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T. Madhavan

C. E. Rupe

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Intestinal Lymphagiectasia with Normal Immunological Function

A Case Report

T. Madhavan, M.D.* and C. E. Rupe, M.D.**

A patient is reported with histologically proven intestinal lymphangiectasia and protein losing enteropathy. The gastrointestinal protein loss and the effect of low fat diet have been demonstrated. The morphological abnormalities with radiological and lymphangiographic findings are discussed. Immunological studies are analyzed. These patients may have normal function both humoral and cellular, in spite of fairly advanced disease. Also the new hereto unreported association of Graves' Disease and intestinal lymphangiectasia has been brought out.

The syndrome of lymphangiectasia with hypercatabolic protein loss was first described in 1961 by Waldmann et al, who reported a group of 12 patients with hypoproteinemia and exudation of proteins into the gastrointestinal tract.[1] The pathologic findings in the small intestine showed pronounced dilatation of the lymphatics of the mucosa and submucosa,[1] and chylous effusions.[2,3] Introduction of newer technics (including Cr^{51} labelled albumin, 1^{131} labelled Polyvinyl pyrrolidone and 1^{131} labelled serum proteins)[1] has enabled the detection and quantitation of this protein loss.[4,5] Immunological investigations have also thrown light on the immunological aspects of this disease.

Report of a Case

A 36-year-old white male was admitted to Henry Ford Hospital for the third time on April 20, 1969, with an illness dating back three years when transient, intermittent pedal edema had first appeared. During hospitalization at that time (June, 1966), all the pertinent laboratory findings were normal except for a total protein of 6.2 gm/100 cc; an albumin of 3.68 gm/100 cc; $a_1$globulin 0.39 gm/100cc; $a_2$globulin 0.67 gm/100 cc, and gamma globulin 0.84 gm/100 cc. A diagnosis of hyperthyroidism was made on the basis of clinical symptoms, presence of diffuse goiter, protein-bound iodine of 10.9 μg/100 cc and 24-hour radioiodine uptake of 71%. Following treatment with Tapazole 10 mg q.i.d. for eight months, there was remission of the disease.

The patient was readmitted in May 1967 with lymphadenopathy involving axillary, posterior cervical, supratrochlear and inguinal nodes which were discrete, hard and slightly tender. He also had a palpable liver about 9 cms below the right costal margin. Laboratory findings were negative. Biopsy of the right axillary node was reported as "reactive hyperplasia." The serum protein pattern was essentially unchanged from that of previous admission. A chest x-ray revealed a small, left pleural effusion. Over the ensuing months the edema became more frequent and severe gradually involving the thoracic and abdominal serous cavities with attendant symptoms of dyspnea, abdominal distension and pedal edema. The patient formerly smoked one pack of cigarettes a day. He had never been jaundiced; bowel habits were regular, although stools were occasionally frothy and floating. There was no family history of chronic and debilitating disorders.

*Department of Medicine
**Fourth Medical Division

Physical examination revealed a well-developed, thin white male, not in acute distress but slightly dyspneic. The blood pressure was 136/86 mm Hg, pulse 90/min and temperature was normal. Integumental changes consisted of thickening and ridging of fingernails. Small lymph nodes were palpable in both cervical, axillary and inguinal regions. They were hard and discrete. Chest examination revealed dullness and diminished breath sounds over the right hemithorax. Abdominal examination revealed moderate ascites with no hepatosplenomegaly. Deep pitting edema of the feet, ankles and pretibial areas was present. All other findings were normal. X-ray films of the chest showed moderate pleural effusions on both sides. An esophagram revealed minimal motor abnormality with a small hiatal hernia. Barium studies of the upper gastrointestinal tract revealed a retroperitoneal mass, probably lymph nodes, pressing on the duodenal loop, possibly with some invasion and infiltration. A small bowel series was compatible with a diffuse infiltrative process, such as lymphoma. The hemoglobin was 15.6 gm/100 cc. There was mild leukocytosis ranging from 10200-16900/cu mm with persistent lymphopenia ranging from 2% to 13%, but on one occasion lymphocytes were 28%. Peripheral smear was normal. Bone morrow studies showed an increased myeloid: erythroid ratio (4.8 to 1). PDD and coccidioidomycosis skin tests were negative. Skin tests for monilia (12 mm), mumps (18 mm) and histoplasmosis (14 mm) were positive. The pleural fluid analysis revealed protein of 3.8 gm/100 cc and specific gravity of 1025. Cultures were negative. The serum albumin concentration was 3.6 gm/100 cc with a total protein of 6.2 gm/100 cc on admission but became progressively lower, dropping to 1.77 gm/100 cc with a total protein of 4.3 gm/100 cc on 6/12/69 (Table I). Serum carotene was 59 mcg%. A xylose tolerance test for intestinal malabsorption revealed no defect in pentose absorption. Lupus erythematosus preparations and antinuclear factors were negative. The electrocardiogram revealed low voltage and poor progression of R-waves in V_{1-3}.

