Adult α_1 -antitrypsin deficiency

E. C. SWEENEY

From the Department of Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W12

SYNOPSIS Three adults with α_1 -antitrypsin deficiency are described. In two of the cases the deficiency was genetically determined (cases 1 and 2), and each demonstrated unusual features of the disease. The liver in case 1 (homozygous) showed cholangiolar hyperplasia which has been recorded only once before. Case 2 (heterozygous) had emphysema and cirrhosis, a combination not previously documented in a heterozygote, in addition to malabsorption. Case 3 represents a case of spurious α_1 -antitrypsin deficiency with cirrhosis included to emphasize the diagnostic importance of phenotyping in such cases.

The rôle of α_1 -antitrypsin (α_1 AT) deficiency in the aetiology of early onset pulmonary emphysema and juvenile hepatic cirrhosis has been well established (Williams and Fajardo, 1974). Recent reports have shown that deficiency of this glycoprotein enzyme inhibitor may be associated with cirrhosis in older age groups also (eg, Ishak *et al*, 1972; Kumar *et al*, 1974). We present here the case histories of three adult patients with α_1 -AT deficiency which demonstrate unusual features of this disorder.

Case Reports

CASE 1

A 60-year-old woman gave a history of repeated episodes of 'bronchitis' as a child followed by a symptom-free adolescence and early adult life. She started smoking in late adolescence and smoked 10 cigarettes daily. Recurrent bronchitic episodes developed at the age of 40 years, and 10 years later she presented with severe breathlessness and purulent sputum. A plain radiograph of the chest showed cardiac enlargement with increase in the size of pulmonary arteries, a low flattened diaphragm, and emphysematous lung fields. Frequent bouts of chest infection accompanied by progressive deterioration in lung function occurred during the ensuing eight years, and ultimately she was admitted with respiratory failure and cor pulmonale. She improved with standard treatment but was noted to have a five-finger non-tender hepatomegaly. At the time of discharge from hospital her vital capacity was 2.05 l, forced expired volume in one second 0.5 l, and

P_vCO_2 58 mmHg. Her terminal admission was with acute on chronic respiratory failure. She was grossly cyanosed and hypercapnoeic (P_vCO_2 95 mmHg) and demonstrated tender five-finger hepatomegaly. On admission respiratory arrest developed and intermittent positive pressure ventilation was begun. Culture of a bronchial aspirate yielded a growth of *Staphylococcus aureus*. The patient became clinically jaundiced with a serum bilirubin of 1.6 mg% and alkaline phosphatase of 14 King-Armstrong units (140 iu). There was a very low α_1 globulin level and the serum α_1 -AT level was 0.23 g/l. The patient became unrousable and died.

Necropsy

The body was that of a slightly icteric elderly woman. The heart weighed 500 g and demonstrated severe right ventricular hypertrophy. There was diffuse centrilobular emphysema in both lungs and extensive atheroma in the pulmonary arteries. The liver weighed 1345 g and had smooth, yellowish-brown capsular and cut surfaces. The remainder of the postmortem examination was unremarkable. Microscopy of the lungs confirmed the presence of centrilobular emphysema. In the liver there was remarkable cholangiolar proliferation without evidence of bile stasis or cirrhosis (fig 1). Staining of diastase-treated sections by periodic-acid Schiff technique (SSD) revealed masses of globular intracytoplasmic inclusions in the hepatocytes mainly adjacent to the portal tracts (fig 2).

