Polymeric IgA myeloma, hyperlipidaemia and xanthomatosis: a further case and review

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Summary

A patient is described who had myeloma of the polymeric IgA variety, together with a striking hyperlipidaemia and xanthomatosis. Investigations into the protein and lipid abnormality failed to demonstrate any mechanism for the hyperlipidaemia. A review of the literature, however, validates this clinical entity and some of the suggested explanations are discussed.

Introduction

The sera of patients with multiple myeloma or Waldenström's macroglobulinaemia may show concurrent hypolipidaemia (Liebetseder *et al.*, 1951; Feiereis and Sehner, 1954; Gross and Weicker, 1954; Lewis and Page, 1954; Kanzow, 1957; Seit-anides, Shulman and Hobbs, 1970), normal lipids (Magalini, Stefanini and Martin, 1956) or hyperlipidaemia. The majority show a depression of their blood lipids and this may relate to the paucity at autopsy of significant atheroma (Spain *et al.*, 1956). Riesen, Nosedá and Butler (1971) have suggested, with experimental evidence, that the hypolipidaemia is due to the formation of lipoprotein 'M' component complexes which are rapidly cleared from the circulation.

During the last three decades several authors have noted the approximately simultaneous occurrence of myeloma and hyperlipidaemia with cutaneous xanthomatosis. The myeloma is usually of IgA or IgG class but IgM paraprotein may also be involved (J. R. Hobbs, personal communication). Beaumont, Jacotot and Beaumont (1967) and Beaumont (1969) have demonstrated complexing of the myeloma paraprotein with the lipoprotein. In one of these cases, an IgG myeloma, he showed the binding activity for the lipoprotein resided in the Fab por-

tion of the molecule. He suggested that these cases were an example of myeloma with auto-antibody activity and that the process of binding decreased the catabolic rate of the lipoprotein. He further suggested that the deposition of this complex in arterial wall and tissues may be likened to the deposition of immune complexes as shown experimentally in serum sickness (Kniker and Cochrane, 1968).

This communication describes a patient with a polymeric kappa IgA myeloma, associated with hyperlipidaemia and a non-familial 'eruptive' xanthomatosis. In this patient no evidence was obtained of the association of the paraprotein with the lipoprotein; the explanation for this clinical entity may have to be expanded to include such cases.

Case report

A 58-year-old white Caucasian, chauffeur and gardener, presented with an influenza-like illness. An erythrocyte sedimentation rate (ESR) of 50 mm/first hour was noted. His symptoms abated but during the next 18 months his ESR varied between 40 and 50 mm/hr. Then 4 months later the ESR was 108 mm/hr, total protein 8.5 g/100 ml with serum albumin of 3.7 g/100 ml, haemoglobin (Hb) 14.6 g/100 ml, and a serum cholesterol of 440 mg/100 ml with neutral fats of 600 mg/100 ml. His serum was 'milky' and the lipid electrophoretic pattern showed a dense β band with additional staining at the origin.

Two years after the onset of his illness the patient developed exacerbation of long-standing lumbar backache and had moderate epistaxis. X-ray showed mid-thoracic vertebral body collapse. The Hb was 40% and a sternal marrow showed diffuse infiltration of large abnormal plasma cells, macronormoblastic erythropoiesis and increased basophils. He was referred to the Radcliffe Infirmary and was admitted

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in January 1973, with the diagnosis of multiple myeloma. Past medical history was non-contributory. The patient rarely drank alcohol. He had eight siblings and two children, with no family history of xanthoma, premature ischaemic heart disease, diabetes or cancer. Six elder siblings were alive and well.

Examination revealed a pale thin man of small build, weight 51 kg. Multiple small (1–3 mm) raised yellow plaques were noted on the extensor aspects of the elbows and knees (Fig. 1), on the front of the chest and abdomen and on the back of the chest. They were not surrounded by cutaneous erythema or induration. In his palmar creases were yellow-orange linear depositions identical to those described in Type III hyperlipoproteinaemia (Fredrickson, Levy and Lees, 1967). No arcus senilis was seen. The liver was slightly enlarged but the spleen was not palpable. The sternum and dorsal spine were tender to percussion. Ophthalmic examination revealed bilateral flame-shaped retinal haemorrhages but no papilloedema. There were no abnormal cardiovascular signs, and the peripheral pulses were palpable and equal.

