Macroglobulinaemia and intestinal lymphangiectasia: a rare association

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SUMMARY Two cases in which macroglobulinaemia was associated with intestinal lymphangiectasia are recorded. Immunoperoxidase stains demonstrated a high content of monoclonal IgM in the intestinal lymph. The seven previously recorded examples of this association are reviewed. It is concluded that the concurrence of these two conditions is not merely fortuitous, and that increased viscosity of the lymph consequent on its high IgM content may be important in the pathogenesis of the intestinal lymphangiectasia.

Since the original description of macroglobulinaemia1 a small number of cases has been recorded in which the macroglobulinaemia was associated with intestinal lymphangiectasia (IL). We wish to record two further examples of this association and to present observations on the pathogenesis of the intestinal changes.

Case reports

CASE 1

An 89-year-old woman was admitted to another hospital in May 1977 when she was found to have anaemia and splenomegaly. Her haemoglobin was 6·1 g/dl, WCC 5·6 × 10⁹/l (neutrophils 60%, lymphocytes 34%); the bone marrow contained 20% lymphocytes. She was treated with blood transfusion alone.

After this admission she became increasingly weak and lost 4 stones (25·4 kg) in weight. In January 1978 she developed vomiting 1–2 hours after meals and there was intermittent diarrhoea with pale, loose stools being passed 5–6 times daily. She had complained of abdominal distension and feeling bloated for many years.

She was admitted to Withington Hospital in February 1978. On examination she was pale with a malar flush. The liver and spleen were enlarged to 4 cm and 13 cm below the costal margins respectively and the abdomen was diffusely tender. There was no palpable lymphadenopathy. An aortic systolic murmur was heard and there was moderate ankle, sacral and abdominal wall oedema. The jugular venous pressure was normal.

Investigations

Haemoglobin 12·0 g/dl; MCV 86 fl; MCH 30·0 pg; WCC 17·7 × 10⁹/l (neutrophils 11%, lymphocytes 80%, prolymphocytes 8%, monocytes 1%); platelets 515 × 10⁹/l; ESR 118 mm/h; plasma viscosity 2·84 cp; prothrombin time 16 s (normal–12 s). Coombs’ test negative. Bone marrow: cellularity increased; normoblastic erythropoiesis; small lymphocytes comprised 50% of the total nucleated cells. Marrow clot sections showed scattered focal aggregates of small lymphocytes with a few plasmacytoid cells peripherally; elsewhere a few plasmacytoid cells were present, some containing Russell or Dutcher bodies. Serum proteins: albumin 28 g/l; globulin 20 g/l (normal 21–38 g/l). Protein electrophoresis showed an M band in the gamma region and immuno-electrophoresis confirmed the presence of IgM (lambda) monoclonal protein. Serum immunoglobulins: IgG 7·5 g/l (normal 8·0–16·0 g/l); IgA 1·3 g/l (normal 1·2–4·0 g/l); IgM 15·0 g/l (normal 0·5–1·6 g/l). Faecal occult bloods: positive × 3. Average faecal fat excretion over three days: 25·5 mmol/day (normal up to 18 mmol/day). Chest x-ray: normal. Barium meal (1977): small sliding hiatus hernia; otherwise normal. Barium enema: gross diverticular disease.

Treatment was begun with chlorambucil 4 mg daily and the WBC fell to 3·4 × 10⁹/l (lymphocytes 66%) over the next 12 days, when chemotherapy was stopped.

CASE 2

A 66-year-old retired librarian underwent a transurethral resection of his prostate gland in June 1980 for benign prostatic hyperplasia. His spleen was palpable 6 cm below the costal margin and his white blood cell count was 27·6 × 10⁹/l (75% lymphocytes); a diagnosis of asymptomatic chronic lymphocytic leukaemia was made. In October 1980 he had two episodes of pyrexia of unknown origin.
He was admitted to the Christie Hospital in November 1980 complaining of left-sided pleuritic pain, rigors and night sweats. It was noted that he had suffered from tropical sprue while in India during the second World War.

On examination he was unwell with a temperature of 39°C. Enlarged lymph nodes were palpable in the left axilla and both groins. Signs of a small left pleural effusion with underlying consolidation were present in the left lung base. The liver and spleen were palpable 3 cm and 8 cm below the costal margin respectively. Fundoscopy was normal with no evidence of the hyperviscosity syndrome.

