

Primary ileal villous atrophy is often associated with microscopic colitis

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Abstract

Three cases of apparent primary villous atrophy of the terminal ileum in women with chronic diarrhoea are reported. Eight cases have previously been reported in the literature. Clinical characteristics are the presence of severe chronic secretory diarrhoea with episodes of hypokalaemia combined with signs of ileal malabsorption and/or efficacy of cholestyramine. Diagnosis is based on ileoscopy and histology. An association with microscopic colitis was present in the three patients and in four cases in the literature. The pathogenesis of primary ileal villous atrophy remains unknown and may involve dysimmunity. Its association with microscopic colitis may indicate a common pathogenesis or support the hypothesis that the faecal stream or bile salts play a role in the pathogenesis of microscopic colitis.

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Keywords: intestinal villous atrophy; ileum; secretory diarrhoea; bile acid malabsorption; microscopic colitis

Villous atrophy of the terminal ileum is usually seen in patients with villous atrophy involving the whole length of the small bowel. The main aetiologies are coeliac disease and immunodeficiency syndromes, including HIV related immunodeficiency, common variable hypogammaglobulinaemia, and IgA deficiency. Ileal villous atrophy is seldom seen in the absence of duodenojejunal atrophy; its aetiologies are listed in table 1.¹ Eight cases of apparent primary ileal villous atrophy (PIVA) have been reported in the literature.¹⁻⁶ We report here three new cases. All three were associated with microscopic colitis, an association already reported in two cases by Einarsson *et al*⁵ and Veress *et al*.⁶

Case reports

The three patients (RM, DO, and ML) were women with severe chronic diarrhoea. Table 2 shows their main clinical characteristics. They were not taking any medication. The history of RM included the alternation of diarrhoea and constipation for 50 years, ovariectomy for benign ovarian neoplasm in 1938, tuberculous pleuritis in 1939, three episodes of intestinal obstruction due to adhesions, and hysterectomy in 1980 to treat an epidermoid carcinoma

of the uterine cervix. The other two patients had no relevant history except for appendectomy.

BIOLOGICAL AND MORPHOLOGICAL EXPLORATIONS

Common features of the three patients were the presence of high erythrocyte sedimentation rate of 35, 30, and 5-42 mm/h for RM, DO, and ML respectively, and a history of transient hypokalaemia (2-3.5 mEq/l). Table 2 presents results of ileal function tests. The results of the following laboratory investigations were in the normal range: haemoglobin; blood urea, glucose, uric acid, calcium, magnesium, iron, folates, and vitamin B₁₂; albumin, globulin fractions, plasma immunoglobulins, cholesterol, prothrombin time, D-xylose test; and stool analysis for pathogenic bacteria and parasites. Repeated searches for laxatives in the stools (phenolphthalein) and urine (anthraquinones) were negative. Faecal osmolarity was normal (280-320 mmol/l), and faecal electrolytes displayed an osmotic gap below 50 mmol/l. Levels of thyroid stimulating hormone (TSH), triiodothyronine, and thyroxine were in the normal range for RM and ML. DO had high TSH values (15.9 µg/ml (normal <4.5) and low triiodothyronine and thyroxine concentrations. Concentrations of serum vasoactive peptide, serotonin, and calcitonin were normal, as was urinary excretion of 5-hydroxyindole acetic acid. Gastrinaemia was normal in DO and ML, and high (1010 pg/ml) in RM, whose gastric basal acid output was undetectable. Investigations for antinuclear antibodies, smooth muscle antibodies, antimitochondria antibodies, and Coombs tests were negative in the three patients. Search for rheumatoid factor was negative in RM and DO. Levels of fraction 3 (C3) and fraction 4 (C4) of the serum complement were normal in RM and DO (not analysed in patient ML). A 50 g glucose breath test was negative in DO and ML. The faecal clearance of α₁-antitrypsin was mildly high (table 2).

TABLE 1 Aetiologies of ileal villous atrophy in the absence of jejunal villous atrophy

Common variable hypogammaglobulinaemia
Radiation enteritis
Laxative abuse
Backwash ileitis during ulcerative colitis
Crohn's disease
Alpha-chain disease
Graft versus host disease
Atrophy in the reservoir after ileoanal anastomosis
Enterocystoplasty
Primary ileal villous atrophy (PIVA)

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TABLE 2 Characteristics of 10 patients with primary ileal villous atrophy (PIVA). Another patient reported in reference 6 had PIVA with collagenous colitis, but his characteristics were not described