Investigations: Hb 11.9 g/100 ml with 6.2% reticulocytes; ESR (Westergren) 156 mm/first hour; WCC 11,500/mm³, 56% neutrophils, 9% eosinophils, 2% basophils, 14% lymphocytes and 12%

monocytes, platelets 320,000/mm³, PCV 25.8%; serum iron 85 µg/100 ml and total iron binding capacity 240 µg/100 ml. Total serum proteins were 11 g/100 ml; albumin 2.4 g/100 ml; serum calcium 13.1 mg/100 ml; inorganic phosphate 3.3 mg/100 ml. Serum protein electrophoresis demonstrated a discrete β band and concentrated urine contained a similarly migrating band which reacted with anti-kappa serum. Serum immunoglobulins were: IgA 700 mg/100 ml; IgG 366 mg/100 ml; IgM 20 mg/100 ml. The Sia water test was negative and cryoglobulins were not demonstrated. The serum was turbid with total fasting cholesterol 356 mg/100 ml and neutral fats 670 mg/100 ml. On agarose gel lipoprotein electrophoresis there were a markedly increased pre-β band and increased density at the β position and at the origin.

Biopsy of the lesion around the right knee showed foamy macrophages within the subcutaneous tissues consistent with the histological features of a xanthoma. Immunofluorescent studies (performed by Dr J. Skinner of the Department of Morbid Anatomy, Radcliffe Infirmary, Oxford) did not detect any IgA within these lesions. The bleeding and prothrombin times and factor VIII and XIII were normal. Platelet aggregation studies (performed by Dr M. Glynn of the Nuffield Department of Surgery, Radcliffe Infirmary, Oxford) showed a normal response to aggregating agents but washing the platelets produced an abnormally large enhancement of aggregation, suggesting the presence of coating protein. Serum viscosity studies (performed by Dr D. Mason of the Department of Pathology, Radcliffe Infirmary, Oxford) using an Ostwalt viscosimeter showed an elevated viscosity at 37°C of 2.8 relative to water (N1.3–1.6). Normal results were obtained for serum electrolytes, fasting glucose, blood urea, uric acid and liver enzymes. Creatinine clearance was 77 ml/min. Radiological studies were incomplete but showed collapse of several thoracic vertebrae.

The patient was treated with cyclophosphamide 50 mg t.d.s. and prednisolone 5 mg t.d.s. and discharged 3 years after onset of illness but was re-admitted a month later with a chest infection and general deterioration including increasing back pain, repeated epistaxis, and nausea. The chest infection was controlled with antibiotics. Some of these features and the retinal haemorrhages suggested the hyperviscosity syndrome and plasmaphoresis was instituted, 4 l of plasma being removed over the next 4 days with some improvement in mentation and general condition. Radiotherapy to the dorsal spine was commenced, the prednisolone increased to 10 mg q.d.s. and over the next week the patient underwent further plasmaphoresis with some improvement. Only small changes in the total protein

FIG. 1. Appearance of xanthomas of right knee.

levels were observed although a considerable amount of protein was removed using a cell separator. Follow-up over the next 2 months showed a gradual response to cytotoxic treatment, the total serum protein dropping to 8 g/100 ml with albumin of 2.6 g/100 ml. The haemoglobin remained in the range 11–13 g/100 ml and little change was observed in blood lipids. Serum remained constantly turbid and the appearance of the xanthomata was unchanged. The patient remained moderately well, then deteriorated 6 weeks before death from pneumonia, 3 years and 4 months after first being seen by us. Autopsy was refused.

Special investigations

Material and methods

Serum electrophoresis was performed in 1% Difco fine agar and 1% 'Miles-Seravac' agarose in 0.05 M barbital buffer, pH 8.4. Azacarmine B, and Oil Red O and Sudan Black were the protein and fat stains respectively. Wellcome immunoglobulin antiserum was used in the immunoelectrophoretic plates. Immunoselection was performed as according to Radl (1970). Gel chromatography was carried out in a 2.5×41 cm column containing Sepharose 6B (exclusion limit of 4×10^6 daltons) in phosphate-buffered saline pH 7.2 with an upward flow rate of 20 ml/hr. The void volume was calibrated with dextran blue. The immunoglobulin levels in the eluates were assayed by radial immunodiffusion. Electrophoresis was also performed on polyacrylamide gel (PA) in the presence of sodium dodecyl sulphate (SDS) according to the method of Weber and Osborn (1969) in 100×6 mm 3.6% and 7% PA gels (T = 3.6% or 7%, B = 3.6%) in 0.2% SDS in tris/acetate/EDTA buffer pH 7.4; 10 μ l of serum diluted 1 : 10 in buffer and 2% SDS was applied with Bromoblue as albumin marker. Reduction of IgA myeloma protein in 2% dithiothreitol,