Table I

Serum Protein Determinations

	T. P.	Albumin	Globulins - 1	- 2	Beta	Gamma
June, 1966	6.2	3.6	0.39	0.61	0.67	0.84
Sept., 1967	6.2	3.9	0.28	0.53	0.69	0.77
April, 1969	5.7	3.2	0.29	0.63	0.80	0.75
June 6, 1969	3.5	1.9	0.17	0.52	0.52	0.35
June 7, 1969	4.5	2.2	0.5	0.7	0.6	0.5
June 12, 1969	4.3	1.77	0.51	0.89	0.72	0.42
June 13, 1969	4.5	2.39	0.41	0.66	0.54	0.5
Low Fat Diet						
June 19, 1969	5.1	2.55	0.50	0.87	0.73	0.46
June 23, 1969	5.3	2.82	0.13	0.83	0.87	0.65

A biopsy of the right inguinal node performed on April 24, 1969, showed chronic lymphadenitis. On June 5, 1969, a peroral biopsy of the small intestine revealed a normal jejunal mucosa. Pleural fluid cytology was negative for malignancy. Lymphagiograms done with "Ethiodol" demonstrated hypoplastic lymph vessels of the lower extremities (Fig 1), and occlusion and dermal backflow below the left knee (Fig 2). The large femoral and inguinal lymph nodes had lower dye uptake, suggestive of chronic infection (Fig 3).

The patient was treated with 80 mgs of Furosemide daily and subsequently discharged.

On June 1, 1969, he was readmitted

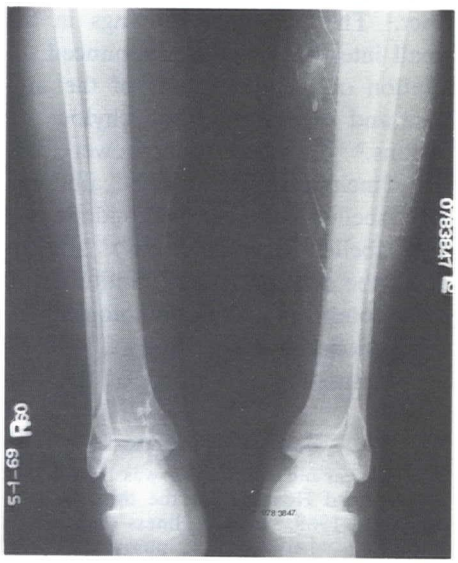

Figure 1
Hypoplastic lymphatic vessels below the knee.

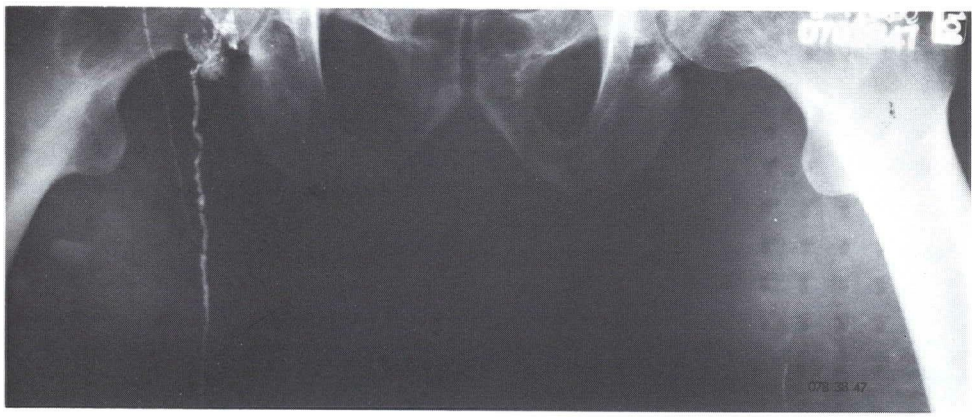

Figure 2

Lymphangiogram demonstrating the dermal backflow.

