Small Intestinal Lymphangioma

J. A. WALKER-SMITH, R. D. K. REYE, G. B. SOUTTER, and K. G. KENRICK

From the Institute of Child Health, Institute of Pathology, and Children's Medical Research Foundation, Royal Alexandra Hospital for Children, Sydney, N.S.W., Australia

The syndrome of idiopathic hypoproteinaemia without proteinuria and with normal hepatic function has in recent years been shown to result from excessive loss of plasma protein into the alimentary tract (Schwartz and Jarnum, 1959; Waldmann *et al.*, 1961; Jarnum and Petersen, 1961). Dilatation of the small intestinal lymphatics (lymphangiectasia) has been a frequent finding in many patients with this syndrome (Waldmann *et al.*, 1961; Jarnum and Petersen, 1961; Waldmann, 1966). The pathogenesis of the hypoproteinaemia in such patients has been attributed to the rupture of dilated lymphatic channels or to protein exudation from intestinal capillaries via an intact epithelium, when there is obstruction of the lymphatic flow (Waldmann, 1966). This syndrome is well recognized in infants and children. In several paediatric reports there has been evidence of a widespread lymphatic abnormality involving lymphatics outside the small bowel, e.g. chylothorax and lymphoedema (Jarnum, 1963; Poley *et al.*, 1967).

The aim of the present report is to present the history of an infant with the syndrome of idiopathic hypoproteinaemia, who had, at necropsy, a diffuse capillary lymphangioma confined to the small bowel and its mesentery.

Case History

The patient, a female infant, was born at full term after a normal delivery, her birthweight being 3.5 kg. After breast-feeding for 5 weeks, she was weaned to dilute cow's milk. This led to diarrhoea with 6 to 7 loose, offensive stools per day and vomiting with each feed, but she continued to gain weight satisfactorily. At 2 months she was started on gluten-containing foods. At 3 months her feeds were changed to goat's milk. Her vomiting ceased immediately, but she still had 4 to 5 loose stools per day. Diarrhoea continued, with satisfactory weight gain, till she was aged 10 months when she began to lose weight.

In November 1967, aged 11 months, she was admitted to the hospital for investigation of persistent diarrhoea and loss of weight. On examination she had a large

'pot belly'. There was no ascites or oedema. Weight 9.5 kg. (on 50th centile); height 72 cm. (between 10th and 50th centile).

Investigation revealed Hb 11.6 g./100 ml., with a dimorphic film suggesting folic acid and iron deficiency; numerous fatty acid crystals in her stool on microscopy; daily faecal fat excretion of 5.5 g./day; total serum proteins 4.1 g./100 ml.; serum albumin 1.9 g./100 ml.; IgG 250 mg./100 ml. (normal 322-1245 mg./100 ml.), IgA 45 mg./100 ml. (normal 17-94 mg./100 ml.), IgM 30 mg./100 ml. (normal 29-216 mg./100 ml.) (normal range of each immunoglobulin class, for age, used in this investigation were those of Allansmith *et al.*, 1968); no proteinuria; serum calcium 7.8 mg./100 ml.; serum phosphate 6.8 mg./100 ml.; liver function tests normal; sweat electrolytes normal; stool cultures negative; stool pH 6; barium meal showed non-specific dilatation of the small bowel; lactose tolerance test indicated a rise of 30/100 ml. in blood glucose after an oral load of lactose.

A small bowel biopsy was taken from the distal duodenum, and when viewed under the dissecting microscope the mucosa was flat (Fig. 1). Though the specimen proved unsatisfactory for histological examination as the surface epithelium was not intact and the section was cut tangentially, the findings were consistent with the dissecting microscope appearance.

A diagnosis of coeliac disease was made and the child was started on a gluten-free diet. Goat's milk was continued.

She was seen again in January 1968, when her stools were stated to be only 2 per day and were firmer. She was then followed as an out-patient for the next 5 months gaining 1 kg. in weight, but intermittent episodes of diarrhoea continued.

