secondary amyloidosis occurs in patients with chronic infectious and inflammatory disease.^{2,3} It is an exceedingly rare complication of cystic fibrosis but should be suspected in patients with unexplained proteinuria, goitre, or hepatosplenomegaly.

Mild proteinuria is not an infrequent finding in young adults with cystic fibrosis.³ However, proteinuria above 1 g/24 hours is rare and warrants further investigation for amyloid. All reported patients with cystic fibrosis related amyloid had evidence of renal disease at necropsy and renal failure contributed significantly to death in most cases.

Our two patients presented with acute onset nephrotic syndrome. One of the unique aspects of these cases was that neither patient had evidence of proteinuria three months previously as outpatients on standard dipstick (Multistix) urinalysis. They both died shortly after diagnosis. Patient 1 developed rapidly fulminant renal failure and had evidence of

widespread amyloid deposition at post mortem examination. This included massive hepatosplenomegaly of which there had been no radiographic evidence at the time of presentation six weeks previously.

Amyloidosis is a surprisingly rare complication of cystic fibrosis, given the chronic inflammatory nature of the condition and the fact that all patients eventually develop marked bronchiectasis. While it has been suggested that undetected cases may explain the apparent rarity of the association, this has not been borne out by retrospective pathological studies.⁴ It is probable that, in the past, the very short life expectancy of patients with cystic fibrosis allowed insufficient time for the development of this complication.

The median life expectancy of children born with cystic fibrosis has improved considerably.⁵ With this improved survival the pattern of disease complication is likely to change. We feel that amyloidosis complicating cystic fibrosis is likely to be seen with increasing frequency as life expectancy improves further.

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