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CASE REPORT

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Autoimmune enteropathy in infants

Pathological study of the disease in two familial cases

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Abstract In two brothers with autoimmune enteropathy there was total villous atrophy in the small intestine and marked lymphoid cell infiltration in the lamina propria of the entire digestive tract, discovered at autopsy in one of these patients. In addition, the pancreas showed diffuse interstitial infiltration by lymphocytes. The liver was enlarged, with extensive haematopoiesis and cholestasis. Similar lesions in the digestive tract were noticed in the second boy, but on immunosuppressive therapy his diarrhoea gradually disappeared. When he was 16 months of age, percutaneous biopsies showed moderately aggressive chronic hepatitis and a focal interstitial lymphoid infiltrate in the kidney. After 3 years of immunosuppressive therapy (prednisone, cyclosporin), the child ate well and total parenteral nutrition was discontinued. The intestinal lesions had regressed but fibrotic lesions of the liver persisted.

Key words Autoimmune enteropathy · Autoimmunity · Enteropathy · Anatomical study

Introduction

Autoimmune enteropathy (AIE) is a rare familial disorder. It is a distinct cause of protracted diarrhoea in infancy and is defined by four characteristics: protracted diarrhoea and severe enteropathy, lack of response to total parenteral nutrition, presence of circulating autoantibodies and/or autoimmune diseases and absence of severe immunodeficiency [1]. Histological and other data have been published [2–25], but no thorough histological studies of the disease are available. We have previously published a study of the autoantibody status in one of the two brothers who are the subjects of this report [2]. We report here the histological features recorded in the two brothers, each of whom had many different histological lesions. For the second case, our findings before and after immunosuppressive therapy are reported.

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Patients and methods

Patients

Patient 1 was the first child of healthy unrelated parents. The boy was vaginally delivered after an uneventful pregnancy. His birth weight was 3.46 kg, and he was breastfed. Severe watery diarrhoea developed when the infant was 15 days old and persisted despite total parenteral nutrition (TPN). The only extradigestive symptom was mild eczema. He died at 6 weeks of age.

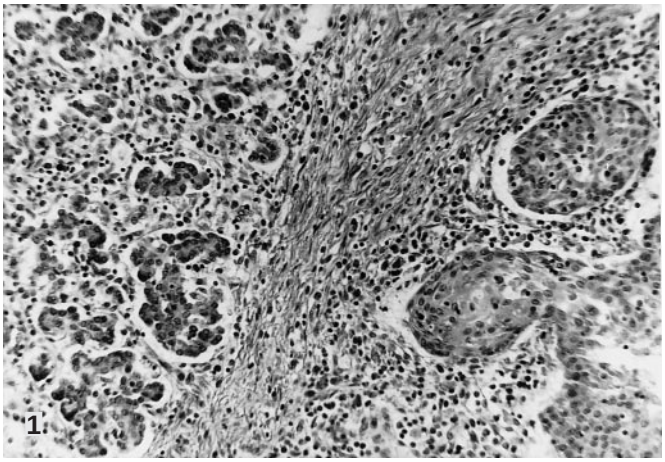
Patient 2 is the younger brother of patient 1 and the fourth child in the family, born 10 years later than the first. (Two sisters born after the first male child are in good health, and there is no evidence of autoimmune disease in the maternal family.) At 3 weeks of age, he developed severe secretory diarrhoea, which continued despite TPN. An extensive evaluation of this diarrhoea was undertaken and revealed the presence of various autoantibodies [2].

