

CASE REPORTS

Hypogammaglobulinaemia with Whipple's disease

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Summary

The patient, a 54-year-old housewife, was well until the age of 40 years when she developed repeated infections. During the next 10 years recurrent attacks of diarrhoea also appeared and were associated with weight loss, increased skin pigmentation, and later the occurrence of arthralgia and polyserositis. She was found to have deficiencies of IgG and IgA. A malabsorption syndrome was established and shown to be due to Whipple's disease by jejunal biopsy. She also had hypocalcaemia and osteomalacia. Weekly injections of human gammaglobulin had no effect on either the diarrhoea or the arthralgia, although the severity of respiratory infections was reduced. Intramuscular injections of vitamin D failed to restore the serum calcium to normal. Continuous oral tetracycline was followed by marked symptomatic improvement, disappearance of the diarrhoea and some weight gain. Steatorrhoea however persisted and the jejunal histology showed only slight improvement. The serum calcium returned to normal possibly as a result of correction of a magnesium deficiency. The relevance of the hypogammaglobulinaemia to the Whipple's disease is discussed, and a search of the literature shows six other cases where both disorders were associated.

HYPOGAMMAGLOBULINAEMIA comprises an uncommon group of disorders which usually occur in infancy but may appear at any age (Hobbs, 1970). The clinical syndrome depends on the results of the immunological defect and associated non-immunological features. In the patient reported here, increasingly severe infections over a 10-year period led to the diagnosis, and a malabsorption syndrome which appeared during this time was shown to be due to Whipple's disease. Since this condition is extremely rare in females, its occurrence with another uncommon disorder made it seem probable that the two

were in some way linked. It is generally agreed that Whipple's disease is infective in origin, and it is suggested that the infection in this case was the result of the hypogammaglobulinaemia. A number of previously reported patients with Whipple's disease also had proved or possible immunological deficiencies.

Case report

The patient, a 54-year-old housewife, was completely well until 1956 when she began to complain of recurrent attacks of malaise, pyrexia and rigors. In 1963 she was admitted to hospital with lobar pneumonia and there were three similar episodes during the next 4 years.

In 1963 she developed episodes of watery diarrhoea usually followed by acute bronchitis or pleurisy, and her weight fell from 50 to 32 kg. She noted that tetracycline given for the bronchitis was invariably followed by remission of the diarrhoea. In 1966 she developed pain and morning stiffness of the knees, wrists and metacarpo-phalangeal joints with a dorsal sheath effusion and the appearance of small nodules at the elbow. In 1967 a diagnosis of hypogammaglobulinaemia was made by plasma electrophoresis and from that time the patient has been given weekly intramuscular injections of 6 ml of human gammaglobulin (HGG). She has had no further pneumonia but the arthralgia has persisted.

She was admitted for assessment of a probable malabsorption syndrome in 1969.

On examination she was a thin, pigmented woman weighing 36 kg. There was no lymphadenopathy but the spleen was palpable 2 cm below the costal margin. Investigations showed plasma albumin 4.4 g/100 ml, globulin 1.3 g/100 ml; quantitative immunoglobulins: IgG, 115 mg/100 ml; IgA 10 mg/100 ml; IgM 270 mg/100 ml. Plasma cells were absent on sternal marrow examination which also showed depleted iron stores. A hypochromic anaemia was present

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(Hb 8.8 g/100 ml, serum iron 40 µg/100 ml). Serum folate and B₁₂ were in the normal range, with the patient on folate supplements. Faecal fat was 96 g in 5 days and only 10% of an oral xylose load was excreted in 5 hr. A jejunal biopsy was reported as showing non-specific villous atrophy. The serum calcium was 7.0 mg/100 ml; magnesium 1.5 mg/100 ml; phosphate 3.3 mg/100 ml; alkaline phosphatase 14 KA units. A calcium balance showed an average negative balance of 4.6 mg/kg body weight/day, and a very low urinary calcium excretion of 15 mg/24 hr. Total urinary hydroxyproline excretion was 64 mg/24 hr. An iliac crest biopsy showed mild osteomalacia. There was no radiological evidence of joint disease and the Rose-Waaler test was negative on four occasions. At that time a diagnosis of hypogammaglobulinaemia with associated malabsorption and arthritis was made. A gluten-free diet was of no benefit over a 6-month period. There was no reticulocytosis after intramuscular iron and the serum calcium remained low in spite of weekly injections of vitamin D₂ 100,000 units.

