

Digestive histopathological presentation of IPEX syndrome

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Immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX) syndrome is a well recognized and particularly severe form of autoimmune enteropathy. It has an X-linked recessive transmission, and is caused by mutations in the *FOXP3* gene. We studied the intestinal morphological changes characterizing IPEX syndrome in a series of 12 children with a molecularly confirmed diagnosis. Histological examination of duodenal, gastric and colonic biopsies were retrospectively reviewed and compared by two independent experienced pathologists. In parallel, the presence of circulating anti-enterocyte antibodies was analysed using an indirect immunofluorescence technique and a quantitative radioligand assay against the 75-kDa autoantigen. The morphology of the inflammatory gut lesions could be categorized into three different entities, namely graft-vs-host disease-like changes (9/12 patients), a coeliac disease-like pattern (2/12) and an enteropathy with a complete depletion of goblet cells (1/12). Our results do not suggest any phenotype–genotype correlation. Circulating antibodies were detected in all 12 patients, with an anti-brush border pattern (11/12) and anti-goblet cell antibodies (1/12), as well as by a radioligand assay. The histological presentation of autoimmune enteropathy is rather variable. However, a graft-vs-host disease-like pattern associated with positive anti-enterocyte antibodies is the most frequent intestinal presentation of IPEX syndrome, and constitutes a very valuable tool for pathologists to suspect this diagnosis.

Modern Pathology (2009) 22, 95–102; doi:10.1038/modpathol.2008.161; published online 26 September 2008

Keywords: enteropathy; autoimmunity; autoantibodies; IPEX

Severe enteropathies potentially causing intestinal failure are a diagnostic and therapeutic challenge in children.¹ Because of the recent development of new diagnostic tools, different causes of early postnatal forms of massive enteropathies could be identified, such as constitutive enterocyte disorders, infectious as well as dysimmune–autoimmune conditions. As the outcome might be fatal for some forms of early-onset enteropathies, a precise and rapid diagnosis can be vital for the patient.^{2,3}

One well-defined form of early-onset enteropathy is IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance; OMIM 304790), a rare recessive disorder

characterized by a profound immune dysfunction secondary to a regulatory T-cell defect. On clinical presentation, these boys show a severe form of autoimmune enteropathy with severe protracted diarrhoea, severe immunoallergic reactions and different forms of endocrinopathies, such as insulin-dependent diabetes mellitus, thyroiditis and adrenal insufficiency. IPEX syndrome is generally lethal if not adequately treated.⁴ Treatment options are limited and are mainly based on the combination of immunosuppressive drugs such as steroids, tacrolimus or sirolimus, or when possible with stem cell transplantation.^{5,6} The diagnosis of IPEX syndrome is confirmed by finding a mutation within the *FOXP3* gene (Xp11.23).^{7–10} Here, we describe the morphological features of intestinal biopsies in patients with IPEX syndrome, including a study of circulating anti-enterocyte antibodies. The aim is to develop different tools to allow early identification of IPEX syndrome from endoscopic biopsy specimens.

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Received 2 July 2008; revised 22 August 2008; accepted 26 August 2008; published online 26 September 2008

Patients and methods

Patients

A total of 12 boys with a molecularly proven IPEX syndrome (ie, with a mutation of the *FOXP3* gene) were included in this study; the biopsies were obtained between 1989 and 2008 (Table 1).

Patient nos. 7 and 8 were brothers carrying a mutation upstream of exon 1, leading to a complete lack of FOXP3 expression.¹⁰ In patient nos. 1, 2 and 11, the mutations are predicted to allow the expression of a truncated protein. Patient nos. 4, 10 and 12 have an identical mutation in exon 7, leading to an in-frame deletion of one residue (E251 del). Patient nos. 3, 5, 6 and 9 carried missense mutations (F367C, F374C, F371C and P187L, respectively) allowing the expression of a full-length FOXP3 protein.

The median age at diagnosis was 12 months with a median weight and median height of -2.77 ± 0.97 and -2.19 ± 1.38 s.d., respectively.

All children presented with severe protracted diarrhoea and a protein-losing enteropathy.

