Macroglobulinaemia and steatorrhoea

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Waldenström (1944) in his original description of primary macroglobulinaemia described one patient with diarrhoea and, subsequently, other patients with this symptom have been recorded (Olmer, Mongin, Muratore, and Denizet, 1960; Debray and Lemaire, 1960). A necropsy of another showed a granular appearance of the mucosa of the small intestine which resembled Whipple's disease; there were enlarged mesenteric lymph nodes, though tests for absorption were normal (Cabrera, de la Pava, and Pickren, 1964). The following patient is described because she presented with a typical malabsorption state and was noted to have a moderately raised level of IgM. Although the level of IgM increased over 10 years, she failed to develop the clinical stigmata of Waldenström's macroglobulinaemia.

REPORT OF CASE

The patient was a 48-year-old married woman when, in 1956, she suddenly developed steatorrhoea and lost 20 kg in weight. She had not previously suffered from coeliac disease or any relevant illness. Two brothers died from carcinoma of the colon, and one sister from rectal carcinoma. A specimen of blood from one brother was examined for abnormal immunoglobulins but none were found.

Physical examination was negative except for non-specific signs of malnutrition, finger clubbing, and slight oedema of the legs. Weight was 38 kg, height 4 ft 11 in. Abdominal distension was moderate. The cardiovascular system was normal, blood pressure 100/70 mm Hg; urine normal. Malabsorption was proved by a faecal fat excretion of between 20 to 40 g daily; there was also a low urine excretion of d-xylose (0.3 g after 5 g orally) and a flat glucose tolerance curve. Barium studies showed a normal small intestine except for dilatation. The pancreatic enzymes and serum amylase were normal and the jejunal biopsy showed minor changes only. The haemoglobin was 11.6 g/100 ml; serum albumin 2.2 g and globulin 3.2 g/100 ml; serum calcium 9.7 mg and phosphorus 3.1 mg/100 ml; alkaline phosphatase 16.3 units/100 ml; serum magnesium 1.39 mg/100 ml; serum iron 28 µg and iron-binding capacity 229 µg/100 ml; serum total cholesterol 150 mg/100 ml and the ESR (Westergren) was 24 mm in one hour.

She was treated by a gluten-free diet for one year but this was ineffective. She was then readmitted because of

further loss of weight, oedema of the legs, and glossitis. The serum albumin had fallen to 1.7 g/100 ml and haemoglobin to 10.5 g/100 ml; erythrocytes 5.6 million/cmm, PCV 36%, MCV 65 cµ, MCHC 29%, WBC 14,400 per cmm (70% polymorphs, 27% lymphocytes). The maximal acid output during the augmented histamine test was 54 m-equiv HCl in one hour. A ¹³¹I PVP test showed less than 1% loss of PVP in the bowel. A Raybar barium meal showed, apart from an incidental small hiatal hernia, a 'saw-toothed' outline of the upper small bowel suggesting mucosal oedema.

The ESR (Westergren) was 48 mm/one hour. Paper electrophoresis of the serum revealed a dense homogenous band, the so-called 'M' band, in the β₂ region (Fig. 1). No evidence of multiple myeloma was found

FIG. 1. Electrophoresis of serum demonstrating increasing intensity of 'M' type protein between 1958 and 1966.

and the urine was normal, without trace of Bence-Jones protein. A sternal puncture was carried out and the bone marrow was found to be hypercellular, normal tissue being largely replaced by sheets of cells like small lymphocytes; these showed marked 'grumeele' pattern of the chromatin, and there were transitional forms between these and plasma cells. Erythroblasts were of normoblastic type and normal myeloid cells at all stages of maturation were present amongst the vast number of lymphocytes. During 10 years her ill health varied from mild incapacity to collapse from severe diarrhoea; vomiting and abdominal colic occasionally occurred for no obvious reason. A duodenal ulcer, perhaps precipitated by prednisone (15 mg daily), perforated in 1959 and was treated surgically. She was troubled with recurrent bronchitis.