Investigations
Haemoglobin 9.3 g/dl; WBC 3.4 × 10⁹/l (neutrophils 66%, lymphocytes 22%, monocytes 12%); platelets 100 × 10⁹/l; blood film: normochromic with microcytosis, anisocytosis and poikilocytosis; lymphocyte morphology normal; ESR 100 mm/h; plasma viscosity 6.56 cp; prothrombin time 17.5 s (control 13.5 s); Coombs' test weakly positive. Bone marrow smear: hypercellular; M:E ratio 8:1; myelodysplastic changes noted; erythron normoblastic; no overall increase in lymphoid cells but occasional large nucleolated lymphoid cells were scattered throughout. Bone marrow clot section: small aggregates of small lymphocytes and an increase in plasmacytoid cells. Serum albumin 26 g/l; serum globulin 25 g/l. Protein electrophoresis showed an M band in the fast gamma region with a low gamma globulin. Immunoelectrophoresis characterised the M band as IgM kappa. Serum immunoglobulin: IgG 4.7 g/l; IgA 0.3 g/l; IgM 20.0 g/l. Cryoglobulins—present. Bence-Jones protein—positive. Plasma volume 5630 ml (expected 2523 ml). Chest x-ray: small left pleural effusion with atelectasis and consolidation of left lung base; atelectasis at right lung base. Ventilation and perfusion lung scan: decreased uptake of tracer at left base on both studies. CT scan of abdomen: hepatosplenomegaly; abdominal aortic aneurysm. Bacteriology and virology screens: negative. It was thought that he had macroglobulinaemia complicated by pulmonary embolism, and superadded infection. He was treated with broad spectrum antibiotics, plasma exchange (three litres on two occasions), and his condition improved greatly. His spleen was only just palpable and his chest x-ray had cleared at the time of discharge on the 19 December 1980.

He was readmitted on the 11 January 1981 with an E coli septicemia which was complicated by acute renal failure, and he died on the 17 January 1981.

CASE 1
Necropsy findings
The spleen was greatly enlarged (1100 g) and its cut surfaces were soft and red with a large infarct at the tip. The liver was enlarged (1900 g) with fine, white mottling on the external and cut surfaces. Red marrow extended into the lower half of the femoral shaft. Mesenteric lymph nodes were slightly enlarged (up to 1 cm diameter) and some were replaced by firm, white cheesy material; other lymph node groups appeared normal.

The small intestinal mucosa showed a striking pattern of tiny white flecks (Fig 1). These began abruptly just beyond the pylorus, covered the entire mucosal surface, and extended well into the ileum where they gradually became less frequent and fainter until they disappeared in the terminal ileum. The serosa of the small intestine showed white nodules and distended lymphatics filled with firm white material (Fig 1).

Fig. 1 Case 1: small intestine showing fine, white mucosal mottling and dilated serosal lymphatics
There was diverticulitis of the sigmoid colon. The heart showed aortic valve calcification of senile type and the mitral valve ring was calcified. No other significant abnormalities were found.

Light microscopy

Bone marrow: The appearances were similar to those in the marrow clot obtained during life, as described above (Fig. 2). In addition in the centre of many of the lymphoplasmacytic foci there were extracellular strands of eosinophilic material which did not stain for amyloid.

Spleen: Lymphoplasmacytic foci similar to those in the marrow were present.

Small intestine: Typical changes of lymphangiectasia were found. Lymphatics in the mucosa, submucosa and serosa were enormously dilated and filled with eosinophilic coagulum (Fig. 3). In places the villi appeared oedematous with abundant eosinophilic material in the interstitium. In the mucosa and submucosa, both inside and outside the lymphatics, groups of foamy histiocytes were present.

No lymphomatous infiltration was found in the many sections examined. Mesenteric lymphatics showed similar appearances to those in the small intestine. Stains for amyloid were negative.

Mesenteric lymph nodes: The sinusoids were greatly distended and contained an eosinophilic coagulum and foamy histiocytes. Almost no lymphoid tissue remained and there was no evidence of lymphoma (Fig. 4).

Other organs: The liver showed fatty change but sections of myocardium, lungs, brain, adrenals, kidneys and pancreas showed no significant abnormalities.

CASE 2

Necropsy findings

The spleen was greatly enlarged (2400 g) and its cut surfaces were soft and faintly mottled. The liver was enlarged (2300 g) and pale.

Lymph nodes in para-aortic, lesser omental, pelvic, splenic hilar, cervical and axillary regions were enlarged up to 3 cm diameter and had fleshy cut surfaces. Mesenteric nodes were also markedly enlarged but had a soft, cheesy consistency when cut.

The small intestine showed appearances identical to those seen in case 1 (Fig. 5).