Endoscopic examinations showed a variable degree of duodenal inflammation with erythema, erosions or ulcerations with altered mucosae. A severe macroscopic colitis was found in three patients: two patients presented with a severe pan colitis and one with a proctitis.

Extradigestive manifestations included atopic dermatitis ($n=8$), insulin-dependent diabetes ($n=7$), Hashimoto's thyroiditis ($n=2$) and a tubulointerstitial nephritis ($n=2$), and a membranous glomerulonephritis was diagnosed in one of these boys (Table 1). Five boys presented with autoimmune thrombocytopaenia, which was associated with an autoimmune haemolytic anaemia ($n=2$) and an autoimmune neutropaenia ($n=1$). At the time of histological analysis, five patients were under immunosuppressive therapy: either in the form of an isolated steroid therapy (patient no. 1) or

with a combined immunosuppression associating steroids, azathioprine or methotrexate and tacrolimus or rapamycin (patient nos. 3, 4, 6 and 12). The remaining seven patients were untreated.

Methods

Histology

Endoscopic mucosal biopsies of duodenal, gastric and colonic mucosae were fixed in 10% buffered formalin. Paraffin sections were cut at 5- μ m thickness and stained with haematoxylin and eosin. The histopathology of the digestive biopsies was analysed by two independent pathologists (NPMS and DC), following defined criteria:

The degree of villous atrophy was graded as normal, partial villous atrophy (crypt/villous less or = 1) or subtotal-total (crypt/villous > 1) villous atrophy.

The goblet cells were analysed as normal, decreased or absent in glandular and surface epithelial cells.

The intensity of the inflammatory infiltrate in the lamina propria was graded as normal, increased moderately or increased markedly. In the epithelium, the number of CD3+ lymphocytes was quantified per 100 epithelial surface cells, and the predominant type of inflammatory cells was characterized as lymphocytes, plasma cells, neutrophils or eosinophils. Immunohistochemistry on paraffin sections from duodenal biopsies was performed using an anti-CD3 antibody (A0452, 1:50; DAKO Corp., Glostrup, Denmark), as described earlier.¹¹

Different glandular modifications were defined: crypt abscesses, partial or total destruction and necrosis. The necrotic or apoptotic cells appeared as single-cell necrosis or clusters of necrotic cells.

Detection of anti-enterocyte antibodies

The presence of anti-enterocyte antibodies was assessed in the serum of each IPEX patient using

Table 1 Clinical, biological and pathological IPEX patient's data

Patient no.	Age at onset (months)	Dermatitis	Diabetes	Others	Pathology
1	1.5	+	-	AIT	GVHD
2	80	+	-	Allergic asthma	GVHD
3	15	-	+	Tubulointerstitial nephritis	GVHD
4	4	-	+	AIHA, AIN, anti-SM, anti-islets, hyper-IgE	GVHD
5	2	+	+	AIT, AIN, hyper-IgE	GVHD
6	4	+	-	AIHA, AIT	GVHD
7	2.5	+	-	Hyper-IgE	GVHD
8	0.75	+	-	Anti-LKM, hyper-IgE	GVHD
9	11	+	-	Anti-TSH receptor, AIT, hyper-IgE, CMPA	GVHD
10	7	-	+	AIT, AIN, hyper-IgE, tubulointerstitial nephritis	CD-like
11	6	+	+	AIHA, AIT, membranous glomerulonephritis	CD-like
12	12	-	-	Anti-GAD65, anti-insulin, anti-prolactin, anti-TSH receptor	Anti-goblet cells

AIT = autoimmune thrombocytopaenia; AIN = autoimmune neutropaenia; AIHA = autoimmune haemolytic anaemia; SM = smooth muscle; anti-LKM = anti-liver/kidney microsomal; CMPA = cow's milk protein allergy.

an indirect immunofluorescence technique. Serum was applied onto the frozen sections of normal human small bowel and kidney cut at 4 μ m. Sections were washed in phosphate-buffered saline (PBS), followed by the application of FITC-conjugated rabbit anti-human IgG and anti-human IgA at 1:20 (DAKO Corp.). After further washing (three times for 5 min in PBS), the slides were coverslipped in an aqueous mounting medium. The slides were analysed on a Leica microscope (Cambridge, UK) using epifluorescence with a mercury HBO 100 light source.