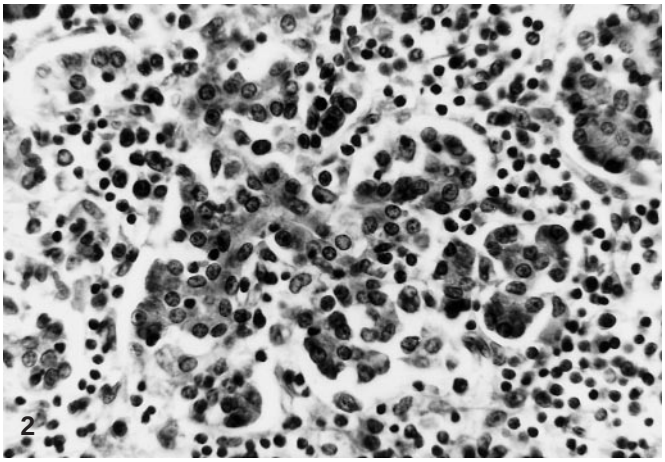
In the second month of his life immunosuppressive therapy (prednisone, azathioprine, cyclosporin) was started, and stool outflow decreased progressively. At 16 months of age, the child was still dependent on TPN. The liver was enlarged and firm. Serum alanine aminotransferase activity was two- or three-fold the normal value, and mild proteinuria was observed. Percutaneous liver biopsy and kidney biopsy were performed.

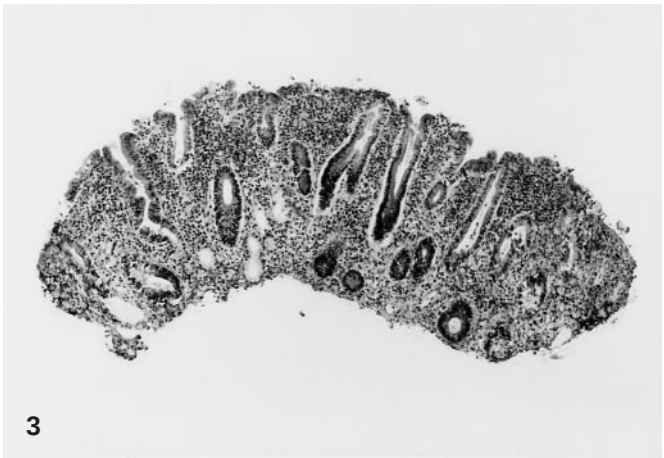
At 2 years of age the child was still being treated with prednisone and azathioprine. He remained dependent on TPN, but also ate a little. Gut and liver biopsies were repeated. Treatment with cyclosporin was started and azathioprine discontinued. At 3 years of age, the child had 1 or 2 normal stools per day and fed well. His growth curves, and his mental and motor development were normal. Diarrhoea had not recurred, and TPN was discontinued. He was still being treated with prednisone (0.15 mg/kg every other day) and cyclosporin. Small and large bowel endoscopic biopsies and percutaneous liver biopsy were performed.

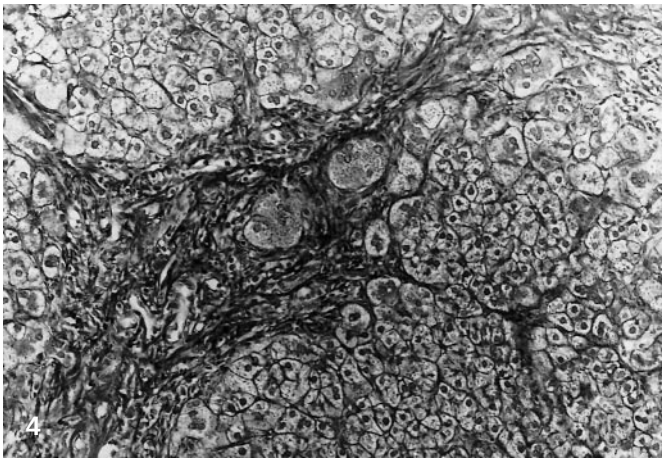
Methods

Tissues obtained during autopsy, endoscopic examinations or percutaneous biopsies were fixed in Bouin's solution, embedded in