Variable	Cases from the literature							Present series		
	Reference (patient)							RM	DO	ML
	2 (KV)	2 (Nj)	2 (MM)	1	3	4	5			
Age at diagnosis (y)/sex	66/F	31/M	36/M	49/F	63/F	60/M	75/M	84/F	55/F	77/F
Age at onset of diarrhoea (y)	41	13	33	47	ND	45	74	34	34	61
Weight loss (kg)	14	0	8	4	16	0	0	No	No	8
Faecal weight (g/24 h)	370	439	411	600–2000	550–1850	490–610	450	940	300–1800	500–800
Faecal fat (g/24 h) (N<7)	2	45	54	45	ND	3.2–3.9	ND	87	ND	2–5
Schilling test with intrinsic factor	N	N	N	Low	N	N	N	N	Low	N
⁷⁵ SeHCAT or cholyglycine test	Low	Low	Low	Low	Low	Low	N	N	N	Low
Efficacy of cholestyramine	Yes	Yes	Yes		Partial	Yes	ND	Yes	No	Yes
Faecal weight during fasting test (g/24 h at days 2/3)	ND	ND	ND	ND	ND	ND	ND	400/500	600/950	480/ND
α_1 -antitrypsin clearance (ml/24 h)*	ND	ND	ND	ND	ND	ND	ND	59	62	5–40
Colon histology	N	N	N	Excess of plasma cells in rectum	LC	N	LC	LC	LC	LC

*Normal <10 ml/24 h. ND, not described.

Diarrhoea persisted in the three patients during a fasting test of 48 to 72 hours (table 2).

Small bowel barium enema was normal, as was the macroscopic appearance of the duodenal and colonic mucosa at endoscopy. Retrograde ileoscopy was performed in the three patients: 10, 40, and 15 cm of terminal ileum respectively was explored. During methylene blue instillation, a mosaic pattern of the terminal ileum was constantly seen.⁷ ML had already had two ileoscopies with biopsies; the conclusion was that these biopsies had probably been performed in the colon because of the absence of villi.

HISTOLOGY

Perendoscopic biopsy specimens were fixed in Bouin's fluid and embedded in paraffin wax. Sections (4 μ m thick) were stained with haematoxylin and eosin safran, periodic acid Schiff, and Masson's trichrome. At least two duodenal, four ileal, and five colonic biopsy specimens were available for each patient. Four sections cut at different levels were studied for each block. In areas where crypts were well oriented, the thickness of the collagen plate was measured with an ocular graticle (12.5/ \times 20; Leitz Wetzlar, Germany). The number of intraepithelial lymphocytes (IEL) in colonic biopsy specimens was measured by counting 200 intercryptal epithelial cell nuclei while noting the number of lymphocytes with an image analysis system (Samba 2005, Unilog, Grenoble, France) with a 25 objective lens. The number of IEL was expressed per 100 epithelial cell nuclei.

In all cases, ileal lesions consisted of subtotal and total villous atrophy (fig 1), without degenerative changes in the enterocytes in patients DO and RM, and with slight modifications in ML—that is, the height of the enterocytes was reduced and their cytoplasm contained some vacuoles. Superficial basal epithelial membrane (SBEM) was slightly thickened (7 mm) in DO and ML, and normal in RM. The numbers of intraepithelial lymphocytes were slightly increased in DO and ML, and normal in RM. Mitoses were few. The lamina propria contained a moderate polymorphic inflammatory infiltrate comprising plasma

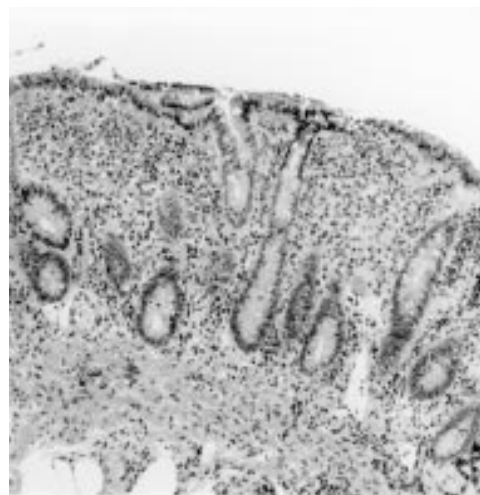


Figure 1: Ileal biopsy specimen from patient DO: total villous atrophy without degenerative changes in enterocytes, and a moderate size polymorphic inflammatory cell infiltrate of the lamina propria (haematoxylin, eosin and safran, original magnification \times 330).

cells in all cases, and mixed with eosinophils in two. No pathogen was identified.

Colonic biopsy specimens of all patients revealed lesions characteristic of microscopic colitis of the lymphocytic type, with an increase in the number of IEL (50, 73, and 66 IEL per 100 epithelial cells for RM, DO, and ML, respectively), moderate degenerative changes in the enterocytes, normal or very slight thickening of the SBEM (6 mm), and a notable inflammatory infiltrate consisting of plasma cells and eosinophils (fig 2).

Duodenal biopsy specimens were normal in patients DO and LM; in patient RM, they exhibited a slightly increased number of intraepithelial lymphocytes, but neither villous atrophy nor degenerative changes in the enterocytes were seen. A moderate inflammatory infiltrate comprising plasma cells and eosinophils was seen in the lamina propria.