Presence of anti-enterocyte antibodies was demonstrated by a linear positivity along the apical brush border. This technique can not only reveal other antibodies, such as anti-goblet cell antibodies, defined by positive staining on the goblet cells, but also anti-smooth muscle or anti-nuclear factor.

Radioligand assay of the 75-kDa autoantigen reactivity was performed as described earlier¹² in the serum of each IPEX patient.

Results

Histology

IPEX patients displayed a spectrum of histological patterns characterized by total or subtotal villous atrophy on duodenal biopsies and inflammation with glandular destruction in all parts of the digestive tract; however, three particular and distinct histological patterns were identified.

Graft-vs-host Disease-like Pattern (Patient nos. 1–9)

Duodenal biopsies

The biopsies displayed total villous atrophy with a moderate-to-marked inflammation of the lamina propria consisting of lymphocytes, plasma cells, neutrophils and eosinophils (Figures 1a and b). The main feature of the histological presentation was the presence of apoptotic cell death of epithelial cells. There was some degree of correlation between apoptotic cell death and inflammatory activity: foci of single-cell apoptosis or apoptotic clusters of crypt cells were preferentially observed in moderately inflammatory disease lesions (patient nos. 1, 2, 3 and 4), whereas partial or total glandular destruction secondary to crypt cell apoptosis was identified in the five patients with the most severe mucosal inflammation (patient nos. 5, 6, 7, 8 and 9). The morphological aspect of these apoptotic lesions is indistinguishable from those observed in classical intestinal graft-vs-host disease^{13,14} (Figure 1b, inset).

In addition, lymphocytic, neutrophilic and eosinophilic infiltration of the epithelium crypts, with crypt abscesses, was always present. A nodular lymphoid infiltrate was observed, and fibrosis of the lamina propria was found in three cases.

In areas with a marked lymphocytic, neutrophilic and eosinophilic infiltrate, a significant depletion of goblet cells was noted. In patient no. 6, gastric metaplasia with mucosal atrophy was observed (Figure 1a). The number of intraepithelial lymphocytes was normal in three boys (patient nos. 1, 2 and 6) slightly increased (40–60 per 100 epithelial cells) in the remaining six children (patient nos. 3, 4, 5, 7, 8 and 9). In seven patients, numerous surface and glandular epithelial cells showed enlarged nuclei, without viral inclusions; immunohistochemistry against cytomegalovirus and adenovirus was negative.

Gastric biopsies

A moderate (patient nos. 1 and 2)-to-severe (patient nos. 5, 6, 7 and 8) gastritis (Figure 1c) with a polymorphic inflammatory infiltrate comprising mononuclear cells, neutrophils and numerous eosinophils was observed. Single-cell necrosis was found in a setting of moderate gastritis, whereas partial or total glandular destruction was present in a setting of severe gastritis.

Colonic biopsies

Seven of the nine patients (except patient nos. 1 and 9) showed a colitis with acute and chronic lesions (Figure 1d) characterized by a mixed neutrophilic, eosinophilic and mononuclear inflammatory infiltrate of the lamina propria. Glandular neutrophilic and eosinophilic infiltration with foci of single-cell apoptosis/necrosis or clusters of cell necrosis with partial-to-total glandular destruction was seen in the four patients with the most severe inflammatory colitis. In patient no. 6, gastric metaplasia with mucosal atrophy and partial-to-total glandular destruction was observed.

Coeliac Disease-like Pattern (Patient nos. 10 and 11)