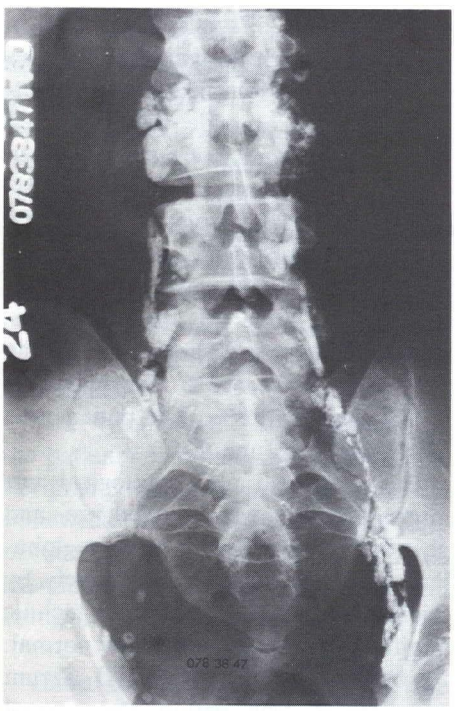

Figure 3

The femoral and inguinal lymph nodes enlarged with less uptake of the dye

for laparotomy. Pleural effusions required repeated aspirations before the operation. The fluid was clear and straw colored. On June 16, 1969, laparotomy was performed under general anesthesia. In the peritoneal cavity 2200 cc of thick chylous ascites was encountered. The upper jejunum was grossly edematous with dilated lymphatic channels. There was milky staining of the mesenteric border of the upper jejunum with visible oozing of the milky fluid at this level (Fig 4). There were numerous tiny elevations which appeared to be lymphatic telangiectasia in the upper two feet of the jejunum but not in the upper ileum. The anterior mesentery of the small bowel, particularly the upper jejunum, was grossly thickened and rubbery with dilated lymphatics. Histopathological studies of the appendix, a mesenteric lymph node and a segment of liver were normal. A yellowish-tan segment of small intestine which included mucosa and submucosa from two levels of the ileum exuded a milky fluid when

Figure 4

Small bowel showing the grossly edematous anterior jejunum with dilated lymphatic channels and milky staining of the mesenteric border.

transected. Numerous single and grouped dilated, sometimes coalescing, endothelial lined spaces were found in the broad folds of the mucosa and to a lesser extent in the submucosa (Fig 5). These were interpreted as lymphatics. Some of the lumens contained a homogeneous, lightly eosin-stained material, a few mononuclear cells and vacuoles of varying size. Weak to moderate staining of the luminal material was obtained with oil red O and osmic acid on unfixed frozen sections. No staining was observed with periodic acid Schiff or alcian blue stains.

Several groups of large mononuclear cells with finely vacuolated cytoplasm containing oil red O positive lipid were found in the submucosa and mucosa and sometime within lymphatics (Fig 6). Only scattered small lymphocytes and plasma cells were seen in the mucosa, with no lymphoid nodules observed in the sections studied. Treatment with Furosemide was continued postoperatively. A low fat diet yielded some improvement in the serum albumin which rose from 1.77 gm/100 cc to 2.82 gm/100 cc. A dose of 50 microcuries of Cr^{51} was injected intravenously on June 23 and stools collected for the next 92 hours showed the Cr^{51} level to be 9.3%. Normal Cr^{51} level is less than 1%. The patient was discharged on June 27.

Both humoral and cytological immune responses were studied pre- and post-operatively. Serum immunoglobulins were determined quantitatively by micro-double diffusion in agar technic and found to be normal or low normal. Results are shown in Table II. Serum complement was within the normal range, as was the beta Ic/IA globulin on two different occasions. Heterophile

Table II

	Serum Immunoglobulins		
	IgG (600-1400)	IgA (30-135)	IgM (40-120)
4/26/69	554	97	44
6/23/69	544	147	52
7/01/69	776	177	31

Table III

Enteric Virus Neut. Antibody Titers: (IgG Quality and Quantity)

(Normal: 1:16)

	Polio			Coxsackie						Echo		
	(1)	(11)	(111)	(A9)	(B1)	(B2)	(B3)	(B4)	(B5)	(6)	(9)	(14)
Sa	-											
Sa_1	-											
Sb 6/23/69	16	32	32	<8	256	NS	128	-	16	<16	16	
Sc 7/01/69	32	64	64	8	256	32?	256	-	32	< 8	16	

