HYPOGAMMAGLOBULINAEMIA WITH NODULAR LYMPHOID HYPERPLASIA OF THE SMALL INTESTINE

Major W. M. WALLACE, M.B., B.Ch., M.R.C.P., R.A.M.C.

Royal Army Medical College, Millbank

SUMMARY: Nodular lymphoid hyperplasia of the small bowel remains a rare cause of malabsorption and may be associated with a variety of immunoglobulin deficiencies. Two new cases are reported with contrasting modes of clinical presentation and the literature is reviewed.

Introduction

Since the syndromes of congenital and acquired hypogammaglobulinaemia were first reported (Bruton 1952; Young and Woulfson 1954) it has been well recognised that a "sprue-like" syndrome of diarrhoea and steatorrhoea may occur, especially in the acquired or "adult" form of the disorder.

It was not until Hermans et al (1965) described the typical histological appearance of lymphoid nodules in the small bowel submucosa that the association was seen as a definite entity. The clinical picture is usually one of :-

(a) Recurrent infections of the upper respiratory tract and, often, also of the lungs.
(b) Intermittent or chronic diarrhoea of varying severity. (c) a degree of hypogammaglobulinaemia usually due to IgA and IgM deficiency and, (d) the very frequent finding of infestation with *Gardia lamblia*.

The two cases to be reported reveal very contrasting modes of presentation for a single disorder and there are now twenty-five cases on record in the literature. Case 2 is believed to be the first reported in a Chinese patient.

Case reports

Case 1

A twenty-two year old white male was admitted to hospital in October 1966 complaining of intractable diarrhoea. During his previous five years of military service he had been on three tours to the Middle East and on each occasion had developed persistent diarrhoea which gradually subsided following his return to England. He was passing six to ten liquid sandy coloured, very offensive stools daily. During an overseas tour in 1965 he lost two stones in weight due to diarrhoea and on several occasions was admitted to hospital for rest and broad-spectrum antibiotics, with temporary relief only. In 1966 while again in the Middle East his diarrhoea became so severe and persistent that he required intravenous fluid replacement at one time and lost a further two stones in weight.

His susceptibility to infection of the respiratory tract was likewise spectacular, commencing when he was two years old with pulmonary tuberculosis for which he was treated for eighteen months. During the remainder of his childhood he suffered repeated upper respiratory tract infections and had pneumonia on four occasions. His military

service was marked by recurrent bronchitis, otitis media and two further episodes of pneumonia.

Physical examination revealed him to be ill, pallid and wasted with mild finger clubbing and a palpable spleen. He weighed 112 lb.

Investigations revealed Hb = 11.4 g/dl, E.S.R. = 50 mm/hr, film mildly macrocytic. Serum iron = 6.4 μ mol/l, Serum folate = 5.4 μ g/l, Red cell folate = 310 μ g/l. Serum B12 = 300 ng/l. Evidence of steatorrhoea was a faecal fat excretion of 14.6 gm per day, D-xylose excretion being low at 14 per cent excretion in 5 hours. Pancreatic function in response to secretin and pancreozymin stimulation was normal. Urinary Indicans levels were persistently elevated being between 183-322 mg per 24 hours.

Total serum proteins were low at 47 g/l, Albumin 32 g/l and Globulin 15 g/l Serum immunoglobulin levels were IgG 4.2 g/l (normal 5.0-16.0 g/l), IgA 0.6 g/l (normal 1.2-4.2 g/l) and IgM 0.12 g/l (normal 0.5-1.7 g/l).

The Heaf test was negative in spite of a previous history of tuberculosis and no agglutinins were detected against *Salmonella typhi* and *paratyphi* A, B and C despite previous inoculations and a booster dose while in hospital. No *Giardia* were seen in the faeces or duodenal juice. A barium meal was of the "malabsorption pattern".

A jejunal biopsy revealed mild villous deformity with lymphocyte infiltration of the lamina propria and discreet areas of lymphoid hyperplasia (Fig. 1). These produced an effacement of the villous pattern of the overlying mucosa and produced a nodular or polypoid appearance. Plasma cell population was normal.

Fig. 1. Case 1, a jejunal biopsy.

Fig. 2. Case 2, a jejunal biopsy.

Case 2

A twenty-three year old Chinese male was admitted to hospital with a four week history of diarrhoea. He was passing four to six copious watery stools daily but apart from some increased abdominal distension and flatulence there were no other constitutional upsets. His diarrhoea was of acute and recent onset and the only other single episode of bowel upset had been a brief self-limiting attack of diarrhoea one year previously. There was likewise no past history of sino-pulmonary infections. He had lost a total of 22 lb in weight.

Physical examination revealed a rather sallow complexion, a tympanitic abdomen and minimal peripheral oedema only.