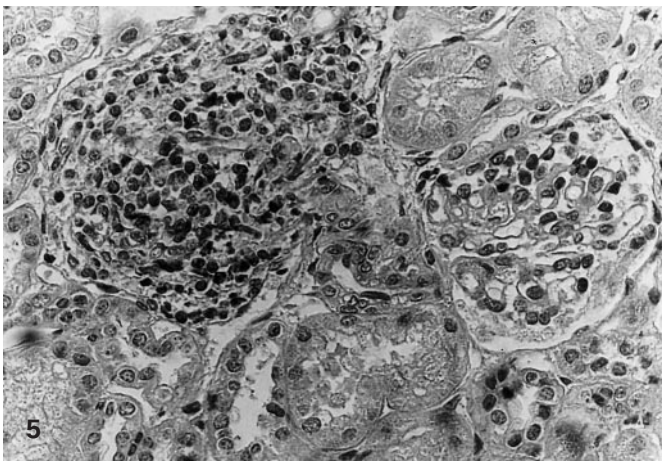


Fig. 1 Pancreas: severe inflammatory infiltration around a pancreatic duct with squamous metaplasia. Haematoxylin-eosin, ×63

Fig. 2 Pancreas: interstitial lymphoid infiltration without fibrosis. Haematoxylin-eosin, ×400

Fig. 3 Duodenal biopsy. Total villous atrophy with crypt hyperplasia and inflammation of the lamina propria. Haematoxylin-eosin, ×160

Fig. 4 Liver biopsy. Portal inflammation and fibrosis with disaray of the limiting plate. Haematoxylin-eosin, ×160

Fig. 5 Kidney biopsy. Lymphoid nodule in the cortical parenchyma. Haematoxylin-eosin, ×400

paraffin and stained with haematoxylin-phloxin saffron. Special stains were required for some specimens.

Immunoperoxidase staining was performed on parraffin sections from the pancreas of patient 1 using monoclonal antibodies to chromogranin, glucagon, somatostatin and insulin. Antibodies to CD3, CD20 and CD68 were used on paraffin sections from the small and large bowel of each of the two patients.

Cryostat sections were stained for CD3, CD4, CD8, CD20, CD25 and HLA DR by the indirect immunoperoxidase method.

Direct immunofluorescence staining was used in patient 2 to evaluate immunoglobulin-secreting cells in the lamina propria of the small and large bowel. Frozen sections of the kidney biopsy were examined by the same method using antisera to IgA, IgG, IgM, IgE, light chains, Fbg, C3, C4 and C19.

Results

In patient 1 (autopsy findings), the external appearance of the entire digestive tract was normal, with no necrosis or haemorrhage. The liver was markedly enlarged (225 g) and cholestatic. The pancreas had a normal consistency and weighed 6.4 g. The kidneys (combined weight 67 g), adrenals, heart, lungs and brain were normal.

Total villous atrophy was demonstrated from the duodenum to the ileum. A dense lymphoid infiltration of the

lamina propria was observed in the entire digestive tract, including the stomach. Plasmocytes, macrophages and eosinophils were also present. Epithelial loss was nearly complete. Only a few, poorly differentiated cells remained at the base of the glands. Occasional micro-ulcerations or micro-abcesses were noted.

The second most severely affected organ was the pancreas. It showed severe diffuse infiltration by lymphocytes, with no fibrosis or acinar dilatation. Inflammation was predominant around the ducts that exhibited squamous metaplasia (Figs. 1, 2). Even though the islets of Langerhans were not the target of the lymphocytes they were difficult to identify on routine sections, being apparently reduced in number, particularly at the level of the head of the pancreas.

The liver had a normal architecture, with no fibrosis, necrosis or giant cell transformation, and exhibited extensive haematopoiesis and biliary deposits. Scattered lymphoid infiltrates were present in the kidneys and in the lungs around the bronchi and bronchioli. The thyroid was devoid of inflammatory changes. Lymph nodes and spleen showed reactive nonspecific lymphoid hyperplasia. The thymus revealed mild involutive atrophy. The heart, adrenals and brain were microscopically unremarkable.

The majority of lymphocytes in the digestive tract and pancreas were T-cells, labelled with CD3 polyclonal antibody. Grimelius and chromogranin-stained islet cells and scattered parenchymal cells were observed in the pancreas. Intensely glucagon- and somatostatin-positive cells were present. Insulin cells were reduced in number and their positivity was low, as was the staining with paraldehyde fuscin.