The ESR (Westergren) increased greatly but readings by Wintrobe's method were hardly abnormal (Fig. 2). Anaemia persisted, occasionally being due to iron deficiency though never macrocytic; it did not respond to folic acid or to vitamin B₁₂ therapy, though the serum folate fell at one time to 1.1 µg/l ml; the serum B₁₂ was 135 µµg/l ml (*Euglena* assay). The malabsorption caused tetany, osteoporosis, probable osteomalacia, and the burning feet syndrome. Radiological examination showed little change in the appearance of the small intestine but a large duodenal ulcer and diverticulum were seen in 1966; the diverticulum had not been seen on five previous barium meals and was not regarded as the cause of the malabsorption. Barium enema was normal. A mild proctitis was seen by sigmoidoscopy and rectal biopsy revealed non-specific inflammatory cell infiltration, as may occur in any chronic diarrhoea.

In 1967, the clinical picture of upper intestinal obstruction developed. No cause could be demonstrated by radiographic examination though gastric stasis was marked. She failed to respond to treatment including potassium therapy, so gastroenterostomy was performed by Professor Geoffrey Slaney. At laparotomy, the entire alimentary tract appeared normal except for the duodenal ulcer and diverticulum; no stricture or diverticula were found in the small intestine. The liver, spleen, and pancreas were normal. Biopsy of the stomach was normal. The jejunal mucosa showed a convoluted mucosa in some areas with some leaf-shaped villi, but most villi were within normal limits and covered by tall columnar epithelium. There was minimal dilatation of lymphatics of the lamina propria and slight increase in plasma cells and lymphocytes. Lipochrome pigment was present in the muscularis externa.

Progress after this operation was slow and vomiting continued because of lack of motility and tone in the bowel. One month later, she developed acute suppurative appendicitis, which caused a granulomatous mass in the right iliac fossa, and local resection of the caecum was performed; histological examination of the ileum was normal, except for oedema. She made an uneventful recovery and was discharged.

INVESTIGATION OF 'M' TYPE PROTEIN

Ultracentrifugal analysis in 1958 (Fig. 3a) showed that the patient's serum contained 9% 19S component (*ie*, 465 mg/100 ml). As, however, 200 mg of this probably comprised α₂ macroglobulin, it was assumed that the 'M' type protein (*ie*, IgM) level in the serum at this time was around 265 mg/100 ml. By comparison, the mean level of IgM in normal subjects' sera (estimated by a specific quantitative immunodiffusion technique) is 89 mg/100 ml (Rowe, McGregor, Smith, Hall, and Williams, 1968).

In 1962, ultracentrifugal analysis revealed that the 19S component level in the serum had increased threefold, whilst it had reached 2,000 mg/100 ml by 1965 (Fig. 3b). Moreover, in accordance with the previous findings of Ratcliff, Soothill, and Stanworth (1963), 29S and 38S components were now detectable. Immunochemical

analysis indicated that only one light chain type, namely kappa, was present in the IgM.

STUDIES ON THE PATIENT'S METABOLISM OF AUTOLOGOUS IgM

To determine the rate of synthesis and distribution of IgM, a radioiodine-labelled preparation of the patient's own IgM was injected intravenously.

This was isolated from serum under aseptic conditions, by the method of Barth, Wochner, Waldmann, and Fahey (1964), and labelled with ¹³¹I by the method of McFarlane (1958). It was found to have a ratio of less than 1 atom iodine per molecule of protein, and shown to be homogeneous by radioimmunodiffusion, by radioimmuno-electrophoresis, and by gel filtration (through Sephadex G200).

The fractional catabolic rate, *ie*, the fraction of intravascular IgM catabolized per day, was determined by measurements of total body, plasma, and urine radioactivity, potassium iodide being given by mouth before and during the study. The radioactivity of blood and urine samples was measured on a twin-channel, automatic gamma ray scintillation counter (Nuclear Enterprises Gammatic). Whole-body radioactivity was measured by the human body monitor at the Queen Elizabeth Hospital (UK10:1 in Directory of International Atomic Energy Agency, Vienna, 1964).