Investigations were Hb = 13.2 g/dl, E.S.R. = 2 mm/hr, blood film normal. Serum iron = 7.2 μ mol/l, Serum folate = 7.2 μ g/l, and Serum B12 = 235 ng/l. Gross evidence of malabsorption was shown by a faecal fat of 57.8 gm per day, nil excretion of 25 gram dose of D-xylose and a flat glucose tolerance curve. Total serum proteins were 47 g/l, albumin = 34 g/l and globulin = 13 g/l. Serum immunoglobulin levels were IgG 2.0 g/l, IgA 0.3 g/l and IgM 0.1 g/l (normal levels as in Case 1). No agglutinins were detected against *Salmonella typhi* and *paratyphi* A, B and C despite previous inoculations. Microscopy of duodenal juice revealed many active motile *Giardia* and ova were seen in the stools. A jejunal biopsy (Fig. 2) revealed severe villous atrophy, lymphocytic infiltration and lymphoid follicles within the lamina propria.

Discussion

Acquired idiopathic dysgammaglobulinaemia may be associated with a spruelike syndrome in about 20 per cent of cases (Gitlin, Gross and Janeway 1959). Lymphoid hyperplasia is reported to occur anywhere in the gastrointestinal tract, but it is known that the colonic involvement described in children (Capitano and Kirkpatrick 1970) is a benign disorder which probably reflects normal developmental hyperplasia. Kahn & Novis (1974) reported a case of small bowel reticulum cell sarcoma developing in a patient with nodular lymphoid hyperplasia. There was no evidence of dysgammaglobulinaemia in this case but the possibility that the neoplasm had evolved from the lymphoid hyperplasia cannot be ignored. Hermans et al (1966) in their original description of eight patients found one carcinoma of the stomach and one of the rectum.

Ajdukiewicz, Youngs & Bouchier (1972) reported a further case and carried out extensive immunological testing to demonstrate impaired humoral immunity. The two patients here described show altered immunity. Case 1 showed a negative Heaf test despite active pulmonary disease in childhood and both cases revealed a failure of antibody response to repeated antigenic stimulation in the form of Typhoid inoculations. Absence of delayed hypersensitivity seems to be a very common finding in this disorder. The immunoglobulin deficiency may be varied and these two cases showed reduction of IgA and IgM in particular. Selective IgA deficiency is reported in association with steatorrhoea. (Crabbe & Heremans 1967).

There have been twenty-five reported cases with seventeen subjects being male and eight female. Upper respiratory infections and pneumonia are frequent associations (72 per cent) therefore Case 2 described is unusual in that respect having no past history of infection. The reason for the absence of such a history in these cases is not clear.

Diarrhoea was present in all but one patient but steatorrhoea is much less common (40 per cent). This may be multifactorial in origin and a consequence of altered immunity, bacterial colonisation of the small bowel and infestation with *Giardia lamblia*. These parasites have been discovered in 75 per cent of cases and when they are eradicated there is generally improvement in the steatorrhoea. It is well known that malabsorption can occur in giardiasis and recent electron microscopy in the mouse model has revealed *Giardia* covering the villi so completely that they act as a physical barrier to absorption. Bacterial contamination of the small intestine is frequently mentioned as an etiological agent but direct evidence of this is lacking as not all cases have been specifically investigated from this point of view. Some patients have had *Entamoeba coli* in the jejunum and

increased urinary indicans and the response to broad-spectrum antibiotics in many cases is indirect evidence of bacterial contamination.

The loss of serum proteins is a finding in many bowel disorders and this should be considered. Studies with I^{131} -labelled albumin in these patients reveal an increased catabolic rate but as this is only partly compensated for by increased albumin production there is hypoalbuminaemia. If hypogammaglobulinaemia occurs in protein-losing enteropathies there is usually marked hypoalbuminaemia as well. The disproportionate decrease in serum globulins with only a mild fall in serum albumin is in keeping with reduced production of globulin rather than increased loss.

Microscopically both cases are similar in revealing large mucosal lymphoid nodules. These partially obliterate the overlying mucosa and are associated with some villous degeneration. Case 2 reveals a degree of villous atrophy which is out of proportion to the secondary mucosal changes usually described. Both sections revealed sparse plasma cell infiltration of the lamina propria which is important in differentiating this disorder from Alpha-chain Disease initially described by Seligmann et al (1968) and more recently by Manousos et al (1974).

These patients have steatorrhoea and hypogammaglobulinaemia but small intestinal biopsy reveals a massive and diffuse mononuclear cell infiltration of the lamina propria with villous distortion. The cellular infiltrate is predominantly of plasma cells and lymphoid nodules are not seen. These patients have alpha chain proteins, free of light chains, in serum, saliva and concentrated urine and jejunal juice.