In 1971 an influenza-like illness was followed by acute pericarditis, which remitted without the use of antibiotics. Later in the same year the patient was admitted during an exacerbation of diarrhoea.

On examination, she was weak, dehydrated and had a grossly distended abdomen. Initial investigations showed severe hypocalcaemia and dilated loops of small bowel. Electrolyte correction and oral tetracycline 250 mg q.d.s. led to rapid improvement in her condition. She was re-investigated with results essentially unchanged since 1969, and the immunoglobulins were IgG, 130 mg/100 ml; IgA, 8 mg/100 ml; IgM, 430 mg/100 ml. The diagnosis of Whipple's disease was made from a second jejunal biopsy.

The patient was given continuous oral tetracycline and reassessed 4 months later. The intramuscular vitamin D and HGG were unaltered. There was no further diarrhoea and she felt considerably more energetic, and had gained 6 kg in weight. A 5-day faecal fat, however, was 65 g. Another jejunal biopsy was taken for light and electron microscopy. A normocytic anaemia (Hb 9.5 g/100 ml) was present and the marrow contained excess iron stores. The serum calcium had risen to 10.0 mg/100 ml, the serum magnesium was 2.1 mg/100 ml and the alkaline phosphatase 8 KA units. A second iliac crest biopsy was normal, showing active mineralization. The nodules near the elbow were examined histologically and showed fibrinoid necrosis with patchy vascular infiltration of lymphocytes, consistent with a rheumatoid nodule.

Jejunal biopsy microscopy. The biopsies obtained with a Crosby capsule were examined initially in normal saline by dissecting microscopy and unusual

nodular clubbed villi without leaf forms of ridging were noted.

The diagnosis of Whipple's disease was made from the histological appearances of the second biopsy in January 1971, which showed characteristic plump granular macrophages staining intensely with periodic acid-Schiff (Fig. 1). These findings prompted a review of the histology of the biopsy taken in 1969. The same features as in the second specimen were then seen. These features comprised crypt hyperplasia with partial villous atrophy. In the lamina propria there were slightly dilated lymphatics and indistinct lipid-filled spaces with adjacent eosinophil and neutrophil polymorphs. The Gram stain showed possible micro-organisms lying free in the lamina propria. The macrophages contained only faint granules when stained for iron and the presence of muciphages and amyloid material was excluded (Hourihane, 1963, 1966). No plasma cells were demonstrated in the lamina propria. The third biopsy, taken after 4 months tetracycline therapy, was examined by electron microscopy and intra- and extracellular rod-shaped bacteria were shown to be present in the lamina propria (Figs. 2 and 3). The epithelium appeared normal but abundant lipid was present in extracellular globular collections within villi, and within some macrophages (Figs. 2 and 4). Numerous macrophages contained lysosomes distended by membrane-like material (Fig. 4) which was presumed to be derived from ingested bacteria (Hendrix & Yardley, 1970).

Discussion

In this patient a dysgammaglobulinaemia appeared at the age of 40, with recurrent infections. It was characterized by very low IgG and IgA with raised IgM levels, corresponding to Type 2 dysgammaglobulinaemia in the terminology of West, Hong &

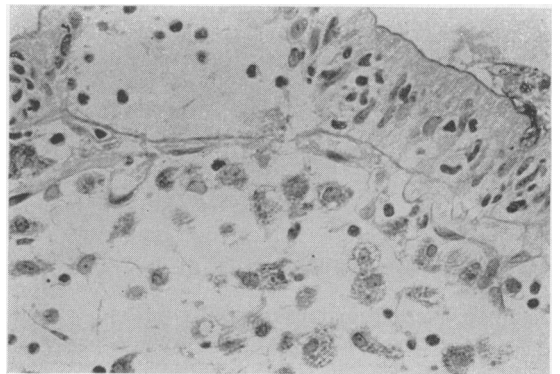


FIG. 1. The tip of a jejunal villus containing in the lamina propria numerous large histiocytes with granular cytoplasm (PAS $\times 180$).

