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CASE REPORT

Protein-Losing Enteropathy in Systemic Lupus Erythematosus

Observations by Magnifying Endoscopy

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We report a 35-year-old man with systemic lupus erythematosus and an associated protein-losing enteropathy that was most likely due to mesenteric venulitis or thrombosis. Evaluation of the patient's intestinal abnormality was aided by the use of magnifying endoscopy; the duodenal villi were lustrous and swollen and of various size, a pattern different from that previously described for intestinal lymphangiectasia. The patient was treated with corticosteroids, resulting in a good clinical response and return of the villi to normal shape and size.

KEY WORDS: protein-losing enteropathy; systemic lupus erythematosus; magnifying endoscopy; venulitis.

CASE REPORT

A 35-year-old man was admitted to the Keio University Hospital because of edema of the legs and diarrhea. Eight years previously the diagnosis of systemic lupus erythematosus (SLE) was made on the basis of arthralgia, butterfly rash, psychosis, positive antinuclear antibody, and positive LE preparation. He was treated with corticosteroids and responded, and the medication was discontinued. Five months before admission he had diarrhea, general malaise, and edema of the legs. He developed dyspnea on exercise, and the diarrhea and edema increased. He had a low-grade fever and tachycardia. His blood pressure was 120/76. There was an ulcer in the oral cavity, edema of both legs, and tenderness and a Homan's sign on his left leg. Examination of his heart, lungs, and jugular venous pulse revealed no abnormalities.

The erythrocyte sedimentation rate was 65 mm/hr, the hematocrit 33.7%, and the white cell count 15,600/mm^3. He had trace proteinuria (250 mg/day) and normal urinary sediment. Urine volume was 320–600 ml/day. Total serum protein was 2.9 g/dl and albumin 0.95 g/dl. The prothrombin time was 13 sec (normal 12–16) and partial thromboplastin time 41.6 sec (normal 28–38). The urea nitrogen was 10.0 mg/dl, creatinine 0.7 mg/dl, and total serum cholesterol 188 mg/dl. The liver function tests were normal. The serum C3 was 32 mg/dl (normal 48–73), and the antinuclear antibody test was positive at 1:160 dilution (speckled pattern). The radioimmunoassay of anti-DNA was 5.5 (normal less than 10). The test for anticardiolipin was negative. Serum immunoglobulins were: IgG 796 mg/dl, IgA 247 mg/dl, and IgM 154 mg/dl. The direct Coomb's test was negative. Chest roentgenogram showed bilateral pleural effusions. An upper gastrointestinal series disclosed moderate coarsening of the folds in the duodenum and jejunum. Barium enema showed no abnormalities. The stool was +++ for occult blood. The half-life of radioiodinated albumin in the serum, measured as described (1), was 1.9 days (normal 10–20 days). Radionuclide venography revealed delayed flow of isotope in his left inguinal vein, although the deep femoral vein was seen to the level of the iliac vein. Collateral veins to the pudendal and superficial epigastric veins were seen. In the delayed image there were two "hot spots" remaining in the left inguinal vein.

The patient's hypoproteinemia and fever (38.5° C) continued after admission, so he was given prednisolone, 30

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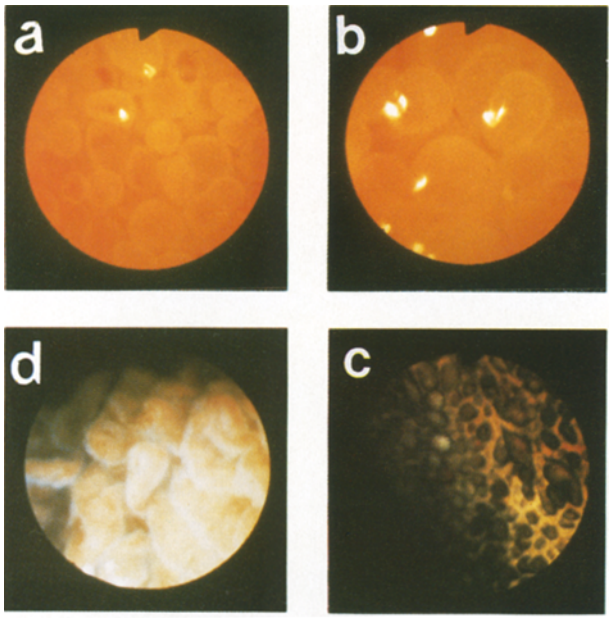