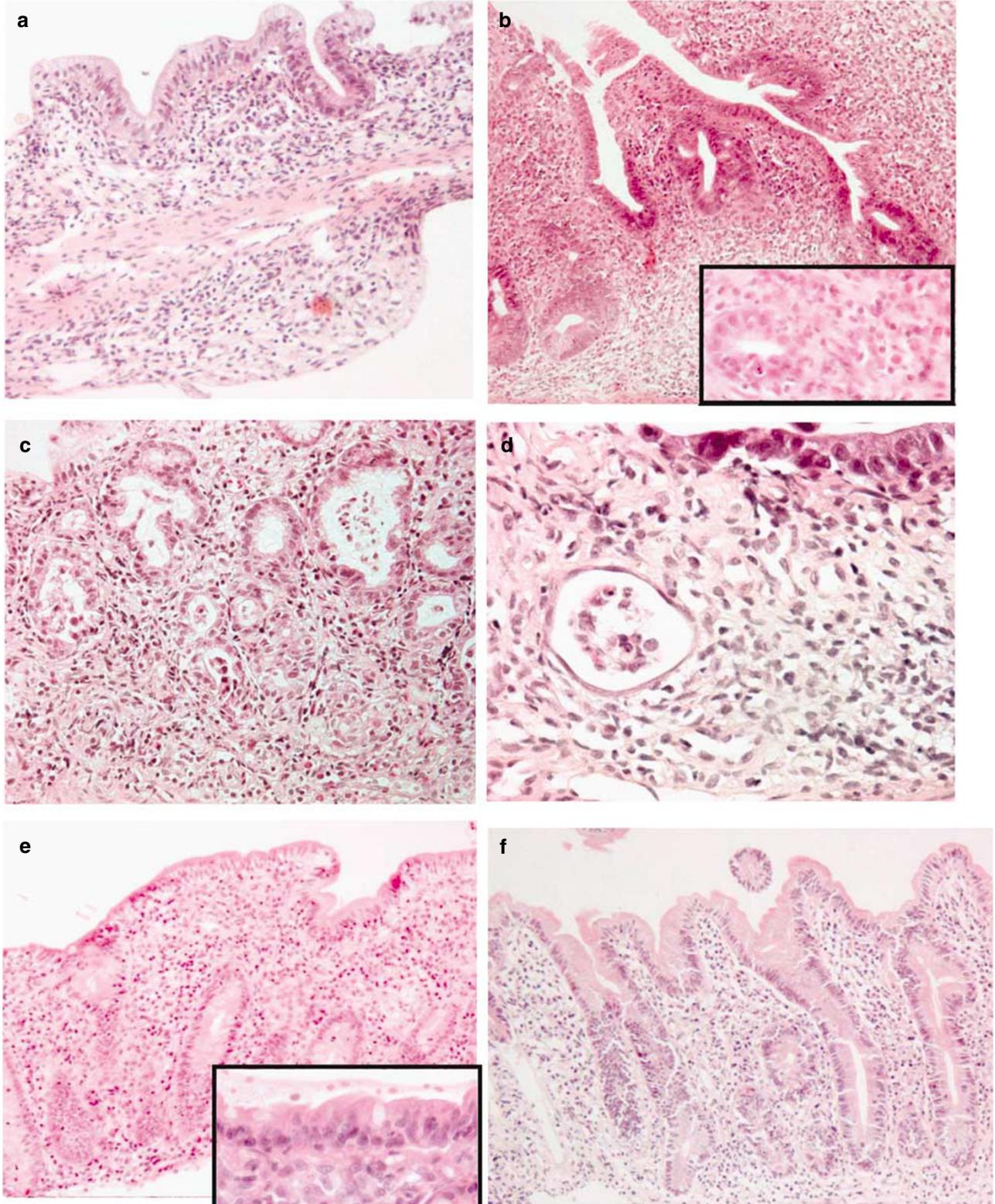
In a subgroup of two patients, a different histological pattern was observed. Duodenal biopsies were characterized by a subtotal villous atrophy, a marked inflammatory infiltrate of the lamina propria consisting of plasma cells and lymphocytes associated with a moderate neutrophilic and eosinophilic component, and crypt hyperplasia. The number of intraepithelial lymphocytes (CD3+, CD8+) was markedly elevated, with 80 lymphocytes per 100 epithelial cells, focally in association with neutrophils and/or eosinophils (Figure 1e).

In these two patients, the gastric and colonic inflammation was moderated; they exhibited only a mild polymorphic inflammatory infiltration of the lamina propria.