Radiological evidence of nodular lymphoid hyperplasia was not seen in these two cases, the appearances being those of a non-specific malabsorption pattern. When fully developed, nodular hyperplasia produces a characteristic radiological appearance with many filling defects which are uniform in size and smooth in contour being a few millimeters in diameter. The involvement of the small intestine may be total or segmental and there is often an abrupt transition from affected to normal bowel.

The radiological findings in these two patients revealed the appearances compatible with a flat mucosa and indeed both biopsies reveal a greater degree of villous atrophy than is usually seen in this condition. Ament and Rubin (1972) investigated eight patients with hypogammaglobulinaemic bowel disease and seven of these were infected with *Giardia*. They found two patients with nodular lymphoid hyperplasia and three patients with hypogammaglobulinaemic sprue where the mucosa was flat and the villi had largely disappeared. The other three patients presented with "mixed lesions" having nodules and villous atrophy to varying degrees.

It was then realised that some of the intestinal changes in immuno-deficiency were related to giardiasis and multiple jejunal biopsies before and after eradication of the parasite were compared. The villous pattern improved considerably following specific therapy and in some cases returned to normal.

It seems likely that the two cases reported here fall into this mixed group with nodules and villous atrophy. This is certainly true in case two where giardiasis was found and eradicated with an improvement in absorptive capacity and steatorrhoea. *Giardia* were not found in case one but we are now more aware of the insensitivities of stool examination and direct microscopy of fresh duodenal juice (usually coincident with jejunal biopsy) is advocated.

There are a great variety of primary immuno-deficiency disorders and all show defective humoral immunity with variable immunoglobulin deficiencies and an inability to produce antibodies to bacteria and common viruses. The two cases described also reveal defective cell mediated immunity as detected in vivo by the failure of the delayed hypersensitivity skin reaction. This defect is present in some patients but has little effect on their short-term prognosis. The Medical Research Council working party (1971) estimate the prevalence of hypogammaglobulinaemia to be 15 per million in men and 4 per million in women but this is probably an underestimate.

The disorder, with its gastrointestinal complication, is seen as a broad spectrum of disorders and the nodular lymphoid hyperplasia probably represents a compensatory defence mechanism on the part of the gut immune system to frequent antigenic insults which cannot be handled by the normal antibody responses.

Conclusion

Attention is therefore drawn to the association of a dysgammaglobulinaemic state with typical intestinal pathology which may lead to a malabsorption syndrome. A history of previous sino-pulmonary sepsis may prove a clue in many cases and immunological profiles will reveal varying IgA and IgM deficiencies. Specific therapy to eradicate giardiasis will effect some improvement as will broad-spectrum antibiotics but the most effective form of treatment to date is the regular injection of gamma globulin. The development of intestinal neoplasms should be considered.

Acknowledgements

I should like to offer my thanks to Major-General W. O'Brien, O.B.E., Q.H.P., M.D., F.R.C.P., Director of Army Medicine and Colonel D. Hamilton, M.B., F.R.C.P., L/R.A.M.C., Consultant Physician for permission to report cases initially under their care.

REFERENCES

- AMENT, M. E. and RUBIN, C. E. (1972). *Gut* **2**, 216-225.
 AJDUKIEWICZ, A. B., YOUNGS, G. R. and BOUCHIER, I. A. D. (1972). *Gut* **13**, 589-595.
 BRUTON, O. C. (1952). *Paediatrics* **9**, 722.
 CAPITANIO, M. A. and KIRKPATRICK, J. A. (1970). *Radiology* **94**, 323-327.
 CRABBE, P. A. and HEREMANS, J. F. (1967). *Amer. J. Med.* **42**, 319-326.
 GITLIN, D., GROSS, P. A. M. and JANEWAY, C. A. (1959). *New Engl. J. Med.* **260**, 72-76.
 HERMANS, P. E., HUIZENGA, K. A., HOFFMAN, H. N., BROWN, A. L. and MARKOWITZ, H. (1966). *Amer. J. Med.* **40**, 78-79.
 KAHN, L. B. and NOVIS, B. H. (1974). *Cancer* **33**, 837-844.
 MANOUSOS, O. N., ECONOMIDOU, J. C., GEORGIADOU, D. E., PRATSKIA-OUGOURLOGLOU, K. G., HADZIYANIS, St.J., MERIKAS, G. E., HENRY, K. and DOE, W. F. (1974). *Brit. med. J.* **ii**, 413-415.
 MEDICAL RESEARCH COUNCIL (1971). On Hypogammaglobulinaemia. *Spec. Rep. Ser. med. Res. Coun. (Lond.)* **310**, 125.
 SELIGMAN, M., DANON, F., HUREZ, D., MILHAESCO, E. and PREUD'HOMME, J. L. (1968). *Science* **162**, 1396.
 YOUNG, I. I. and WOLFSON, W. Q. (1954). *Clin. Res. Proc.* **2**, 101.