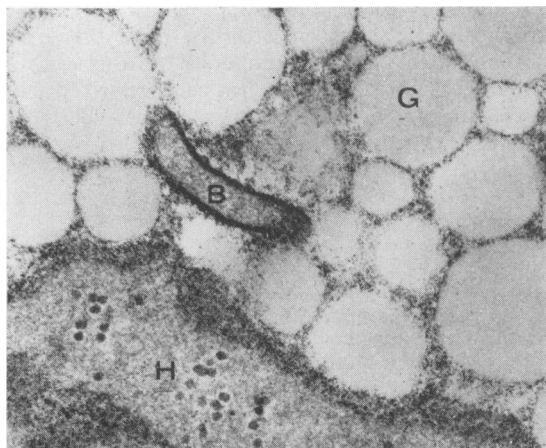


FIG. 2. A bacilliform organism B is present in the lamina propria among abundant extracellular globular lipid G (electron micrograph $\times 32,000$). H is a histiocyte.

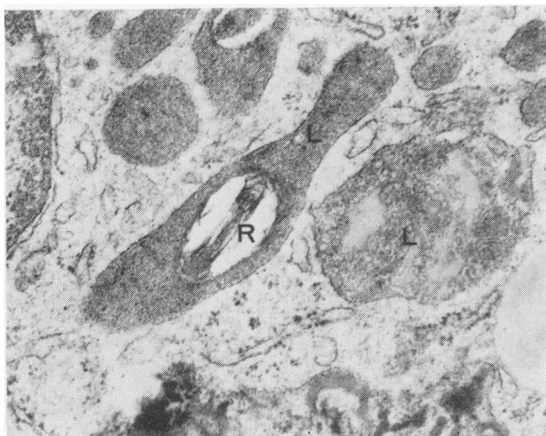


FIG. 3. Histiocyte lysosomes L contain recognisable bacterial remnants R (electron micrograph $\times 29,400$).

Holland (1962). Subsequently she developed the clinical picture of Whipple's disease with a malabsorption syndrome and progressive wasting accompanied by arthralgia and polyserositis. However, the diagnosis of Whipple's disease was not made until examination of jejunal tissue showed characteristic changes, emphasizing the point made by Hendrix & Yardley (1970) that the pathologist should be prepared to suspect this condition from routine histological preparations.

The pathogenesis of Whipple's disease is obscure but has been fully discussed by Hendrix & Yardley (1970) and by Maizel, Ruffin & Dobbins (1970). It is however, agreed that invasion of the gut with small

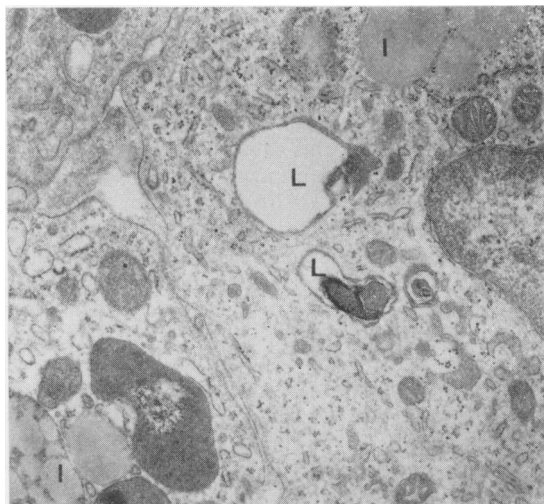


FIG. 4. Some intra-cellular lipid I is present in a histiocyte with dilated lysosomes L containing presumed bacterial remnants (electron micrograph $\times 13,200$).