CASE 2

A 50-year-old man gave a history of chronic bronchitis from the age of 40 years. He smoked 10-15

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Fig 1 *Case 1.*
Demonstrating
cholangiolar
hyperplasia.
SSD × 160
(approx)

Fig 2 *Case 1.*
Intracytoplasmic
globules in the
liver. SSD × 160
(approx)

Fig 3 Case 2. *Partial villous atrophy.*

cigarettes and drank 3-4 pints of beer daily for many years. At the age of 48 years he had developed cor pulmonale. One year later steatorrhoea became manifest accompanied by weight loss and abdominal distension. After a further year the patient was admitted to hospital for investigation. Physical examination revealed clubbing of the fingers, hepatosplenomegaly, and evidence of emphysema. While in hospital he developed a left pneumothorax and a chest radiograph after drainage demonstrated bilateral basal bullous emphysema. A jejunal mucosal biopsy showed partial villous atrophy (fig 3). Faecal fat excretion was 60 g/24 hours but excretion of d-xylose was 5.4 g in 5 hours after a 25 g oral dose. A needle biopsy of the liver revealed some infiltration of the portal tracts by chronic inflammatory cells and accumulation of SSD positive globules within the hepatocytes (fig 4). Serum protein electrophoresis demonstrated a low albumin, a lack of rise in α_2 globulin, and a raised γ globulin, with β/γ fusion, typical of cirrhosis. The α_1 globulin was low, and measurement of α_1 -AT yielded a value of 1.2 g/l, suggesting that the patient was heterozygous for the deficiency. An attempt was later made to determine the patient's genotype but unfortunately the serum had deteriorated on storage. A barium meal and follow-through examination showed loss of mucosal pattern and dilatation of the upper jejunum with some thickening of the bowel wall and a small area of ulceration in this region. The patient was discharged on a gluten-free diet in addition to digoxin and diuretics. At subsequent reviews there was little change in the patient's jejunal biopsy or faecal fat excretion.

Two months after discharge the patient was readmitted with a perforation of the mid-jejunum. At

laparotomy the liver was noted to be slightly enlarged and pale, with an irregular surface. The spleen was of approximately normal size. The small bowel was generally distended but there was a 30 cm long constriction in the mid to lower jejunum with a mottled greyish serosal surface. In the centre of this was a 3 mm perforation. Two similar but shorter constricted segments were present elsewhere in the small bowel. The perforation was excised. Postoperatively the patient developed irreversible cardiac arrest.

Necropsy

The body was that of a wasted middle-aged man. There was widespread centrilobular emphysema, more marked in both lower lobes. The heart weighed 350 g and demonstrated moderate right atrial and right ventricular dilatation. In the abdomen the loops of small bowel were loosely adherent and covered with fibrinous exudate. The mucosa of the proximal jejunum was flattened, and at the jejuno-ileal junction there was a 12 cm long stricture showing the site of the previous perforation covered by an intact patch. Similar shorter constricted areas were present in the ileum. In these areas the bowel lumen was reduced to approximately one-half without thickening of the wall. Microscopy of the stenotic zones showed mucosal ulceration with massive submucosal infiltration by lymphocytes and plasma cells and formation of numerous lymphoid follicles. The muscularis propria was thickened. The liver weighed 2875 g and showed fine irregular nodularity of the capsular surface with a coarse trabecular pattern on the cut surface. Microscopy demonstrated portal fibrosis with prominent bile duct reduplication surrounding hyperplastic nodules

Fig 4 Case 2. Intracytoplasmic globules (arrowed) in liver. SSD $\times 200$ (approx)

Fig 5
Case 2.
Demonstrating proliferation of the small bile ducts in the liver. H and E $\times 120$

of hepatocytes (fig 5). Examination of multiple levels of this tissue failed to reveal any of the SSD positive material which had been seen on biopsy.

CASE 3

A 53-year-old man gave a history of one episode of malaise and loin pain with dysuria at the age of 40. He was asymptomatic for a further six years and was then hospitalized for investigation of nausea. Chronic renal disease with hypertension was diagnosed and the patient was treated with dietary restriction and antihypertensive drugs.

At the age of 50 years the patient was admitted for treatment of renal failure. Renal transplantation was not feasible because of donor incompatibility, and long-term haemodialysis was started. During the next three years the patient remained well but intractable hypochromic anaemia necessitated frequent transfusions (214 units over three years). Serum protein estimation before one of these transfusions showed a total of 6.1 g/100 ml with an albumin of 3.5 and a globulin of 2.6. Electrophoresis revealed a low α_1 globulin and the estimated level of α_1 -AT was 40-44 mg/100 ml. However, proteinuria

was present (110 mg/100 ml) and concentrated urine electrophoresis revealed a non-selective pattern with an excess of α_2 , γ and even β_2 compatible with severe proliferative glomerulonephritis (fig 6).