Enteropathy with Intestinal Goblet Cell Autoantibodies (Patient no. 12)

A single patient showed a different histological presentation, duodenal biopsies were characterized by a subtotal villous atrophy with total goblet cell

depletion and a moderate lymphocytic and plasmocytic inflammatory infiltrate of the lamina propria. Intraepithelial CD3+ lymphocytes were increased (55 intraepithelial lymphocytes per 100 epithelial cells) (Figure 1f). A moderate gastritis was observed with a polymorphous inflammatory infiltrate with



total goblet cell depletion. In contrast, this patient developed a marked colonic involvement with deep ulcerations on macroscopic examination. On histological analysis, colonic lesions were focal and severe with ulcerations and numerous eosinophils in the lamina propria, along with a moderate lymphocytic and plasmacytic infiltration. The colonic goblet cells were severely reduced in numbers but not totally absent.

Anti-enterocyte Antibodies

All 12 IPEX patients had positive IgG antibodies on immunofluorescence analysis using normal human duodenal sections. A typical staining along the epithelial brush border was detected in 11 of 12 serum samples of boys with IPEX syndrome (Figure 2a). In addition, on kidney sections, one of the four serum samples tested was positive against the proximal tubular brush border (Figure 2b) (patient no. 11). The serum from one patient (patient no. 12) did not react with the brush border, but stained goblet cells of duodenal, gastric and colonic origin (Figures 2c and d).

Other antibodies could be observed such as anti-smooth muscle (Figure 2e) in two children or anti-nuclear factor (Figure 2f) in three children.

All of the 12 serum samples tested were positive for anti 75-kDa antibodies; the highest level was observed in patient no. 12, who exhibited anti-goblet cell autoantibodies.

Discussion

IPEX is a rare and very severe autoimmune disorder, involving the small bowel in all patients and to a variable degree other parts of the gastrointestinal tract. Onset of the disease is most often within the first months of life. This disorder evolves extremely rapidly and the clinical course is most often lethal. Therefore, therapeutic measures to stabilize the patient are urgent.^{1–4,15,16} Given the large spectrum of diarrhoeal disorders with early onset, it is important to develop diagnostic tools that help to easily distinguish or at least orient the diagnosis of severe and persistent diarrhoea in young children.

From a pathologist's point of view, the aetiology of severe and persistent diarrhoea must often be sought

on small intestinal biopsies. The described histopathological appearance of autoimmune enteropathy is variable. Most commonly, duodenal biopsies show moderate-to-severe villous atrophy and a variable degree of crypt hyperplasia. The number of intraepithelial lymphocytes can be significantly increased in the duodenum, stomach and colon.^{17–20} Typically, patients with an autoimmune enteropathy develop circulating anti-enterocyte antibodies; however, as recently reviewed, the presence of these antibodies is of secondary nature, an accessory finding rather than pathogenic.²⁰ In various pathologies, the intestinal architecture can be preserved, and intraepithelial lymphocytes are not increased but goblet cells, Paneth cells and endocrine cells may be absent.¹⁸ Finally, some patients presenting with autoimmune enteropathy show a combination of these patterns.¹⁸ However, all these inflammatory changes are known to be nonspecific and do not allow to discriminate histologically autoimmune enteropathies from other inflammatory disorders. Characteristic antibodies against enterocytes or goblet cells and particularly the antibodies against the 75 kDa autoantigen can help to confirm the diagnosis of autoimmune enteropathy in IPEX syndrome.^{21,22}

Therefore, on the basis of this, we wanted to evaluate and describe the intestinal morphological changes in a well-characterized population of 12 children in whom IPEX syndrome was confirmed by a molecular analysis.

In keeping with previous reports, the histological changes of autoimmune enteropathy are rather variable, even within our group of IPEX patients. Lesions occurred throughout the gastrointestinal tract; their morphological characteristics allowed them to be separated into three distinct categories. The graft-vs-host disease-like pattern was the most frequent form observed (9 of 12 patients, 75%); a coeliac disease-like pattern was found in two patients (16%) and one child had an enteropathy characterized by a depletion of intestinal goblet cells along with the presence of anti-goblet cell autoantibodies. When considering the different genotypes of our patients, we could not find any correlation between phenotype and genotype. An identical mutation was observed in three unrelated boys, each of whom presented with a different morphological pattern.