Gram-positive bacilli is the first step and a failure of lysis of the membranes of the micro-organisms by macrophages leads to the PAS-staining granules formed within these cells. The actual organism responsible has not been identified but it seems likely that man has a high resistance to it, accounting for the low prevalence of the disease, of which only about 150 cases have been described. In our patient, the infection was almost certainly the result of the immunological defect, and this might also be true of other cases of Whipple's disease. A paucity of plasma cells in the lamina propria is a feature of untreated Whipple's disease (Dobbins & Ruffin, 1967) and examination of the published series shows that a number of cases had immunological deficiencies of some kind (Table 1). Furthermore, there is a well established association between malabsorption and hypogammaglobulinaemia (Conn & Quintiliani, 1966) and Whipple's disease was not excluded in all of the reported cases.

In our patient, tetracycline always brought about a remission of the diarrhoea, but even after 4 months'

TABLE 1. Immunological defects in previously reported cases of Whipple's disease

Authors	Date	Defect
Sandor & Kozmer	1957	Hypogammaglobulinaemia
Martel & Hodges	1959	Case 1: Hypogammaglobulinaemia
Anton	1961	Hypogammaglobulinaemia
Maxwell <i>et al.</i>	1968	Impaired lymphocyte activity
Berens, Cohen & Sichwabe	1969	IgM deficiency
Mazel <i>et al.</i>	1970	IgA deficiency

continuous therapy steatorrhoea persisted and there was no definite improvement in the histological lesions in the jejunal mucosa. There are many cases reported where there has been rapid clearing of the organisms with antibiotic therapy, and the incomplete success in this case may have been due to the co-existing hypogammaglobulinaemia. Strober, Blaese & Waldmann (1970) have shown that IgA is only transferred from serum to mucosal surfaces in minimal quantities, so that intramuscular administration of HGG, which furthermore contains little IgA, would be unlikely to protect the patient from gastro-intestinal infections. Nonetheless, the patient appears to benefit from the therapy in that severe respiratory infections have been prevented.

The hypocalcaemia was not corrected by large doses of parenteral vitamin D₂ given over 18 months, but shortly after tetracycline was begun the serum calcium rose to normal levels for the first time. This may have resulted from the spontaneous correction of a magnesium deficiency (Heaton & Fourman, 1965) since the serum magnesium had risen to normal levels (Fig. 5). The second bone biopsy showed active mineralization in contrast to the previous specimen. The anaemia did not respond to haematinics, but refractory anaemias are a feature of many inflammatory processes including Whipple's disease.

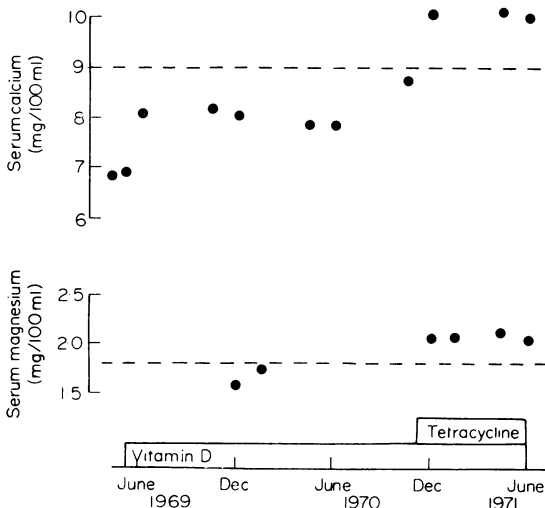


FIG. 5. Serum calcium and magnesium changes with therapy.

The relation of the arthralgia to the other symptoms is not clear. The joint pain and stiffness of hands, wrists and knees with minimal swelling and an absence of erosions is completely consistent with Whipple's syndrome. However, the fibrinoid necrosis

in the biopsied nodules supports the alternative diagnosis of rheumatoid arthritis. Joint disease indistinguishable from rheumatoid arthritis with a negative Rose-Waaler test has been described with hypogammaglobulinaemia (Bywater & Ansell, 1969), but the arthritis of Whipple's disease is also seronegative.

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