In the second boy, repeated duodenal biopsies during his first 2 years demonstrated total villous atrophy with crypt hyperplasia and focal superficial epithelial desquamation (Fig. 3). Diffuse infiltration of the lamina propria by lymphocytes, macrophages, plasmocytes, eosinophils and increased intraepithelial lymphocytes was striking. An identical inflammation of the lamina propria was observed in the stomach, colon and rectum, associated with few crypt abscesses, epithelial loss but only mild crypt distortion. Discrete inflammatory infiltrates were present in the oesophagus. Immunofluorescence staining revealed an increased number of immunoglobulin-secreting cells in the lamina propria of the duodenum and sigmoid, with a predominance of IgM. IgA-secreting cells were also numerous. IgG- and IgE-secreting cells were sparse. Immunoperoxidase staining on paraffin sections revealed an increased number of CD3+ lymphocytes mixed with CD68+ macrophages. Scattered aggregates of CD20+ B cells were also observed. On frozen sections CD4 and CD8+ lymphocytes were equally increased. CD25+-activated cells were present, resembling lymphocytes or macrophages. HLA Dr was expressed in both the crypt and the surface epithelium.

The biopsies were repeated when the patient was in clinical remission at the age of 2 years. The histological lesions improved progressively. The boy had short regenerated villi at 34 months of age, and near-normal villi at 43 months. The inflammatory T-cell infiltrate decreased in the duodenum and colon and in the stomach; CD25+ cells disappeared as well as HLA Dr expression in the crypts. We noted that an increased number of B-lymphocytes and lymphoid follicles and labelled with CD20 appeared in these different sites.

Three liver biopsies were performed in the course of the disease when the patient was 16, 24, and 43 months of age. The first biopsy showed moderately aggressive chronic hepatitis with extensive bridging fibrosis, mild piecemeal necrosis and moderate lymphoid portal inflammation (Fig. 4). In the second biopsy the portal lymphoid infiltrate had decreased but fibrosis remained unchanged. In the third biopsy portal fibrosis progressed with a nodular tendency. Portal inflammation and piecemeal necrosis were mild and associated with a lymphoid follicle in a portal tract.

A kidney biopsy performed in the course of cyclosporin therapy at 16 months of age showed focal interstitial lymphoid infiltrates and mild fibrosis with no significant tubular lesions (Fig. 5). Three out of 10 glomeruli were sclerotic, and 1 had segmental hyalinosis. Immunofluorescence study revealed mild diffuse mesangial and focal subendothelial granular deposits of IgM and C1q.

A skin biopsy was obtained when the boy was 10 months of age. It showed a thickened epidermis with parakeratotic hyperkeratosis, acanthosis, focal spongiosis, and mild exocytosis. Significant dermal lymphohistiocytic infiltrates were noted around the capillaries. The overall appearance was consistent with chronic lichenoid eczema.

Discussion

Since 1974, 51 male infants under 2 years of age with AIE have been reported in 22 publications [2–24], and as in our 2 cases, the disease is frequently a familial disorder [4, 5, 11, 15, 18, 22]. These observations confirm the hypothesis that some cases of autoimmune diarrhoea may be X-linked, but AIE has also been observed in older children [5, 8, 23–26] and in female subjects [1, 5–7, 27], interestingly with less bowel involvement in most cases.

In these different reported cases the main organ affected (small bowel) was usually the only one studied [25]. Therefore, no extensive analysis of this disease is available. Moreover, it is of importance to note that histological changes are not always correlated with clinical changes and that with no systemic evaluation some histological lesions can remain unnoticed. This is clearly illustrated by patient 1, where we found severe lymphoid infiltration of the pancreas during autopsy examination, and in patient 2, who apart from the small bowel lesions, had serious histological lesions of the stomach and colon, which were found during systematic endoscopic examination.