STUDIES WITH INTESTINAL PERFUSIONS

Explorations with a triple lumen tube were performed in patient DO in 1986 and 1989 respectively to search for intestinal secretion in the terminal ileum or whole small bowel. To



Figure 2: Colonic biopsy specimen from patient RM: lymphocytic colitis with an increase in intraepithelial lymphocytes, degenerative changes in superficial enterocytes, and an infiltrate comprising plasma cells and eosinophils (haematoxylin, eosin and safran, original magnification, $\times 330$).

assess ileal secretion, the intestinal perfusion method of Isaacs *et al*⁸ was used, with polyethylene glycol as a marker.⁹ The ileal flow rate of liquid was also measured in 1986 over 24 hours, using a slow marker technique, and standardised meals.¹⁰ No ileal secretion was seen.

DRUG EFFICACY

Cholestyramine suppressed diarrhoea in RM and ML but was ineffective in DO. Mesalazine (2 g/day), steroids (1 mg/kg/day), a gluten free diet, and somatostatin were all ineffective in patient DO. In patient ML, mesalazine, octreotide, omeprazole, and various antibiotics had been unsuccessful in previous trials before referral to our centre. Loperamide and codeine partially reduced diarrhoea in patients DO and ML.

Discussion

The diagnosis of primary ileal villous atrophy (PIVA) was confirmed in our three patients, who also had lymphocytic colitis. Eleven cases have now been reported (including our three),¹⁻⁶ and this apparently exceptional entity often seems to be combined with microscopic colitis.

Our three patients presented with chronic diarrhoea and signs of ileal malabsorption. The diagnosis of ileal villous atrophy was suspected by ileoscopy which showed a mosaic pattern after methylene blue instillation,⁷ and was confirmed by histological examination. Our patients had isolated ileal atrophy without significant morphological or functional duo-

denojejunal abnormalities; usual aetiologies of ileal atrophies were ruled out, and the ileal atrophy was therefore considered to be primary.

The main characteristics of 10 of the 11 cases of PIVA reported (including our three) are indicated in table 2. Details concerning the remaining patient were not available.⁶ All subjects complained of chronic severe diarrhoea. In seven cases, diarrhoea had begun between the age of 33 and 45. Weight loss was observed in half the patients, and only one case showed signs of jejunal malabsorption. One patient had significant steatorrhea,¹ two had ileal malabsorption of vitamin B₁₂,² and seven had abnormal tests for ileal bile salt reabsorption. Abnormal ileal capillaries were observed in one case.¹ The therapeutic efficacy of cholestyramine was observed in seven out of eight cases, and mesalazine, sulphasalazine, corticosteroids, somatostatin, and octreotide proved ineffective in three cases (including the present series).³

Several mechanisms may cause diarrhoea. The absence of a significant osmotic gap and persistence of the diarrhoea in our three patients during a fasting test showed a secretory mechanism also indicated by hypokalaemia and abundant diarrhoea. A moderate increase in faecal clearance of α_1 -antitrypsin revealed protein losing enteropathy in all three cases. The results of our intestinal perfusion studies did not argue in favour of hypersecretion, either in the atrophic ileum or whole small bowel; colonic hypersecretion was thus likely. This may be due to bile salt malabsorption¹¹ and/or to the presence of microscopic colitis. Bile salt malabsorption was observed in some but not all cases. Colonic lesions were seen in seven of 11 patients. They consisted of lymphocytic colitis in five cases (including the present series),^{3,5} collagenous colitis in one case,⁶ and increased numbers of plasma cells in the rectum in one case.¹

Cases of microscopic colitis of the collagenous or lymphocytic type, either with an ileal extension or associated with coeliac disease, have been reported.¹³⁻¹⁸ This suggests either that there is a common pathogenesis for intestinal and colonic involvement or that ileal disease has a role in the pathogenesis of the colonic lesions. Dysimmunity may have a role in microscopic colitis,^{6,12} and the hypothesis that it has a role in PIVA has also been suggested.² Alternatively, one may postulate that in patients with PIVA, ileal dysfunction favours the passage to the colon of intraluminal substances with colonic toxicity. Indeed, the faecal stream, bacterial toxins and/or bile salts have been suggested to be involved in the pathogenesis of collagenous colitis.¹⁹⁻²¹

In summary, PIVA can be diagnosed if ileoscopy and biopsies are performed systematically in patients with unexplained chronic diarrhoea and if the site of biopsy is not erroneously interpreted. The frequent association of PIVA with microscopic colitis suggests a common pathogenic mechanism. However, this association seemed exceptional in the series of patients with microscopic colitis who underwent ileal exploration.^{12,18,22}

- Two of the three cases have previously been published in abstract form (Atrophic iléale primitive: une nouvelle entité. *Gastroenterol Clin Biol* 1990; **14**: A32).
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