Figure 1 (a and b) Duodenal biopsies (H&E × 100). Duodenal biopsies showing total villous atrophy, a marked inflammatory infiltrate of the lamina propria consisting of lymphocytes, plasma cells, neutrophils and eosinophils, total (patient no. 6, a) or partial glandular destruction (patient no. 8, b) with focal single-cell necrosis or apoptosis (b, inset, × 400). A gastric metaplasia with mucosal atrophy was observed in patient no. 6 (a). (c) Gastric biopsy (H&E × 200) and (d) colonic biopsy (H&E × 200) of IPEX syndrome with graft-vs-host disease-like. A severe (patient no. 7) gastritis (c) and severe colitis (d) (patient no. 5) were observed, characterized by a neutrophilic and eosinophilic inflammatory infiltrates of the lamina propria. Note the glandular polymorphonuclear infiltration with foci of single-cell necrosis or clusters of cell necrosis with partial or total glandular destruction. (e) Duodenal biopsy (H&E × 100) of IPEX syndrome with a coeliac disease pattern (patient no. 11). The duodenal biopsy was characterized by subtotal villous atrophy, a marked polymorphous inflammatory infiltrate of the lamina propria with crypt hyperplasia. Lymphocytic infiltration of the epithelial cell was marked (inset e × 400). (f) Duodenal biopsy (H&E × 100) of IPEX syndrome with intestinal goblet cell autoantibodies (patient no. 12). A subtotal villous atrophy with total goblet cell depletion was noted on the surface epithelium with a moderate lymphocytic and plasmacytic inflammatory infiltrate of the lamina propria.