Skin pigmentation, testicular atrophy, and gynaecomastia gradually developed, suggesting progressive liver disease. A liver biopsy revealed increased amounts of fibrous tissue in the portal tracts and an abundance of haemosiderin pigment in both Kupffer and parenchymal cells. No SSD positive material was identified in the hepatocytes.

The arteriovenous shunt that had been inserted for haemodialysis became infected with *Pseudomonas aeruginosa*, and bacteraemia resulted in bacterial endocarditis and perforation of a mitral valve cusp. Replacement of the mitral valve was performed using a Starr-Edwards prosthesis but the patient suffered irreversible postoperative circulatory collapse and died.

Necropsy

The body was that of a thin pigmented middle-aged man with gynaecomastia and small atrophic testes. The heart weighed 570 g and showed moderate left ventricular hypertrophy. The mitral valve had been replaced by a prosthesis. The remaining valves were normal. Both lungs were oedematous but no emphysema was present. The liver weighed 2746 g and had a uniform yellowish colour with a strong positive staining reaction for iron on the cut surface. Both kidneys were small, each measuring 7.5 × 4 × 1.8 cm with numerous cortical cysts measuring 0.2-2 cm in diameter and an indistinct cortico-medullary demarcation. The remainder of the necropsy was unremarkable. Microscopically the liver showed essentially the same features as the previous biopsy but with hyperplasia of the parenchymal cells in the centre of the nodules. Again no SSD positive material was seen. Massive amounts of iron pigment were present not only in the liver but also in the spleen, lymph nodes, pancreas, and thyroid. The kidneys demonstrated gross reduction in the number of glomeruli but those which remained appeared normal. A minor degree of tubular atrophy was present also. The appearances were consistent with a longstanding focal glomerulitis.

Discussion

The low molecular weight glycoprotein α_1 -AT is synthesized in the liver and has the capacity to inhibit a variety of proteolytic enzymes. Different types of α_1 -AT exist which can be separated on the basis of their electrophoretic mobility. Twenty alleles constitute the Pi system (Fagerhol, 1971; Cook, 1974). The common genotype giving normal

Fig 6 Case 3. Superimposed urine and serum protein electrophoretic graphs. Note the disparity between the α_1 globulin levels.

levels of α_1 -AT (1.80 to 5.00 g/l) is PiMM whereas homozygously deficient individuals have the genotype PiZZ. In the latter cases the serum level of α_1 -AT is approximately 10% that of normal (less than 0.50 g/l). Intermediate levels are found in heterozygotes, in association with the Pi^s and Pi^p alleles, and zero levels may be found with the Pi^{null} allele (Talamo *et al*, 1973). Homozygous (PiZZ) individuals constitute approximately 0.1-0.2% of the general population whereas heterozygotes (PiSZ, PiMZ, PiMS, etc) constitute approximately 12%.

The diseases which have been associated with a deficiency of α_1 -AT are principally pulmonary emphysema of early onset (Eriksson, 1964) and juvenile hepatic cirrhosis (Sharp *et al*, 1969). It has been estimated that two-thirds of individuals homozygous for the deficiency will develop emphysema (Eriksson, 1965) but the reason why the remaining third do not develop it is obscure. Cirrhosis occurring in adult homozygous individuals has been described both with (Berg and Eriksson, 1972; Babb *et al*, 1973; Cohen *et al*, 1973) and without (Ishak *et al*, 1972; Kumar *et al*, 1974) emphysema. In heterozygous individuals emphysema does occur (Kanner *et al*, 1973; Stevens *et al*, 1971) and cirrhosis has also been described in two heterozygotes (Campra *et al*, 1973; Brand *et al*, 1974), but the combination of cirrhosis and emphysema in the heterozygous state has not been reported before. In the livers of all homozygously deficient individuals (Berg and Eriksson, 1972) the hepatocytes contain globular SSD positive intracytoplasmic masses of material antigenically similar to α_1 -AT. This suggests that release of the inhibitor from the cells is impaired and that this might in some way be due to abnormal molecular configuration of the variant antienzyme (Lieberman *et al*, 1972). The same authors and others (Gordon *et al*, 1972) also found intracytoplasmic globules in the livers of heterozygous patients with emphysema. The histological features of cirrhosis occurring in α_1 -AT deficiency are distinguishable from other forms of cirrhosis only by these intracytoplasmic globules.