8 M urea and 2% SDS was terminated after 1 hr at 37°C with 1.5 M iodacetamide. Electrophoresis at 3 milliamps/gel was stopped when the marker dye approached the bottom of the gels; the gels were stained in Coomassie brilliant blue and de-stained electrophoretically. Electrophoretic mobility was calculated distance marker dye/pre-stained gel length $\times$ distance band/post stained gel length. To verify that the abnormal bands were IgA, the gels were longitudinally sliced, one section being stained and the other placed in agar containing anti-IgA and cross electrophoresis at 0.25 milliamps/cm was performed.

Serum cholesterol and triglyceride estimations and lipid electrophoresis were performed by the methods discussed by Lewis and Niteckis (1970). Post-heparin lipolytic activity was assayed according to Boberg (1970). Ultracentrifugation was performed using the method of Hatch and Lees (1968).

Results

Electrophoresis and immunoelectrophoresis confirmed the presence of a migrating kappa IgA 'M' band with suppression of immunoglobulins G and M (Fig. 2). No other abnormal precipitates in the immunoelectrophoresis plate were noted apart from non-specific staining at the origin. The results of gel filtration are seen in Fig. 4, the polymeric nature of the IgA being observed, with no IgA in the void volume, this being occupied by very low density lipoprotein (VLDL). The polymers of IgA were verified in SDS PA gels and the abnormal bands were confirmed by cross electrophoresis in agar containing anti-IgA. The 7S–19S fractions from gel filtration were also electrophoresed in SDS PA gels and the mobility for the abnormal bands plotted against molecular weight as depicted in Fig. 5. An unexpected finding was the double bands for each member of the polymer series, the difference between the

FIG. 2. Electrophoretic pattern in 1% agarose stained for protein. Upper, normal serum; lower, patient's serum. Anode on left.

FIG. 3. Lipogram, stained with Oil Red O in 1% agarose. Upper, normal serum; lower, patient's serum. Anode on left.

FIG. 4. Gel chromatography studies. (a) Profile of patient's serum at diagnosis: —●—●—, patient's serum; ...●...●..., normal serum; - - -●- - -, IgA in eluant of patient's serum. (b) Patient's serum following therapy (2 months later). (c) Gel filtration of isolated VLDL + IgA myeloma protein showing lack of association.

FIG. 5. Molecular weights of abnormal bands seen in SDS polyacrylamide electrophoresis and of α chain on reduction and alkylation.

two members of each individual polymeric species being 20–40,000 daltons. On complete reduction and alkylation, α chain with mol. wt 66,000 and light chain (and presumably J chain) were obtained (Fig. 5).

Fasting serum cholesterol and triglycerides were 242 mg/100 ml and 5.7 mmol/l respectively (normal upper limit 2 mmol/l). The abnormal lipoprotein pattern consisted of a heavy band occupying the preposition on agarose gel and cellulose acetate electrophoresis. The ultracentrifugation results are as depicted in Table 1; similar results were obtained on a further serum sample.

It has been suggested (Glueck *et al.*, 1969) that one mechanism for hyperlipidaemia in myelomatosis is an inactivation of the lipoprotein lipase system by a heparin-binding antibody associated with the paraprotein; this would have the effect of decreasing uptake of triglyceride from plasma,

especially by adipose tissue and muscle. To assess this process we twice measured lipolytic activity in plasma after injection of heparin. The post-heparin lipolytic activity 10 min after 500 units heparin was 0.25 and 0.35 μ Eq/min/ml (laboratory normal range 0.25–0.45).

Thirty minutes after the heparin injection there was a 14% fall in serum triglyceride concentration (mean of two measurements before and two after heparin).

In addition, we sought evidence for a lipoprotein-binding antibody associated with the IgA protein, such as has been described by Beaumont (1967).