There was severe coronary and cerebral atheroma and an aortic atheromatous aneurysm was present below the renal arteries. The lungs were oedematous and the kidneys were overweight (240 g each) with mottled cortices.

Light microscopy

Small intestine and mesenteric lymph nodes: There were similar changes to those seen in case 1, although in the villi dilated lymphatics were less obvious and there was more emphasis on interstitial oedema. In addition some of
the mesenteric nodes showed a combination of lymphangiectatic and lymphomatous features (see below) and in these nodes the lymphoma cells were mixed with foamy histiocytes. There was no lymphomatous infiltration of the intestine.

Stains for amyloid were negative.

Non-mesenteric lymph nodes: The normal architecture was obscured by a diffuse proliferation of small lymphocytes with non-cleaved nuclei and plasmacytoid cells (Fig. 6). Russell and Dutcher bodies were not found. The appearances were interpreted as malignant lymphoma, lymphoplasmacytoid (Kiel nomenclature).

Spleen and bone marrow: Numerous foci of lymphocytes and plasmacytoid cells.

Liver: Portal tracts were infiltrated by lymphoplasmacytoid cells.

Kidneys: Evidence of acute tubular necrosis.

Lungs: Focal lymphoid infiltration.

Myocardium, Adrenals, Thyroid, Prostate, Pancreas—normal.

IMMUNOPEROXIDASE STAINS FOR IMMUNOGLOBULINS

Method

The peroxidase anti-peroxidase technique was used on formalin-fixed, wax-embedded tissues for the demonstration of IgA, IgM, IgG and kappa and lambda light chains.

In case 1 no predigestion of sections was employed but
in case 2 staining was carried out both with and without predigestion with trypsin.

(a) Lymphoid tissues
Case 1: The marrow and spleen contained an excess of plasmacytoid cells staining for IgM and lambda light chains. The extracellular eosinophilic material in the lymphoid foci stained heavily for all heavy and light chains.

Case 2: The lymphomatous tissue at all sites showed a clear-cut monoclonal staining pattern for IgM and kappa light chains.

(b) Small intestine and mesenteric lymph nodes
The findings are summarised in Table 1. They indicate or suggest that in both cases the lymphatic coagulum and interstitial material in the lamina propria of the small intestine were rich in IgM (Fig. 7 (a)-(e)). Staining for light chains indicated that the IgM was probably monoclonal in each case and that it corresponded in type to that demonstrated in the serum in life.

Table 1  Immunoglobulin staining patterns in the small intestine and mesenteric lymph

<table>
<thead>
<tr>
<th>Site</th>
<th>Case</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>κ</th>
<th>λ</th>
</tr>
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<tbody>
<tr>
<td>Intralymphatic coagulum</td>
<td>1</td>
<td>−</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Interstitial hyaline material</td>
<td>1</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>++</td>
</tr>
</tbody>
</table>

In case 1, where stains were done both with and without trypsin predigestion, the trypsin abolished the positive reaction for IgM, κ in the intralymphatic coagulum, the enzyme having dispersed the entire content of the lymphatics.

Discussion
In each case the haematological presentation was remarkably similar with an initial modest lymphocytosis just sufficient to meet the defining criterion for chronic lymphocytic leukaemia of >15.0 x 10⁹ lymphocytes per litre of blood. In case 2 this lymphocytosis apparently subsided spontaneously pari-passu with the development of peripheral lymphadenopathy. In both cases there was marked splenomegaly and in both the marrow histology was similar, with scattered foci of small lymphocytes and an increase in plasmacytoid cells. In both cases there was
Table 2  Cases of macroglobulinaemia with associated intestinal lymphangiectasia.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Intestinal lymphangiectasia</th>
<th>Extracellular hyaline in villi</th>
<th>Malabsorption proven/probable</th>
<th>Protein-losing enteropathy</th>
</tr>
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<tbody>
<tr>
<td>Cabrera et al</td>
<td>M</td>
<td>64</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Khilnani et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>F</td>
<td>55</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Becker et al</td>
<td>F</td>
<td>60</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bedine et al</td>
<td>F</td>
<td>64</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pruzanski et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>F</td>
<td>69</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Tubbs et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>F</td>
<td>58</td>
<td>+</td>
<td>+</td>
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</tr>
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</table>

Macroglobulinaemia. The one major difference between the cases was the absence of lymph node involvement in case 1 so that, whereas case 2 can reasonably be categorised as malignant lymphoma, lymphoplasmacytoid (Kiel), the position is not as clear-cut in case 1. This difference, however, may be related to the chemotherapy given in case 1 and both cases are examples of B cell malignancy with associated macroglobulinaemia.