Various facets of the three cases reported here are of interest:

CASE 1

This patient presented as a classical case of α_1 -AT deficiency with emphysema and developed clinical evidence of liver disease only terminally. The extremely low level of α_1 -AT in the serum indicated that the patient was homozygous for the deficiency, and the finding of intracytoplasmic globules in the liver was not unexpected. However, the histology of the liver was unusual, showing as it did pronounced cholangiolar hyperplasia without portal fibrosis or

bile stasis. Such an appearance has been described only once before (Gherardi, 1971) also in a homozygously deficient individual, but in that case the presence of intracytoplasmic globules was not recorded. Whether this represents an early stage in the development of cirrhosis or an alternative reaction to injury in this deficiency disease remains conjectural.

CASE 2

The initial development in this patient was emphysema. The aetiology of the malabsorption that subsequently developed is obscure as is its relationship to the α_1 -AT deficiency. The biochemical and histological evidence argues in favour of it being adult coeliac disease in which condition stricture formation and perforation of the small bowel have been recorded before (Bayless *et al*, 1967). It was unfortunate that the genotype of this patient could not be determined, but judging by the serum α_1 antitrypsin level he was heterozygous for the deficiency and probably represents the first heterozygous case in which both emphysema and cirrhosis have been recorded. A point of interest is the discrepancy between the amount of intracytoplasmic material seen in the initial needle biopsy and the lack of it in the postmortem material. This is at variance with the findings of other authors (Gordon *et al*, 1972) who noted that necropsy specimens of liver seemed to contain more α_1 -AT globules than biopsy specimens. They attributed this to α_1 -AT being an acute phase reactant and postulated that it is produced and (in its abnormal forms) accumulates to a greater extent in acutely ill patients.

CASE 3

This patient has been included in this report as a reminder that all that glitters is not gold. The low serum α_1 -AT level which fell within the homozygous range was not due to an inherent deficiency but to loss of the glycoprotein in the urine. Had this been a true case of α_1 -AT deficiency then the typical SSD positive globules would have been present in the liver. The hepatic cirrhosis was entirely explicable on the basis of excessive iron deposition.

To date four cases of renal disease have been recorded in association with α_1 -AT deficiency (Miller and Kuschner, 1969; Hobbs, 1971). The case of Miller and Kuschner appears to have been a genuine homozygously deficient individual who developed emphysema and some years later a necrotizing arteritis and glomerulonephritis with massive proteinuria. Strangely, the characteristic intracytoplasmic hepatic globules were not seen. To date the three cases recorded by Hobbs have not been described in sufficient detail to compare with our

case. Case 3 highlights the need for phenotyping and exclusion of protein loss in all apparent cases of α_1 -AT deficiency.

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Addendum

Since this paper was submitted for publication a case of adult α_1 -antitrypsin deficiency with intestinal mucosal atrophy, cirrhosis, and emphysema has been reported (Greenwald, A. J., Johnson, D. S., Oskvig, R. M., Aschenbrener, C. A., and Randa, D. C., α_1 -Antitrypsin deficiency, emphysema, cirrhosis and intestinal mucosal atrophy (1975) *J. Amer. med. Ass.*, **231**, 3; 273). The patient had a severe deficiency of the antienzyme (50 mg/100 ml) and gluten sensitive 'coeliac-like' disease. The authors speculate that the association is more than fortuitous.