RESULTS The two exponentials of the plasma radioactivity curve (by the method of Matthews, 1957) were defined as follows:

First exponential: intercept (C₁) = 66.4
slope = 0.113
Second exponential: intercept (C₂) = 33.6
slope = 1.09

Therefore the fractional catabolic rate (K₁₂) was 0.169, the percentage of the total IgM which was intravascular being 74%. The plasma volume was found to be 60.5 ml/kg. The absolute catabolic rate was 204 mg/kg/day, as determined by substitution of the following formula:

$$\frac{\text{FCR} \times \text{serum IgM (mg/ml)} \times \text{plasma vol (ml)}}{\text{weight (kg)}} \\ = \frac{16.9 \times 20 \times 2,728}{100.45}$$

IgM is catabolized in normal individuals at a rate of approximately 18% per day, *ie*, at a rate comparable to that of catabolism of IgM in the patient, and its rate of synthesis in normal subjects was found to be approximately 7 mg/kg/day (Barth *et al*, 1964). It was concluded, therefore, that the elevated IgM level in the patient's serum was due solely to a greatly increased rate of synthesis.

DISCUSSION

This patient's clinical condition resembled idiopathic steatorrhoea. The presence of a raised ESR

FIG. 2. The rise of the erythrocyte sedimentation rate following the discovery of 'M' type protein in the plasma.

(Westergren) led to examination of plasma proteins by electrophoresis, and 'M' protein was found in the β_2 region. Both the ESR and the macroglobulin progressively increased during the 10-year period of observation (Figs 2 and 3). The possibility that the macroglobulinaemia was secondary to the intestinal lesion was considered. A protein-losing enteropathy might cause a low serum albumin from leakage into the gut with retention of larger globulin molecules. This is unlikely, for plasma proteins of different sizes are lost through the intestinal mucosa at similar rates (Barth *et al.*, 1964), unlike in the nephrotic syndrome where the size of the protein molecule determines the rate of urinary loss (Blainey, Brewer, Hardwicke, and Soothill 1960). Moreover, no evidence of protein-losing enteropathy was found by the ^{131}I -labelled polyvinyl-pyrrolidone (PVP) test, though this was only performed once. If selective retention of IgM did exist it would lead to increased amounts of both light chain types of IgM in the serum. In our patient only kappa light chains could be demonstrated after isolation of IgM by Sephadex G200 gel filtration. This finding also made unlikely

FIG. 3. Ultracentrifugal analysis of patient's serum.

(a) 1958: solvent barbiturate buffer (pH 8.6, 0.05 ionic strength, containing 0.20 M NaCl). Time 48 min.

(b) 1965: solvent phosphate buffer (pH 7.5, 0.01 M containing 0.15 M NaCl). Time 48 min.

the possibility that the elevated IgM reflected the response to an immunogenic stimulus, perhaps from an antigen in the gut; for then both light chain types would be detectable, unless a prolonged stimulus could eventually lead to neoplastic proliferation of the particular clone of cells involved.

Crabbé and Heremans (1966 a and b) described patients with steatorrhoea with a lack of IgA in the serum, where the jejunal mucosa showed a greatly diminished number of IgA-secreting cells, and an increased number of IgM-secreting cells. Crabbé examined material obtained by jejunal biopsy from our patient and found that the immunoglobulin-containing cells were more sparse than in a normal biopsy. Moreover, among these cells the IgA-secreting cells predominated, and IgM-secreting cells were the least numerous.

The finding of only one light chain type of IgM defines the diagnosis as 'monoclonal gammopathy' (Waldenström, 1961). Waldenström's (primary)

macroglobulinaemia may involve the small intestine (Cabrera *et al.*, 1964). Our patient, however, has never developed clinical features of primary macroglobulinaemia such as enlargement of liver, spleen, or lymph nodes. Nor were there any signs (retinal changes, haemorrhages, disturbances of the central nervous system, or congestive cardiac failure) of the hyperviscosity syndrome which may complicate this disease; these, however, usually appear when the serum viscosity (relative to water) reaches levels of 6 or 7 whereas the viscosity of this patient's serum was only 2.15. Her symptoms and signs could all be attributed to the small intestinal disorder, except for the presence of an 'M' type protein. Furthermore, the small intestinal mucosa appears nodular in Waldenström's macroglobulinaemia, like Whipple's disease, and there is mesenteric lymph node enlargement. Microscopically, plasma cell and lymphocyte infiltration, blunted villi and lymphangiectasia in the villi with cells staining PAS-positive, can all be seen. The jejunum from our patient did not show such microscopic features, and examination at laparotomy failed to reveal any macroscopic change. This, together with survival for 10 years, made Waldenström's macroglobulinaemia less probable, for the recorded survival of the majority of such cases varies from 30 to 67 months from the first symptom. However, an occasional survival for 15 years has been recorded (Cabrera *et al.*, 1964), and the first patient reported by Waldenström (1944) lived for at least eight years.