Using double immunodiffusion in 1% agarose, chromatographically-isolated IgA from the patient was set up against the three ultracentrifuged lipoprotein classes from the patient's serum and from a normal serum sample: no interaction was detectable. We also carried out rocket electrophoresis of the patient's serum and of his three lipoprotein classes

TABLE 1. Ultracentrifugation studies

	Patient		Normal (men 40–69 years)	
			Mean	95th percentile
VLDL	Cholesterol	102 mg/100 ml	22 mg/100 ml	55 mg/100 ml
	Triglycerides	4.6 mmol/l	0.69 mmol/l	2.08 mmol/l
LDL	Cholesterol	83 mg/100 ml	160 mg/100 ml	215 mg/100 ml
	Triglycerides	0.41 mmol/l	—	—
HDL	Cholesterol	45 mg/100 ml	—	—
	Triglycerides	0.25 mmol/l	—	—

into agarose gel containing anti-human IgA; on staining with fat red 7 B, no lipid-containing rockets were detected.

The selective immuno-electrophoresis Radl procedure was carried out by Dr Brenda Slavin: the patient's serum was electrophoresed into agarose gels containing antisera prepared in this laboratory to the three main apolipoprotein groups, apo-A, apo-B and apo-C, and into control gels not containing antiserum. Subsequently, anti-IgA was added to the troughs; the pattern of the arcs was not affected by the presence of antisera to lipoprotein peptides.

VLDL from two patients with Type IV hyperlipidaemia, and IgA myeloma protein, were partially purified by repeated gel filtration and verified by immunoelectrophoresis and electrophoretic mobility and staining.

No association could be detected in gel filtration between purified IgA myeloma protein from the patient and VLDL from the two other patients (Fig. 4). It is realized that the dilution during gel filtration could cause dissociation of a weak IgA/lipoprotein union. No precipitation was seen when both the patients' serum and purified patients' IgA were diffused in agar using standard double diffusion techniques, against sera from a number of normal and pathological sera (including the patients' own serum).

Discussion

A review of the literature has revealed some twenty-seven reports of similar cases. The first observation was probably reported by Cremer in 1937 (cited by Neufeld, 1964). Males predominate in the ratio 4 : 1 and generally present in their sixth decade with cutaneous xanthomatosis. A minority has a positive family history of xanthomatosis and/or hyperlipidaemia (Kayden, Franklin and Rosenberg, 1962; Osserman and Takutsuki, 1963; Cohen *et al.*, 1966). After a short but variable period, symptoms and signs of myelomatosis follow. Associated atheromatous occlusive vascular disease is a common feature (Lewis and Page, 1965).

Cutaneous xanthomata tend to be generalized and persistent and of an 'eruptive' maculopapular nodular nature and are especially prominent in the palmar creases and extensor surfaces of the elbows and knees (Cohen *et al.*, 1966). Visceral (Brehmer and Lubbers, 1950; Levin *et al.*, 1964) and marrow (Short, 1964) xanthomatosis has also been described. Xanthomata are sometimes absent (Waldenström, 1952; Ozer *et al.*, 1970) and cutaneous xanthomatosis without palmar lesions can occur (Frame, Pachter and Nixon, 1961; Marten, 1963; McKenzie, 1964).

The xanthomata in this patient were of an eruptive type on elbows, knees and trunk and there were

palmar xanthomata in the palmar streaks (Fig. 1). The palmar streaks are usually a feature of the 'broad β ' (Type III) hyperlipoproteinaemia but have also been seen in pre- β -hyperlipoproteinaemia (Chait, A. and Lewis B., unpublished).

Usually in this condition, xanthomatosis is associated with hyperlipidaemia but cases have been recorded with xanthoma despite normal levels of blood lipids (Marten, 1963; Thannhauser, 1958; Kint, 1961). A turbid serum with elevated cholesterol and triglyceride is, however, the most common abnormality. Ultracentrifugation has demonstrated quantitative (Lennard-Jones, 1961; Mullinax, Himrod and Berry, 1971) and qualitative defects (Beaumont *et al.*, 1967; Cohen *et al.*, 1966; Lewis and Page, 1965) in both very low density and low density lipoproteins. The myeloma protein is usually an IgA (Beaumont *et al.*, 1967; Ozer *et al.*, 1970;) occurring twice as commonly as IgG (Kayden *et al.*, 1962; Cohen *et al.*, 1966; Levin *et al.*, 1964).

If IgA paraprotein is present it can be either predominantly monomeric (Ozer *et al.*, 1970) or polymeric (Lewis and Page, 1965). The hyperviscosity syndrome has previously been reported in this disorder (Beaumont *et al.*, 1967) and is probably due to the large number of circulating high molecular weight protein molecules.