At 21 months the child was readmitted because weight gain had ceased. On examination her weight was 10.3 kg., and she had a 'pot belly'. Investigation showed Hb 13.0 g./100 ml., with a normal blood film; WBC 12,000 (lymphocytes 480 cu.mm.); total serum proteins 3.0 g./100 ml.; albumin 1.8 g./100 ml.; protein-bound iodine 2.1 mg./100 ml. (normal 4-8 mg./100 ml.); serum calcium 6.2 mg./100 ml.; serum phosphate 5.2 mg./100 ml.; no fat globules or fatty acid crystals in stools. Daily faecal fat was not estimated.

Small bowel biopsy was repeated from the proximal jejunum just beyond the duodeno-jejunal flexure. Under the dissecting microscope the mucosa was characterized by tongues, leaves, and short thick ridges

Received January 20, 1969.

FIG. 1.—*Flat duodenal mucosa.* ($\times 18$.)

FIG. 2.—*Jejunal mucosa with dilated lacteals in lower right corner.* ($\times 18$.)

(Fig. 2). Dilated lacteals containing white material could be seen. Histologically there was a degree of partial villous atrophy and well-marked dilatation of the lacteals (Fig. 3).

In view of the biopsy findings, she was given a trial of medium-chain triglyceride milk, as this has been shown to be of value in intestinal lymphangiectasia (Holt, 1964). However, once again her diarrhoea

FIG. 3.—*Section of jejunal mucosa with a dilated lacteal.* ($\times 100$.)

became worse and she lost weight. Goat's milk was restarted and she was sent home.

She was readmitted 2 weeks later, with a 4-day history of oedema of the feet and ankles. At this time her total serum proteins had fallen to 2.8 g./100 ml., albumin 1.4 g./100 ml., and serum calcium 4.8 mg./100 ml. Using a micro-Ouchterlony double immunodiffusion test system (Kenrick and Walker-Smith, 1969) antibodies to cow's milk, goat's milk, ovalbumin, crude egg albumen, egg yolk extract, sheep muscle extract, and bovine muscle extract were shown. No gliadin antibodies were found. A lymphangiogram was performed, with injection into the vessels on the dorsum of the left foot. This revealed a normal lymphatic system in the left leg and abdomen and no obstruction to the thoracic duct.

The child was given a 4-day course of intravenous albumin and was started on calcium gluconate and vitamin D. These measures led to an improvement in her general condition, with loss of oedema. While in hospital she had intermittent diarrhoea, and on 2 occasions a small amount of blood was seen in her stools. Sigmoidoscopy showed a friable mucosa which was reddened and bled easily. She was placed on a strict milk-protein-free, high-protein, gluten-free diet and was discharged. When seen as an out-patient a week later she was much improved. However, her oedema rapidly returned and she was readmitted 18 days after discharge with gross oedema, and for the first time ascites was present.

On investigation Hb 12.6 g./100 ml.; WBC 11,000 (lymphocytes 1800/cu.mm.); total serum proteins 2.4 g./100 ml.; albumin 0.9 g./100 ml.; IgG 290 mg./100 ml.; IgA 36 mg./100 ml.; IgM 63 mg./100 ml.

Steroids were started (40 mg./day). However, she failed to take feedings orally and had to be fed via an intragastric tube using a homogenized high protein mixture. It proved difficult to maintain a normal protein intake. Three days after being admitted albumin infusions were again given as the serum albumin level had not risen (0.8 g./100 ml.). However, her clinical condition deteriorated, and she died the next day aged 21 months.

Necropsy

Gross. All tissues were oedematous; there were effusions in both pleural cavities (right 250 ml., left 50 ml.). Both lungs were partially collapsed and very oedematous. The heart was small and the myocardium was flabby. Ascites was present (550 ml. transudate). The mucosa of the small intestine was greatly thickened and the rugae were very prominent. The colonic wall was also thickened and congested.

Dissecting microscope appearances of small bowel. The small bowel was allowed to stand in water for 24 hours, the epithelial cells sloughing off. The connective tissue cores of the villi were then stained with ordinary ink. The mucosal architecture was examined under the dissecting microscope, along the length of the small bowel, as described by Creamer

and Leppard (1965), G. Nicholson (1965, personal communication), and Walker-Smith (1969).