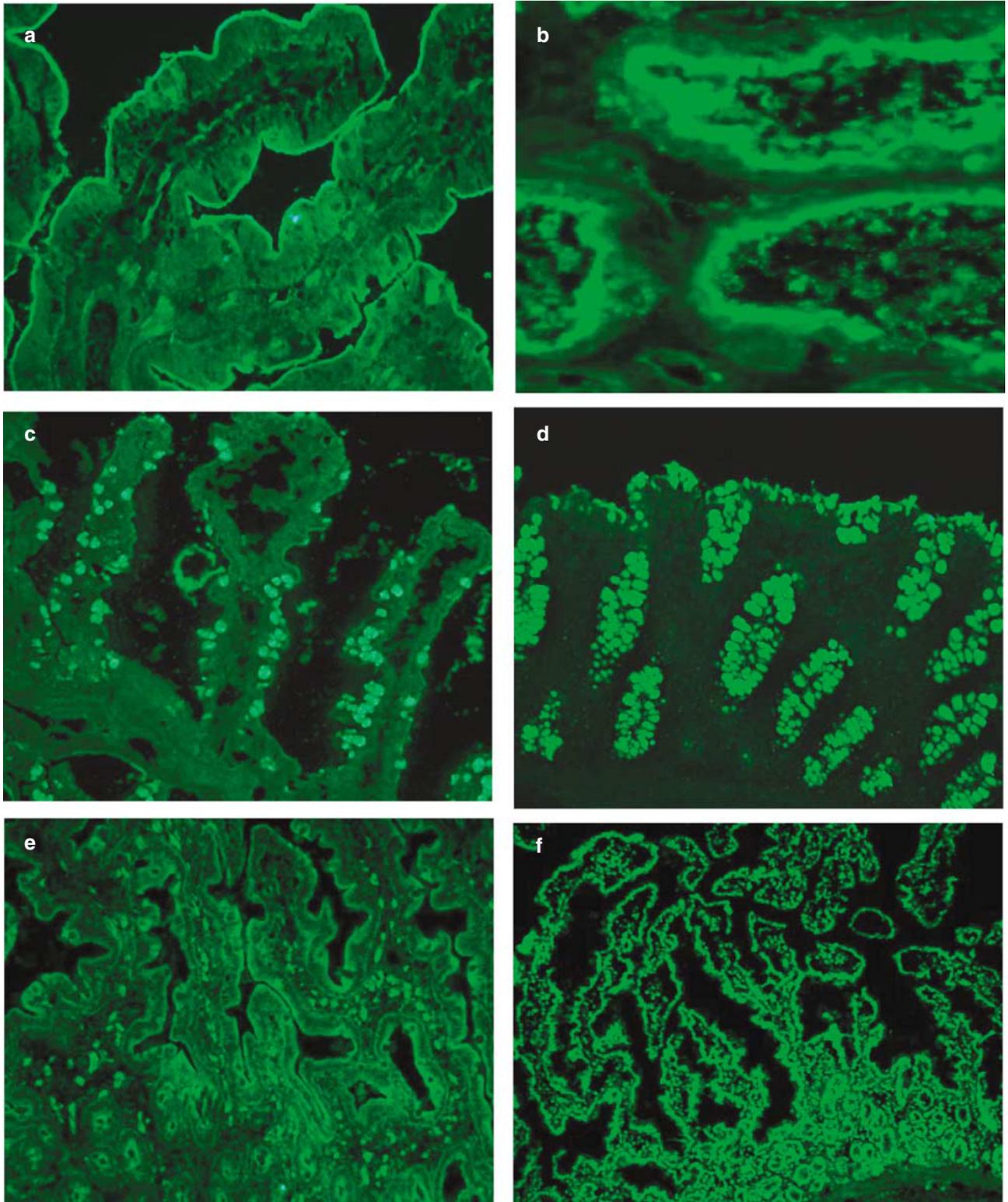


Figure 2 Indirect immunofluorescence for autoantibodies: a bright staining of the brush border on the intestinal epithelial cells (**a** $\times 200$) and proximal tubules of the kidney (**b** $\times 200$) was observed with the serum of patient no. 11. Serum from IPEX patient no. 12 reacted with goblet cells on duodenal (**c** $\times 200$) and colonic mucosae (**d** $\times 200$). In few cases, other autoantibodies could be observed, such as anti-smooth muscle (**e** $\times 200$) or anti-nuclear factor (**f** $\times 200$).

It is important to emphasize that these lesions are not specific for IPEX or non-IPEX autoimmune enteropathies, as already exemplified by the nomenclature, because true graft-vs-host disease, coeliac-like disease and intestinal goblet cell autoantibody enteropathy are entities.¹⁸ However, these histological changes are very distinct from those of inflammatory bowel disease (eg, ulcerative colitis and Crohn's disease). Whenever autoimmune enteropathy is suspected in a patient, especially in infants with severe protracted diarrhoea, the detection of circulating anti-enterocyte or anti-goblet cell antibodies should be combined with the histological analysis to rapidly orient the diagnosis.

In IPEX syndrome and other autoimmune enteropathies, antibodies directed against enterocytes are frequently detected, as well as other autoantibodies such as anti-smooth muscle, anti-nuclear or anti-liver/kidney microsomal.¹⁸ These antibodies are usually not considered to be specific. However, circulating antibodies directed against the brush border have been described either in coeliac disease or in other inflammatory bowel diseases; their detection is simple, and appears to be specific and highly sensitive in the diagnosis of autoimmune enteropathy in IPEX syndrome.^{17,21,23} On the other hand, circulating antibodies reacting with goblet cells have been described in inflammatory bowel diseases, but the histology allowed a correct diagnosis because the morphological patterns are most often totally different in IPEX syndrome compared with other inflammatory diseases.²⁴

The nature and the role of the 75 kDa autoantigen remain unclear. It seems to be a PDZ domain-containing protein expressed in the differentiated epithelial cells of the intestine and kidney, and it may be involved in protein-protein interactions.²¹ Our results and those of others^{17,21,24} suggest that in the IPEX syndrome, the intestinal damage results from the autoimmune reaction against the common components of this 75 kDa protein; hence, the circulating anti-75-kDa autoantibodies sought to confirm the diagnosis are also the cause of the enteropathy. Such antibodies are not involved in other autoimmune enteropathies.

In conclusion, a graft-vs-host disease-like pattern suggests the diagnosis of IPEX syndrome in the proper clinical context. This diagnosis should be confirmed by the demonstration of circulating autoantibodies against the brush border of enterocytes or against goblet cells in conjunction with the presence of 75-kDa autoantigen autoantibodies.

Acknowledgement

We thank Sophie Candon and Lucienne Chatenoud (Department of Immunology, Necker Hospital, Paris, France) for anti-AIE-75 kDa detection.

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