	Herpes Group				
	H. Simplex	H. Zoster	Cytomegalo	Heterophile	CRP
Sa 4/26/69	-			Neg.	-
Sa_1 6/07/69	-			-	-
Sb 6/23/69	-			Neg.	0.3 mg%
Sc 7/01/69	64	4	8	Neg.	0.6 mg%

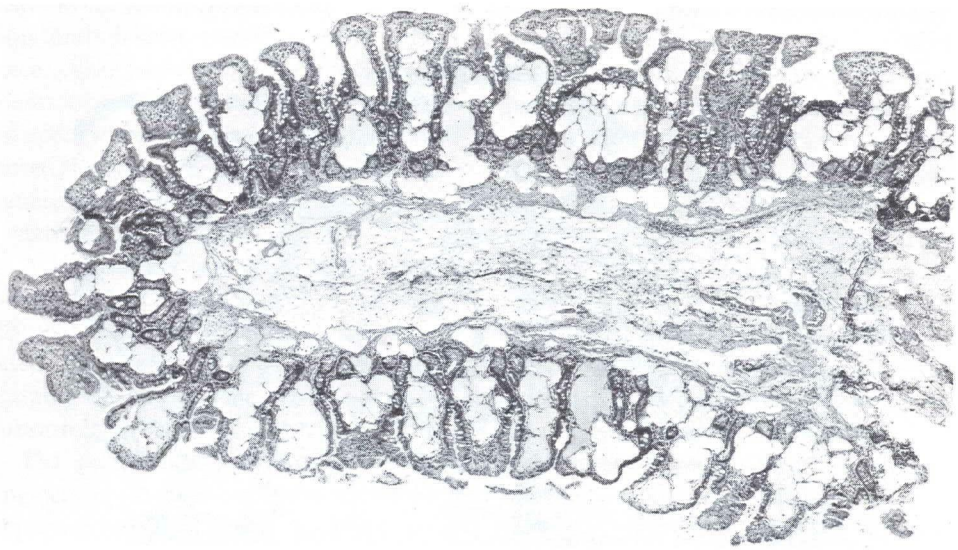

Figure 5

Numerous empty and filled dilated lymphatics are present principally in the mucosa producing widened blunted muscosal folds. H and E X35

titers were negative and CRP was normal. Enteric virus neutralizing antibody titers were also normal (Table III). Skin windows using Dr. Rebuck's technic and diphtheria toxoid[15] revealed an early neutrophilic response (3 hrs), followed by a moderate number of monocytes (6 hrs and 9 hrs) and later a small number of lymphocytes (12, 14 and 24 hrs). Overall inflammatory response was below normal limits.

Ten lymphocyte cultures utilizing the patient's lymphocytes were studied. Peripheral lymphocytes stimulated by pokeweed mitogen in tissue culture produced a 34-fold increase in tritiated thymide uptake, compared to control cultures.

Discussion

Intestinal lymphangiectasia is the most common and most recently recognized protein-losing enteropathy characterized by early onset of massive, frequently asymmetrical edema, mild gastrointestinal symptoms and generalized disorders of lymphatic channels including dilated telangiectatic lymphatic vessels of the submucosa of the small bowel. The immunologic phenomena associated with this syndrome include hypogammaglobulinemia, lymphocytopenia and impared homograft rejection. The 9.3% fecal loss of intravenously injected Cr^{51} establishes that our patient had loss of serum proteins thru the gastrointestinal tract. There was slight increase in the amount of serum albumin after dietary fat restriction as noted in previous studies.[6-8]

Roentgenograms of the small bowel revealed coarsening of the folds, most pronounced in the jejunal area, separation of the loops with suggestion of bowel wall thickening, compatible with diffuse infiltrative process. These findings are consistent with previously re-

