Resolution of nephrotic syndrome caused by amyloidosis following surgery for Crohn's disease

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CASE REPORT

A 16-year-old apprentice electrician was referred with nephrotic syndrome. He had a 3-month history of swelling of the ankles, eyelids and face. Asthma had been diagnosed at the age of 11 years and had been treated with inhaled salbutamol and beclomethasone. As a young child he had also required intermittent courses of oral prednisolone. In his mid teens he had been referred to his local paediatrician for investigation of short stature. Between the ages of 11 and 15 years his height and weight had fallen from the 92nd to the 12th and from the 85th to the 3rd centiles respectively. After investigation the growth retardation was attributed to his oral steroid use.

On examination he appeared well. Secondary sexual characteristics were absent, blood pressure was 100/70 mmHg, there was moderate ankle and periorbital oedema. No other abnormalities were detected. Investigations were as follows: 12.3 g urinary protein/24 hours, serum creatinine 95 mmol/litre, creatinine clearance 64 ml/min, serum cholesterol 7 mmol/litre, erythrocyte sedimentation rate 90 mm/hr, haemoglobin, 11.3 g/litre and mean corpuscle volume 69 fl. Tests for thyroid function, ferritin and iron studies, blood sugar, C-reactive protein, immunoglobulins and serum electrophoresis, complement levels, antinuclear antibody, extractable nuclear antigen antibodies, antineutrophil cytoplasmic antibodies and antiglomerular basement antibody were all normal or negative. The proteinuria was shown to be highly selective and he was treated empirically with prednisolone 40 mg daily, ranitidine 150 mg twice daily and frusemide 40 mg daily.

His nephrotic syndrome proved refractory to treatment and he was admitted with worsening leg oedema. The diuretic dosage was increased and with informed consent a percutaneous renal biopsy was performed. This showed glomerular deposition of structureless eosinophilic material in the mesangium that extended into the glomerular basement membrane. The material stained positive for amyloid by Congo red. Electron microscopy confirmed the presence of typical amyloid fibrils in the glomeruli, vessels and around the tubules. Histopathologically it was impossible to determine whether this was primary or secondary amyloidosis.

A search for causes of secondary amyloidosis was undertaken. In view of the history of asthma a salt sweat test and chest computed tomography were performed. These showed no evidence of cystic fibrosis or bronchiectasis respectively. Belatedly the patient mentioned that he had longstanding but intermittent central abdominal discomfort which he had always considered to be 'normal'. He had, however, noticed that it had improved while he was on steroid treatment. A subsequent barium meal and follow-through showed a tight elongated stricture of the terminal ileum of approximately 10–20 cm.

The patient was referred for right hemicolectomy. Preoperatively he was shown to have abnormal short and long synacten tests but the operation proceeded with hydrocortisone cover.

Two macroscopically typical lesions of Crohn's disease measuring 2 and 15 cm were found affecting the terminal ileum. The other abdominal organs and pelvis were normal. A routine right hemicolectomy was performed. The patient recovered from the operation uneventfully.

Histological examination of the terminal ileum showed a chronic transmural infiltrate with granulomata. The mucosa was ulcerated and fissured. Amyloid deposition was noted in the submucosal vessels (*Figure 1*).

His immediate postoperative course was uncomplicated. Over the following months and years his ankle oedema disappeared and he achieved sexual maturity. The proteinuria fell and when last measured, 4.5 years after the procedure, was 0.8g/24 hours (*Figure 2*). The serum albumin also rose to the normal range. His hydrocortisone was discontinued in 1995 following which a repeat short synacthen test was normal. Creatinine clearance rose to 110 ml/min. A repeat renal biopsy was considered to be unnecessary.

INTRODUCTION

Renal amyloidosis is generally regarded as a disease with a poor prognosis, which responds poorly to treatment and usually progresses rapidly to end-stage renal failure. The condition carries a significant mortality and morbidity. The authors report a case of renal amyloidosis, which presented as nephrotic syndrome, moderate renal failure, growth retardation, pubertal delay and hypoadrenalism in a 16-year-old boy. The disease was subsequently shown to be secondary to Crohn's disease of the terminal ileum. Complete resolution of oedema, proteinuria,

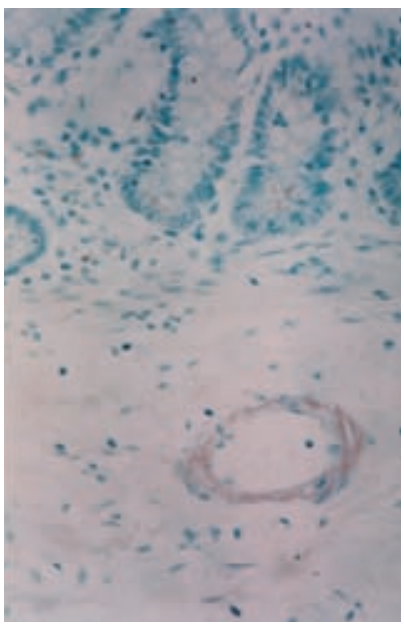

Figure 1. Section of resected small bowel, stained with Congo Red, showing amyloid deposition around a submucosal blood vessel.