The diagnosis of a benign instead of malignant proliferation of her IgM-secreting cells, a 'benign monoclonal gammopathy', is another possibility. This term was introduced by Waldenström in order to avoid the confusion that arises when patients with an 'M' type protein in their serum are, and continue to be, free from any other features of multiple myeloma or macroglobulinaemia. In this patient benign monoclonal gammopathy and steatorrhoea may have occurred together by chance. Axelsson, Bachmann, and Hällén (1966) examined the sera for 'M' type protein from 6,995 healthy people in Sweden over the age of 25 years and living in one county. They found 'M' type proteins in 64 of the 6,995, and in five of the 64 the 'M' band protein was IgM; so one patient in a hundred had 'M' protein bands demonstrable, and one in a thousand had a band due to IgM. The incidence increased with age so that 5.7% of people 80 to 89 years old had an 'M' type protein in their serum. When patients with 'M' bands were investigated, multiple myeloma was strongly suspected in three of the 64 but no cause was found for the others.

Whether 'benign' monoclonal gammopathy is merely a step in an essentially malignant condition,

or a separate entity, is unknown. Kyle and Bayrd (1966) described a 49-year-old woman who had an IgG 'M' type serum protein for more than 16 years without clinical evidence of multiple myelomatosis, but she developed obvious multiple myeloma 18 years after its discovery and died within a year. Waldenström suggested the following criteria for diagnosing benign monoclonal gammopathy: slight degree of anaemia only; normal serum albumin; gamma globulin less than 3.0 g/100 ml, preferably less than 3% and not more than 5% plasma cells present in the bone marrow, all of which should be mature types; and a fairly constant level of 'M' protein. Initially monoclonal gammopathy was likely in our patient, but later she developed biochemical and cellular signs of Waldenström's macroglobulinaemia: low albumin, anaemia, low levels of the other immunoglobulins, and increasing serum IgM levels due solely, as the turnover studies showed, to an increased rate of synthesis. The criteria for benign monoclonal gammopathy are, therefore, not satisfied but the chance of the low albumin and anaemia being caused by malabsorption cannot be excluded.

SUMMARY

A woman with steatorrhoea was found to have a raised ESR (Westergren). Paper electrophoresis revealed a band of 'M' protein in her serum. Ultracentrifugal analysis showed that this was due to an increased level of the 19S component, which immunochemical analysis attributed to IgM comprising light chains of only one type (kappa). Hence 'monoclonal gammopathy' was diagnosed. She developed no clinical stigmata of Waldenström's macroglobulinaemia over a period of 10 years' observation, although ultracentrifugal analysis of her serum ultimately revealed a similar pattern to that seen in advanced cases of this disease.

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ADDENDUM

The patient died from bronchopneumonia in 1968. Necropsy showed the effects of malnutrition such as atrophic tongue, fatty liver (1,110 g) and osteoporosis. There was no localized neoplasm. The alimentary tract was normal apart from the results of surgery and a fine nodularity of the mucosa of the jejunum, the nodules measuring approximately 1 mm in diameter. The pancreas, gall bladder, and bile ducts were normal. There was only minimal atheroma in the coronary arteries and aorta. The

spleen was enlarged (415 g) and there was extensive hyperplasia of the bone marrow.

Histological studies showed widespread lymphocytic infiltration of all organs including the alimentary tract. These appearances resembled a reticulosis, such as lymphosarcoma. Features of Waldenström's macroglobulinaemia, where there is retention of a reticulin pattern in the lymph nodes and PAS-positive inclusions in the nuclei of the lymphoid cells, were not present.

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