Fig 1. Views of duodenal mucosa through the magnifying endoscope. (a) About 20 times magnification. (b) About 40 times magnification. The villi are swollen and lustrous. (c) About 10 times magnification after spraying the mucosa with methylene blue. Various sizes of villi are evident. (d) About 40 times magnification after six weeks' treatment with prednisolone. The villi are fingerlike, and the swelling and congestion have disappeared.

mg daily. The fever subsided within a few days, and edema of his legs receded. Serum levels of total protein began to increase, reaching 6.0 g/dl by four weeks after the start of treatment. The oral ulcer and tenderness of his legs disappeared. Six weeks after the onset of treatment, proteinuria (2–4 g/day) appeared temporarily. The dose of corticosteroids was tapered to about 5 mg/day without recurrence of edema or diarrhea.

Magnifying Endoscopy Observations. The duodenal mucosa was visualized through a magnifying fiberendoscope (Olympus GIF HM), inserted to the descending portion of the duodenum after fasting. When examined soon after admission, without magnification, the mucosa looked a little edematous, but scattered white spots and white villi were not observed. Under 40× magnification, the villi appeared swollen and edematous, with fresh and lustrous surfaces, resembling salmon roe (Figure 1a, b). After spraying the mucosa with methylene blue, various sizes of villi were clearly contrasted, and a few white villi became apparent (Figure 1c). Several biopsy specimens of the intestine showed large, swollen villi, with moderate edema and an infiltration of plasma cells, neutrophils, and eosinophils (Figure 2a). The epithelium was intact, and venules and lymphatics in the lamina propria were only slightly dilated (Figure 2b). Vasculitis was not found in the lamina propria and could not be evaluated in the submucosa because of the limited depth of the biopsies. When magnifying endoscopy was performed after six weeks of corticosteroid treatment, the shape and size of villi were normal (Figure 1d), and the arrangement of villi sprayed by methylene blue was regular. The biopsy specimen showed neither edema nor dilatation of venules and lymphatics.

DISCUSSION

This patient's case is of interest for two reasons. First, not many cases of protein-losing enteropathy (PLE) associated with SLE have been reported. Second, we used the innovative technique of magnifying endoscopy to aid in making the diagnosis of the intestinal abnormality and following the patient's course. We can find only 13 reported cases of PLE in SLE (summarized in Table 1), and ours is the first description of the small intestinal villi in that condition as observed by magnifying endoscopy.

Among the reported cases of PLE in SLE, the cause of the PLE usually was not explained, even though small intestinal biopsies were performed in most (10 of 13) cases. Definite intestinal lymphangiectasia was present in only two cases (8, 9), and in those there was no evidence of increased central venous pressure or lymphatic obstruction. In other cases, the biopsies showed only enlarged villi and inflammatory cell infiltrates (10, 13, 14). One patient had pericarditis and pericardial effusion, which may have caused the intestinal protein loss (2). Vasculitis was not present in any of the biopsy specimens but was present in one full-thickness specimen in which there was severe, diffuse vasculitis mainly involving the veins of the submucosa and muscularis externa (8). Thus, perhaps mesenteric vasculitis is more commonly a cause of PLE in SLE than is suggested by the findings in mucosal biopsies. Improvement with modest doses of corticosteroids was reported in all patients, except for one who had intestinal lymphangiectasia (9).