There was a considerable variation in appearance along the bowel (Fig. 4). The villous cores in the duodenum and first part of the jejunum had the appearance of thin ridges and tongues, some containing white material. Further on, in the jejunum, the mucosa was characterized by short thick ridges and tongues and the white material became more prominent. From about 60 cm. beyond the duodeno-jejunal flexure, globular structures, some fused into masses and containing white material, were seen. These became more common distally, where the appearance was most unusual with villous cores ranging in shape from fat fingers to globular masses (Fig. 5). This white material was most obvious in the ileum, but was irregularly distributed. On histological section it was shown to correspond to dilated lymphatics, though these were empty after processing (Fig. 6). These ileal appearances were strikingly different from those seen in infants and children dying from non-gastro-enterological disease (Fig. 4) (Walker-Smith, 1969).

Histology. Histological sections taken at various levels of the small bowel, and in the mesentery attached to these sections, showed a diffuse proliferation of lymphatic vessels. The vessels became more prominent as the more distal parts of the bowel were reached. These vessels were principally located in the mesentery and in the serous and submucosal coats of the bowel, and they were for the most part thin-walled and tortuous channels (Fig. 7), though the amount of smooth muscle in the walls varied and was sometimes quite thick even in vessels of small calibre. The lumina were empty and there were no lipid-containing cells in relation to them. Autolytic changes rendered the mucosal detail indifferent, but in some of the better preserved villi the cores could be seen to be occupied by distended lacteals. In a section taken to include a group of mesenteric lymph nodes the overgrowth of lymph vessels could be seen to surround and extend into the nodes to occupy part of the nodal tissue (Fig. 8). There was patchy congestion of the mucosa of the colon, but otherwise the colon was normal.

The appearances seen are best described as a diffuse capillary lymphangioma involving the small bowel and its mesentery.

Discussion

This child had severe progressive hypoproteinaemia with extreme reduction of the serum albumin, a low serum IgG, a low protein-bound iodine, and lymphopenia, as typically occurs with enteric protein loss (Waldmann, 1966). Such protein loss is often accompanied by enteric calcium loss leading to hypocalcaemia (Mistilis and Skyring, 1966). A significant hypocalcaemia was present here. Indeed, despite the absence of a confirmative radio-isotope study, all the evidence available suggests that this child had protein-losing entero-

FIG. 4.—Diagrammatic representation of small bowel morphology in patient and in a child of the same age dying from congenital heart disease.

pathy, as a sequel to an abnormality of the lymphatics of the small intestine. McKendry, Lindsay, and Gerstein (1957) described similar multiple dilated lymphatic channels in the small intestine and its mesentery, with the histological appearance of a lymphangioma. However, the term intestinal lymphangioma has not often been used in the literature, as the term intestinal lymphangiectasia is usually used when referring to dilated intestinal lymphatics. This has been described either as a primary abnormality, congenital or acquired, of the small intestinal lymphatics (Fisher, 1966) or as a secondary phenomenon, e.g. as a consequence of constrictive pericarditis (Petersen and Hastrup, 1963). In this report the term small intestinal lymphangioma is preferred, as there was no evidence of lymphatic abnormality outside the small intestine and its mesentery, either with lymphangiography or at necropsy, and the histological features were characteristic of lymphangiomata.

The management of this patient presented many difficulties. First, in life the diagnosis was uncertain. Coeliac disease, congenital abnormality of the intestinal lymphatics, and milk protein intolerance were at different times considered to be the principal diagnoses. Secondly, assessment of her response in the last part of her illness to various dietary regimens was clouded by variable oedema, making weight response an unsatisfactory guide. Thirdly, there was considerable difficulty in maintaining adequate protein intake orally. Fourthly, the clinical response to albumin infusions was brief. Finally, steroids appeared to have no clinical benefit, but were probably administered too late to assess their effect.