In young children, as in our 2 cases the main feature revealing AIE is protracted diarrhoea, and the digestive tract always seems to be affected. Small bowel biopsy shows total villous atrophy and crypt hyperplasia, diffuse inflammation of the lamina propria and focal desquamation [3–5, 14, 18, 24]. It is important to note that the large bowel and the stomach are also affected [4, 5, 9, 13–15, 24]. Few immunohistochemical analyses are available, and these are incomplete [15, 19, 24, 29]. These analyses agree with our findings and show the presence of an increased number of CD3+ (CD4+ and CD8+) lymphocytes, CD25+ lymphocytes (activated), plasmocytes and CD68+ macrophages. An increased number of intraepithelial lymphocytes and expression of HLA DR antigens on crypt enterocytes are also observed [8, 15, 19, 24]. In patient 2 histological and immunohistochemical analysis was also performed; the patient was in remission. In this condition, the mucosa became progressively normal. The number of lamina propria T cells and intraepithelial lymphocytes decreased. CD25+ cells and HLA DR expression in the crypts disappeared.

As observed in these 2 cases, other organs are also frequently affected in AIE. Pancreatic lesions are usually observed in patients with exocrine or endocrine insufficiency [4, 5, 9, 10, 14]. Diabetes mellitus may be the first symptom of the disease, occurring prior to the diarrhoea [5, 22]. A diffuse or focal (nonspecific) lymphocytic infiltration of the pancreas is the most frequent histological feature [4, 5, 9, 14, 21, 22]; in 3 cases, examination even failed to reveal islets of Langerhans [14, 22]. Thyroid insufficiency was noted in 7 patients [4, 9, 10, 15, 18]. An autopsy examination showed lymphoid cell infiltration of the thyroid in 6 patients [4, 5, 9, 18], and fibrosis was noted in 2 [9, 8]. Renal involvement is not uncommon in AIE and can be revealed by proteinuria or tubular dysfunction. As observed in our patient 2, biopsy specimens can show interstitial inflammatory nephritis [3, 4, 8, 10, 15] or membranous glomerulonephritis [2, 4, 8, 17, 19, 20], sometimes associated with linear deposition of immunoglobulins along the tubular basal membrane. The liver is also affected in AIE. The liver injury is usually revealed by hepatomegaly associated with moderately elevated serum transaminase levels [12, 21]. Liver insufficiency was observed in only 1 case [20]. A percutaneous liver biopsy was performed in 7 patiens, showing periportal or extensive fibrosis [7, 12, 20] and/or chronic or aggressive hepatitis [10, 12, 15, 21]; we note that these kinds of lesions are not usually observed in patients receiving TPN [30]. Lung and bronchiole lesions were also observed. In 3 patients, lymphocytic infiltration of the lung was observed at autopsy [4, 9, 18], but in our case 1 the infiltration was only noted around bronchi and bronchioli. A high level of IgE is observed in some patients [2, 4, 7, 11, 12, 17, 21], mostly associated with dermatitis. Histological findings in the skin biopsy in patient 2 were concordant with the diagnosis of eczema. In this case, the dermatitis disappeared and IgE levels decreased when the disease was in remission.

The value of immunosuppressive therapy was first noted by Harner et al. [3]. Since their report, an improvement has been observed in some patients receiving different immunosuppressive therapies [6–9, 13, 15, 21], including cyclosporin A [13, 17, 20]. In our patient, the efficacy of the therapy first became apparent because the clinical features improved (stool outflow); the improvements in the histological abnormalities in the small and large bowel were not seen until a few months later. At 3 years of age, the child was asymptomatic and feeding well, and eczema had not recurred. Small and large bowel biopsies were normal and a percutaneous liver biopsy showed marked regression of the inflammatory lesions.

It is interesting to consider this disease as a generalized autoimmune disorder affecting mainly young males and histologically characterized by an inflammatory reaction that can involve several organs in one individual. These can include the small and large bowel, the pancreas, the thyroid, the kidneys, and the liver. We observed clinical remission and histological improvement of the intestinal and liver lymphocytic infiltrate after treatment. Therefore it seems important to explore those different organs systematically when a patient with features suggesting an AIE is evaluated. On the basis of the immunological findings immunosuppressive drugs were used, and they seem to be able to control this disease.

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