The remarkable feature of both cases which prompts this report is the presence of typical and extensive intestinal lymphangiectasia. Unfortunately, the investigation of intestinal function during life was incomplete but in case 1 the symptoms of diarrhoea with pale, offensive stools, together with high faecal fat levels are definite evidence of malabsorption. In case 2 there was no evidence of malabsorption or protein-losing enteropathy although there was a story of tropical sprue many years before the final illness and one transient episode of diarrhoea shortly before death.

Seven previously reported cases of macroglobulinaemia and IL<sup>4-9</sup> appear directly comparable with the two recorded here. The main features of all nine cases are summarised in Table 2. In the case reported by Bedine et al lymphatic dilatation was not described in the jejunal biopsy but possibly some of the hyaline deposits in the lamina propria were, in fact, in lymphatic lumina; in all other respects this case resembles the other eight and it is therefore included in the series.

In our case 2 there was no convincing evidence of malabsorption or protein-losing enteropathy but it is included because the pathological changes are identical to those in the other cases.

A case reported by Bradley et al<sup>10</sup> in which a 48-year-old woman developed steatorrhoea followed one year later by macroglobulinaemia has been excluded from Table 2 because there was no convincing histological evidence of IL or hyaline deposits.

There now seem to be sufficient cases on record to establish that the association between macroglobulinaemia, IL, malabsorption and protein-losing enteropathy is not merely fortuitous, although it is extremely rare. However, the pathogenesis of the intestinal lesions is far from clear and various possibilities merit consideration.

Firstly, pre-existing IL might predispose to the development of lymphoma with consequent macroglobulinaemia. A relation between IL and lymphoma has been proposed by Waldmann et al<sup>11</sup> who have recorded three cases of malignant lymphoma developing amongst 50 patients with established IL, although none had macroglobulinaemia. They suggest that in IL there is defective immunosurveillance due to loss of immunoglobulin and T cells into the gut and that this predisposes to the development of lymphoma. This mechanism seems unlikely in the cases under discussion here since in all of them the intestinal abnormality appears to have declared itself concurrently with the macroglobulinaemia. Furthermore all of the patients were 55 yr or older, whereas idiopathic IL usually presents in children and young adults.<sup>12</sup>

This evidence seems to suggest that the IL in these cases is acquired and secondary either to the macroglobulinaemia or to associated lymphomatous infiltration of the mesenteric lymph nodes with obstruction to lymphatic drainage. The latter is also unsatisfactory as a general explanation since in only two instances have the mesenteric nodes clearly been documented as being heavily involved by lymphoma (our case 2 and Tubbs et al<sup>2</sup>; in the other four cases where mesenteric nodes were examined only lymphangiectasia is described (Cabrera et al<sup>4</sup>, Khilnani et al<sup>5</sup> and our case 1).

It seems probable, therefore, that the macroglobulinaemia itself leads to lymphatic stasis perhaps because of increased viscosity of the lymph. In three of the four cases where immunohistochemistry has been performed (Pruzanski et al<sup>8</sup> and our two cases) the lymph and the extracellular hyaline in the lamina propria was shown to be rich in IgM which was apparently monoclonal. In the fourth case<sup>8</sup> all classes of heavy chains and both light chains were demonstrated in the lymphatics by a direct immunoperoxidase technique. This inconsistency may reflect technical problems.

Further evidence that the macroglobulinaemia itself may lead to IL is provided by the case recorded by Tubbs et al<sup>2</sup> where, after chemotherapy, the macroglobulinaemia resolved and, pari-passu, the intestinal function returned to normal with the degree of IL appearing reduced as judged histologically. It is difficult, however, to explain why this process of lymphatic stasis and IgM deposition should be so strictly confined to the small intestine and its
mesentery; presumably the explanation lies in some anatomical or functional peculiarity of these structures.

The relative importance of the lymphangiectasia and the extracellular IgM deposits in producing the intestinal malfunction is not clear. The presence of both malabsorption and protein-losing enteropathy in the case where IL was not specifically documented suggests that the deposits in the lamina propria might be the more important but against that is the fact that both malabsorption and protein-losing enteropathy are common manifestations of idiopathic IL. Probably the interstitial IgM deposits are the result of oedema due to leakage from the obstructed lymphatic system and any attempt to separate their functional effects is unnecessary, but the way in which they produce the intestinal malfunction is not apparent.

References