In our patient, PLE was the only reasonable cause of his hypoproteinemia, and mesenteric venulitis or thrombosis, with increased permeability of vessels beneath the mucosa, seems a likely explanation for the PLE. The hypoproteinemia could not be attributed to abnormal liver function, albuminuria, or gastrointestinal malignancy or ulcers. Our

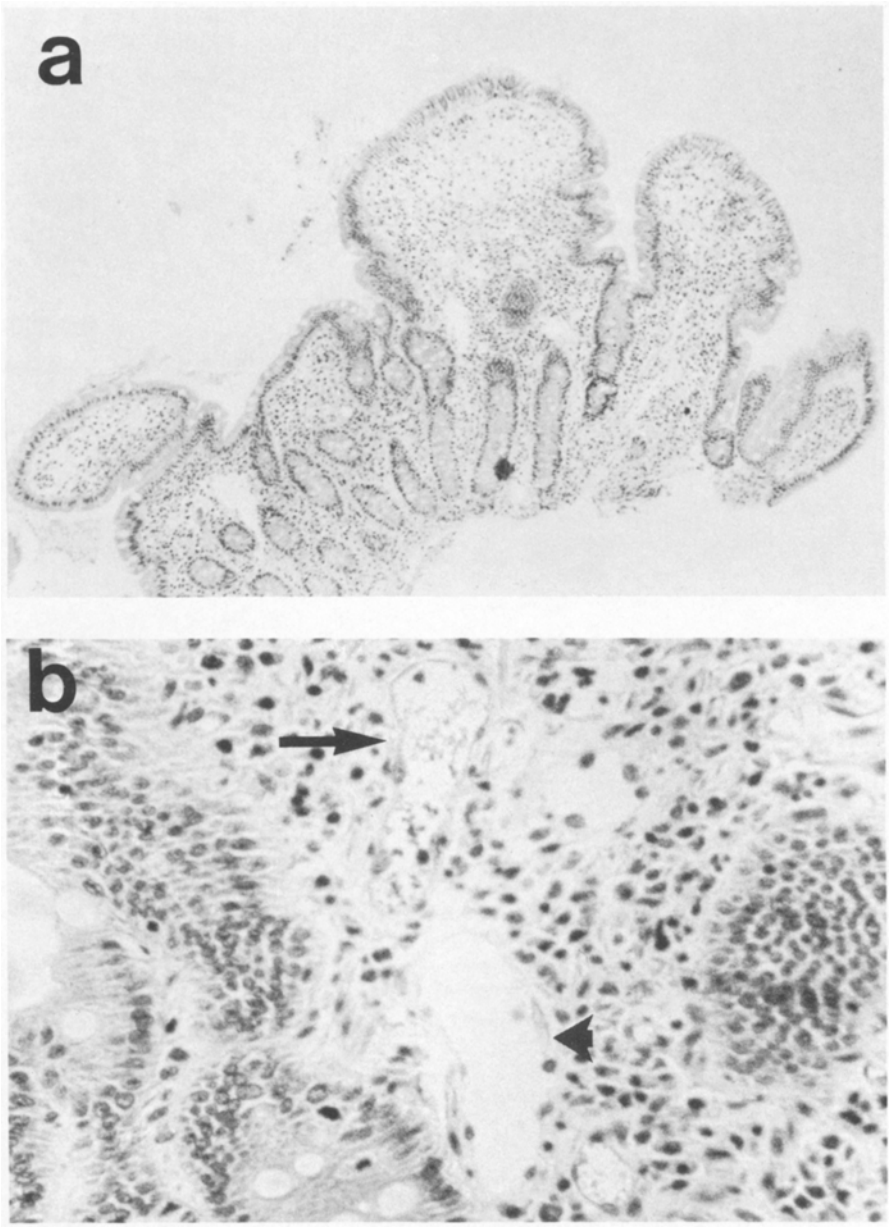

Fig 2. Biopsy specimen of duodenal mucosa taken at endoscopy. (a) Variable-sized villi, some very large and distended, with edema and an infiltration of plasma cells, neutrophils and eosinophils are present (40×). (b) A dilatated venule (arrow) and lymphatic (arrowhead) are evident at higher magnification (400×).

patient had thrombosis of his left leg and a prolonged partial thromboplastin time, findings suggestive of the presence of a lupus anticoagulant, which has a striking association with thrombosis (15, 16). Furthermore, the presence of histologically remarkable edema and dilatation of veins in the intestinal lamina propria suggested the presence of venulitis or thrombosis beneath the mucosa, despite no vasculitis in the lamina propria. Although we observed mild lymphangiectasia in the lamina propria, the lymphatics were not nearly as dilated as those seen in typical intestinal lymphangiectasia; the mild dilatation might have resulted from increased drainage of intestinal fluid rather than from obstructed lymphatics (8, 14).