On reviewing the available evidence in this child, though there was a flat intestinal mucosa on the first biopsy, with improvement in mucosal morphology after gluten restriction, the presence of gluten sensitivity remains uncertain. In addition the

FIG. 5.—Post-mortem ileal appearances. (×18.)

FIG. 6.—Section of ileum in Fig. 5. Dilated lymphatics in mucosa and in submucosa. (×40.)

FIG. 7.—Tortuous submucosal lymphatics.

FIG. 8.—Section of mesenteric lymph node.

significance of the demonstrated serum antibodies and the role of possible intolerance to various dietary proteins in this patient's illness also remain uncertain.

Dissecting microscope examination of the connective tissue cores of the villi, at necropsy, proved a valuable way to study the distribution and extent of the lymphatic abnormality. It showed that the ileum was chiefly affected, but that its distribution was irregular. The abnormal appearance of the villous cores particularly in the ileum could be due to congenital abnormality of the villous architecture.

Summary

The case history and post-mortem findings are presented of a female infant with the syndrome of idiopathic hypoproteinaemia, who at necropsy was found to have a diffuse capillary lymphangioma confined to the small bowel and its mesentery. Dissecting microscope examination of the small bowel mucosa at necropsy after standing 24 hours in water, proved a valuable way to study the extent and distribution of the lymphatic abnormality along the small intestine.

REFERENCES

- Allansmith, M., McClellan, B. H., Butterworth, M., and Maloney, J. R. (1968). The development of immunoglobulin levels in man. *J. Pediat.*, **72**, 276.
- Creamer, B., and Leppard, P. (1965). Post-mortem examination of a small intestine in the coeliac syndrome. *Gut*, **6**, 466.
- Fisher, D. A. (1966). Obscure and unusual edema. *Pediatrics*, **37**, 506.
- Holt, P. R. (1964). Dietary treatment of protein loss in intestinal lymphangiectasia. The effect of eliminating dietary long chain triglycerides on albumin metabolism in this condition. *ibid.*, **34**, 629.
- Kenrick, K. G., and Walker-Smith, J. A. (1969). Immunoglobulins and dietary protein antibodies in childhood small bowel disease (to be submitted for publication).
- Jarnum, S. (1963). *Protein-Losing Gastroenteropathy*. Blackwell, Oxford.
- , and Petersen, V. P. (1961). Protein-losing enteropathy. *Lancet*, **1**, 417.
- McKendry, J. B. J., Lindsay, W. K., and Gerstein, M. C. (1957). Congenital defects of the lymphatics in infancy. *Pediatrics*, **19**, 21.
- Mistilis, S. P., and Skyring, A. P. (1966). Intestinal lymphangiectasia: therapeutic effect of lymph venous anastomosis. *Amer. J. Med.*, **40**, 634.
- Petersen, V. P., and Hastrup, J. (1963). Protein-losing enteropathy in constrictive pericarditis. *Acta med. scand.*, **173**, 401.
- Poley, J. R., Lesch, P., Hitzig, W. H., and Prader, A. (1967). Chylöser Ascites: Untersuchungen über den Eiweissstoffwechsel und über den Einfluss des Nahrungsfetts auf die Ascitesproduktion. *Helv. paediat. Acta*, **22**, 81.
- Schwartz, M., and Jarnum, S. (1959). Gastrointestinal protein loss in idiopathic (hypercatabolic) hypoproteinaemia. *Lancet*, **1**, 327.
- Waldmann, T. A. (1966). Protein-losing enteropathy. *Gastroenterology*, **50**, 422.
- , Steinfeld, J. L., Dutcher, T. F., Davidson, J. D., and Gordon, R. S., Jr. (1961). The role of the gastrointestinal system in 'idiopathic hypoproteinaemia'. *ibid.*, **41**, 197.
- Walker-Smith, J. A. (1969). Small bowel morphology in childhood. *Med. J. Aust.*, **1**, 382.

Correspondence to Dr. J. A. Walker-Smith, Institute of Child Health, Royal Alexandra Hospital for Children, Camperdown, N.S.W. 2050, Australia.