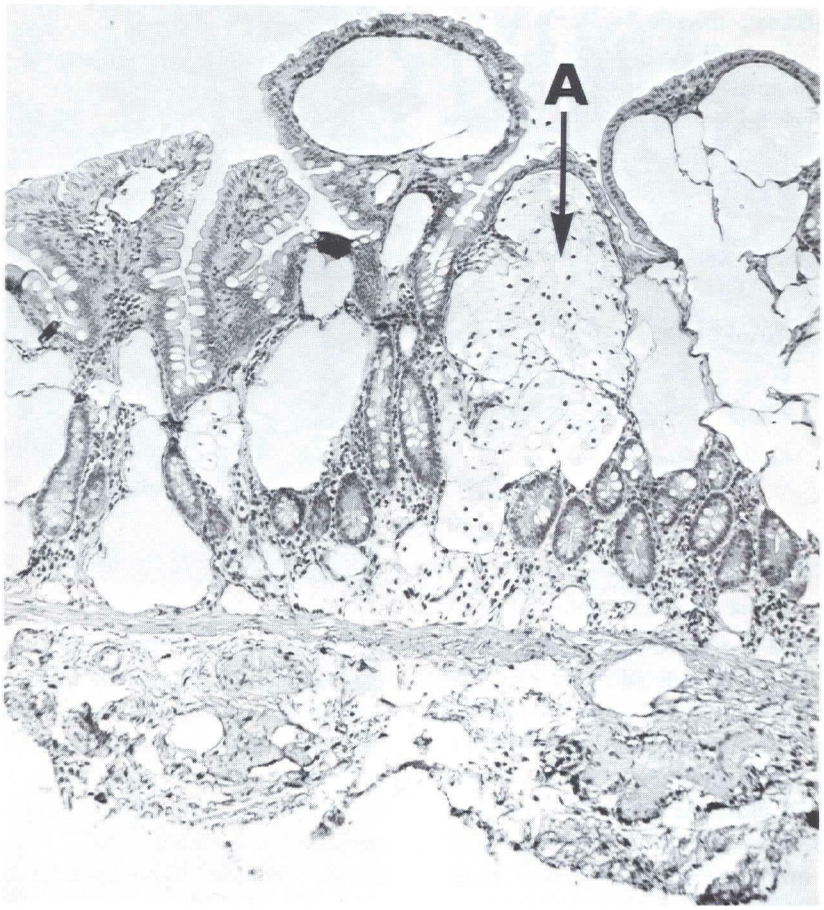

Figure 6

Details of the lymphatics, some of which contain vacuolated macrophages (A), and mucosal distortion are noted here. H and E X115

ported cases of intestinal lymphangiectasia.[4]

Pomerantz and Waldmann reported the lower extremity lymphangiograms on four patients with this syndrome.[9] Three patients exhibited hypoplasia of the lower extremity lymphatics. The fourth patient had agenesis of the inguinal, pelvic and retroperitoneal lymph nodes. This patient also demonstrated a tortuous double thoracic duct as well as several large supraclavicular lymph nodes.

Another case reported by McGuigan et al demonstrated dilatation of the lacteals with normal appearance of the retroperitoneal lymphatic system.[10] It was assumed that there was accompanying congenital atresia of the lymphatic vessels draining the hands and wrists. Our patient showed similar peripheral lymphatic findings: hypop-

lastic lower lymph vessels with obstruction and dermal backflow below the knee. Also he had significant enlargements of groups of lymph nodes with no specific histologic pattern. This supports the view that this is part of a generalized disorder of the lymphatic system.[11]

A laparotomy was required to demonstrate the hallmark lesion of this disease: edematous jejunum with dilated lymphatic channels and milky staining of the intestine. This was later substantiated by histopathology.

The occurrence of intestinal lymphangiectasia in four of seven cases of nephrotic syndrome was reported recently from Portugal.[12] Also a malabsorption syndrome has been reported by Dobbins consisting of congenital beta lipoprotein deficiency and intestinal lymphangiectasia.[13] The association of hyperthyroidism and intestinal lymphangiectasia in our patient is unusual and the relationship between the two is yet to be evaluated.

In a review of immunological functions of 18 patients with this disease, Strober et al clearly demonstrated that these patients have greatly reduced serum concentration and total body pool of each immunoglobulin.[14]

Surprisingly in our patient all the three immunoglobulins (IgA, IgM, and IgG) were found to be normal or low normal. These patients also exhibit slightly impaired circulating antibody response. Here again our patient's viral neutralizing antibody titers were within normal range. The isolated elevation of herpes simplex titer of 64 could represent subclinical viral infection during the postoperative period.

Lymphocytopenia is consistent with the previously reported cases. Anergy and impaired homograft rejection in patients with intestinal lymphangiectasia have suggested a deficiency of lymphocyte-mediated immune responsiveness. Our patient exhibited a positive response to monilia and mumps antigens. The delayed hypersensitivity was also subsequently demonstrated in the skin windows but with lesser number of lymphocytes. Lymphocytes from our patient's blood, though reduced in number, were capable of responding to mitogenic stimulation. There appears to be no demonstrable cellular defect of lymphocyte function. This correlates very well with McGuigan's observations.[10]

Acknowledgement

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