Magnifying endoscopy has been used extensively in Japan for close observation of the gastrointestinal mucosa in its natural state. The normal villous

TABLE 1. SUMMARY OF REPORTED CASES OF PROTEIN-LOSING ENTEROPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS*

Case	Sex	Age	Serum Protein (g/dl)	Serum Albumin (g/dl)	Urine protein (mg/day)	Antinuclear antibodies	Anti-DNA	Response to steroids	Small intestine biopsy	Associated etiological factor	Refs
1	ND	ND	ND	ND	ND	ND	ND	ND	ND	Pericarditis	2
2	F	59	5.6	1.9	WNL	ND	ND	+	Normal		3
3	F	50	5.3	2.1	100–400	1:256 (+)	ND	+	Normal		4
4	F	23	3.8	1.2	WNL	1:64 (+)	16% (N: < 20%)	+	ND		5
5	M	12	4.2	1.3	15–90	1:160 (+)	1:160 (+)	+	ND		6
6	F	29	4.8	1.3	30	Neg	ND	+	Shortened, enlarged villi; moderately dilated lymphatic vessels	Intestinal lymphangiectasia	7
7	F	22	3.0	0.7	200–450	1:320 (+)	1:40 (+)	+	Intestinal venulitis; thickened basement membrane of epithelial cells	Intestinal venulitis	8
8	F	12	3.8	1.2	50	1:160 (+)	+ 78% (N: <25%)	Temporarily	Swollen villi; dilated lymphatic channels	Intestinal lymphangiectasia	9
9	F	29	4.9	2.1	WNL	1:640 (+)	1:1280 (+)	+	Shortened villi with edema and mild infiltration with plasma cells and lymphocytes		10
10	F	29	ND	1.4	WNL	1:256 (+)	Neg	+	Bloated villi		11
11	F	21	4.5	0.48	130–400	1:2560 (+)	1.20 (+)	+	Normal		12
12	F	22	ND	1.6	WNL	1:10,240 (+)	+ 14% (N: <5%)	+	Increased number of submucosal lymphocytes		13
13	F	33	4.5	1.8	WNL	1:10 (+)	Neg	+	Enlarged villi; dilated lymphatic channels		14
14	M	35	2.9	0.95	250	1:160 (+)	Neg	+	Enlarged villi; slightly dilated venules and lymphatic channels		This paper

*ND, not determined; WNL, within normal limits; N, normal; Neg, negative.

pattern as seen through the magnifying endoscopy has been described as finger-shaped with a regularly arranged ridged, convoluted pattern (17, 18). The appearance of our patient's intestinal villi at initial examination differed markedly from the normal pattern, in being very swollen and lacking the convoluted arrangement. The villi also differed from the description of villi in intestinal lymphangiectasia, which have been observed to be more distended, somewhat dull, and to be whitish or have scattered white spots, perhaps due to the exudation of chyle (19, 20). After corticosteroid treatment, our patient's villous pattern dramatically changed towards a normal appearance in conjunction with clinical evidence of resolution of his PLE. Magnifying endoscopy was useful in diagnosing and evaluating the course of PLE in our patient, and we suspect it may be similarly useful in other small-bowel diseases.

SUMMARY

We describe a 35-year-old man with a protein-losing enteropathy associated with systemic lupus erythematosus. The use of magnifying endoscopy to examine the intestinal villi helped to identify the intestinal abnormality and to distinguish it from intestinal lymphangiectasia.

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