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hypoalbuminaemia and renal impairment occurred following right hemicolectomy. In addition the patient attained full sexual maturation.

DISCUSSION

The association between inflammatory bowel disease (IBD) and systemic reactive (AA) amyloidosis was first noted in 1948 (Cohen and Fishman, 1949). Clinically amyloidosis complicating IBD is much rare; in Greenstein's series of over 3 000 IBD patients there was a total incidence of systemic amyloidosis of less than 1% (Greenstein et al, 1992). Amyloidosis appears to complicate ulcerative colitis less frequently than Crohn's disease (Shorvon, 1977). No consistent factors predisposing patients with chronic inflammatory disease to amyloidosis have been identified (Hawkins et al, 1998). However, male patients with suppurative complications of Crohn's disease are more commonly affected (Greenstein et al, 1992).

Regression of AA amyloid following both medical and surgical treatment of the underlying inflammatory condition has been consistently reported in rheumatoid arthritis and osteomyelitis (Gertz and Kyle, 1991). Therefore the rationale for the treatment of amyloidosis complicating Crohn's disease with surgery seems to be intuitively correct.

Early reports were disappointing with high perioperative mortality (Wallenstein et al, 1966). Fitchen reported the index success (Fitchen, 1975). This was of a 28-year-old male patient who presented with nephrotic syndrome and ileocaecal Crohn's disease. Renal biopsy confirmed amyloid within the glomeruli. He underwent a right hemicolectomy with subsequent remission of both the IBD and nephrotic syndrome, which has been maintained over 19 years (Mandelstam et al, 1989). Repeat renal biopsy has confirmed marked histological improvement of amyloidosis, although only one intact glomerulus was obtained.

Rashid et al (1980) reviewed published reports of Crohn's disease complicated by amyloidosis between 1949 and 1979. There were 28 patients and fourteen resections of affected bowel. Six died in the immediate postoperative period and a further four required indefinite renal replacement therapy. In only one (Fitchen's case) was the amyloid unequivocally shown to regress.

Therefore it appears that these patients appear a particularly poor surgical risk. However in Rashid's series the 14 patients that did not undergo surgery also fared badly; eight died within 6 years, and one was alive on haemodialysis. The outcome was unknown in three. Given that the number of published cases is small, it is unlikely that definite predictors of surgical outcome will be identified.

It is possible that the high perioperative death rate is secondary to undiagnosed adrenal dysfunction. In one series of sixteen systemic amyloidosis patients tested seven were shown to have adrenal dysfunction (Danby et al, 1990). The authors advocate preoperative testing in all amyloid cases. HM

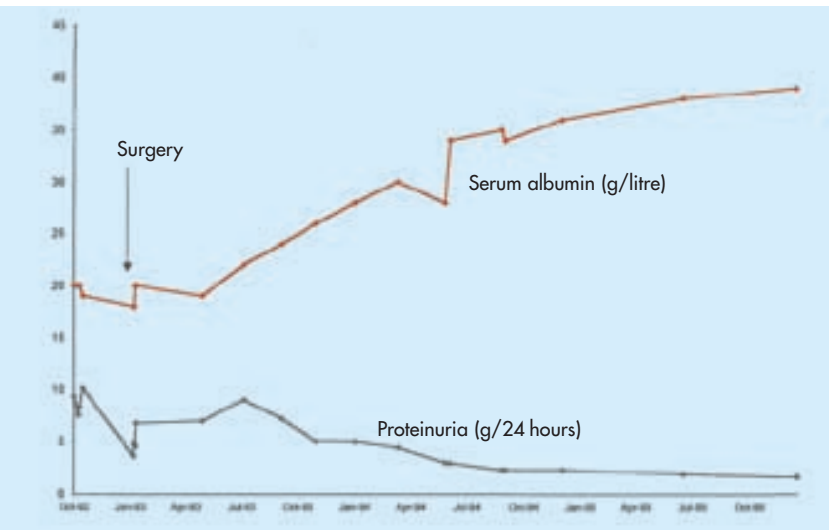

Figure 2. Resolution of proteinuria and hypoalbuminaemia following right hemicolectomy.

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