Cytotoxic therapy and dietary manipulation do not usually affect the serum lipids (Beaumont *et al.*, 1967; Lewis and Page, 1965; Lennard-Jones, 1961; but some workers have observed depression of blood lipids with therapy using D penicillamine which may be immunosuppressive (Beaumont *et al.*, 1967; Mullinax *et al.*, 1971). The course and duration of this clinical entity appears to be similar to that of the myeloma component. As seen in Table 2, myocardial infarction is frequently the cause of death, and coronary and peripheral vascular disease is frequently evident during life.

In some cases, evidence has been presented for immune complex formation between the myeloma protein and the lipoprotein, the affinity between the components of the complex varying from strong (Beaumont *et al.*, 1967; Lewis and Page, 1965) to weak (Beaumont, 1969; Kayden *et al.*, 1962). Other authors (Osserman and Takutsuki, 1963; Cohen *et al.*, 1966), even after extensive investigation, could not demonstrate any complex formation.

The present case of myeloma with hyperlipidaemia has many features similar to those described in the literature for this entity. The myeloma was of a kappa IgA polymeric variety, but the nature and significance of the doublets in the polymer series is not known although it is also seen in other IgA polymeric myelomas without lipaemia (unpublished observation). On complete reduction and alkylation

TABLE 2. Clinical features of twenty-seven cases of myeloma and hyperlipidaemia with xanthomatosis†

Myeloma (27)*	Present in all twenty-seven cases
Hyperlipidaemia (24)	Present in 88%
Xanthomatosis (20)	Present in 90%
Family history of xanthomatosis	Present in 14%
Family history of serum lipid disorders	Present in 21%
Sex ratio (20)	M : F = 4 : 1
Age at diagnosis (19)	Mean 55 years—Range 40–60 years
Presentation (13)	Ischaemic heart disease (2) Xanthomata (8) Myeloma (1) Infection (2)
Mean duration (10)	2–85 years
Clinical evidence for occlusive atheromatous disease (10)	Intermittent claudication in one case Angina pectoris noted in seven cases
Cause of death (10)	Myocardial infarction (5) Infections (4) Renal failure (1)
Myeloma type (14)	IgA = 70%; IgG = 30%
Bence Jones proteinuria (9)	Present in 45%
Osteolytic lesions (12)	Present in 66%
Hyperviscosity Syndrome	Present in two cases

* Number refers to number of cases where information is available.

† Data from references cited.

of this paraprotein only α chain and light chain (and J chain) were noted. On ultracentrifugation, the abnormal lipoprotein floated at a background density of 1.006 retaining pre- β mobility. The D 1.006 fraction contained 46% of the total serum cholesterol and 88% of the total serum triglyceride. The features were those of elevated VLDL or pre- β -lipoprotein levels (Type IV in WHO classification). As sometimes occurs in this abnormality, low-density lipoprotein (LDL) cholesterol was low (below fifth percentile).

There was no evidence in this patient of impairment of the response to injected heparin as assessed by measurements of lipolytic activity and by the fall in serum triglyceride concentration. There was no evidence for an unrelated aetiology for his hyperlipidaemia: no relative had xanthomata or premature ischaemic heart disease; his alcohol intake was negligible, there was normal glucose tolerance and the blood urea was normal.

In this patient no definite evidence could be obtained to suggest the aetiology of the lipid abnormality. Immune complex formation as the mechanism for the hyperlipidaemia in this patient appears unlikely in view of the following findings: (1) the lack of abnormal precipitate arcs in immunoelectrophoresis of the patient's serum; (2) the negative findings using the method of Radl as described

above; (3) the absence of any detectable activity of the patient's serum and isolated IgA myeloma protein against the patient's and other sera in agar double diffusion experiments; (4) the absence of any detectable activity of the patient's isolated protein against the patient's and normal lipoprotein classes; (5) the lack of IgA in the biopsied xanthoma; (6) the lack of lipid depression with effective cytotoxic therapy.

We have, therefore, failed to show the presence of lipoprotein antibody in this patient's IgA and could not demonstrate the presence of circulating immune complexes containing lipoprotein. Although the clinical association of myeloma and a lipoprotein abnormality appears to be a definite clinical entity we were unable to identify the mechanism for this patient's hyperlipidaemia. Beaumont has suggested that one mechanism for the hyperlipidaemia in this entity is due to the anti-lipoprotein antibody activity of the myeloma protein. Glueck has demonstrated that a second mechanism may occur with the presence of heparin-binding antibodies and subsequent interference in the lipoprotein lipase system. A further mechanism, as yet unidentified, may exist, as seen in the present patient.

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