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ORIGINAL ARTICLE

Hyperlipidemic myeloma: review of 53 cases

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Abstract Hyperlipidemic myeloma is a rare and poorly understood variant of multiple myeloma. We report the case of a 53-year-old woman with hyperlipidemic myeloma, skin xanthomas and hyperviscosity syndrome who underwent allogeneic bone marrow transplantation. A comprehensive literature search identified 52 additional cases with plasma cell disease and hyperlipidemia. A detailed analysis revealed several characteristics of these patients as compared to multiple myeloma with normal lipid status: (1) IgA paraprotein was present in the majority (53% vs. 21% in classical multiple myeloma). (2) Skin xanthomas, especially in the palmar creases, elbows, and knees were common (70%). (3) Hyperviscosity syndrome occurred more often (26% vs. 2–6%). While conventional lipid-lowering therapy had only marginal effects, successful anti-myeloma therapy also reduced hyperlipidemia. Analyses of the mechanisms leading to hyperlipidemia documented complexes of paraprotein and lipoprotein in 75% of the 32 cases tested, suggesting an inhibitory role of the paraprotein on lipid degradation. In conclusion, the clinical characteristics, the therapeutic options, and the pathophysiologic mechanisms of hyperlipidemic myeloma are comprehensively reported using the available data from all 53 published cases in the literature.

Keywords Hyperlipidemic myeloma · Myeloma · Multiple myeloma · Paraprotein · Cholesterol · Triglyceride · Hypercholesterolemia · Hyperlipidemia · Skin xanthomas · Hyperviscosity syndrome

Abbreviations

CR	complete response
ESR	erythrocyte sedimentation rate
FD	familiar dysbetalipoproteinemia
HLM	hyperlipidemic myeloma
LDL	low density lipoprotein
MGUS	monoclonal gammopathy of unknown significance
N/A	not applicable
n.a.	not available
NR	no response
PR	partial response

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TGL triglyceride
VLDL very low density lipoprotein

Introduction

Hyperlipidemic myeloma (HLM) is a rare variant of multiple myeloma [4]. While it may present as an isolated laboratory finding, in some cases it is associated with skin xanthomas and/or hyperviscosity syndrome, dominating the clinical picture. Since previous comprehensive reports of HLM date back 30 years [4, 11, 43, 52, 63] and due to its low incidence, symptoms, the clinical course, and the best therapy of HLM remain largely unknown. Even though the unusual lipid patterns, occasionally manifesting as a grossly lipemic and highly viscous serum were studied extensively in some cases, the underlying mechanism of HLM remains unknown. According to one hypothesis, the paraprotein binds to lipoproteins and, thereby, inhibits their degradation [2, 4, 6, 13, 37, 63]. This view has been challenged, and evidence for an affinity of the paraprotein to heparin or the low-density lipoprotein (LDL) receptor was provided, leaving the matter open for debate [12, 13, 52, 66]. Here, we present a patient with HLM who was treated with allogeneic bone marrow transplantation, as well as an extensive literature research revealing a total of 52 additional cases.

Case presentation

In 2003, a 53-year-old woman with HLM was referred for allogeneic hematopoietic stem cell transplantation; the time course of events is shown in Fig. 1. The patient had been well until 1993, when pain in both shoulders and the neck accompanied by an elevated erythrocyte sedimentation rate (ESR) occurred. A paraprotein (IgAκ, 5.95 g/l, normal range 0.7–4) was discovered and her bone marrow was infiltrated by 15–20% atypical plasma cells. Peripheral blood count, calcium, creatinine, β2-microglobulin levels, and bone scan were unremarkable. A diagnosis of smoldering multiple myeloma was made. In March 1999, orange skin xanthomas were noted in the folds of the hands and feet and at the surface of the fingers below her rings (pressure points). The myeloma had progressed, causing anemia with a hemoglobin of 10.3 g/dl, the IgA level was 25.1 g/l with a β2-microglobulin of 2.75 mg/l (<2.4), and the ESR was 110 mm/h. Elevated cholesterol levels (11 mmol/l, <5.2) were treated with simvastatine and subsequently with atorvastatine and quantalan without success. Skin biopsy demonstrated the presence of foam cells in the upper corium. The patient was not obese (170 cm, 78 kg, body mass index: 27 kg/m^2) and free of cardiovascular complaints. There were no cardiac risk factors besides a history of smoking; electrocardiography, stress test, and echocardiography were normal. The family history for hyperlipidemia and xanthomas was negative. In the summer of 2001, the patient reported headache, blurred vision, and gait instability indicating hyperviscosity syndrome. Examination of the ocular fundus revealed dilated segmented veins, cotton wool spots, and ocular bleeding. Skin xanthomas now also involved the thighs, knees, and the forearms. Anemia had progressed, and the bone marrow was now infiltrated by 35% atypical plasma cells. IgA had risen to 39.4 g/l, total protein to 98 g/l, and cholesterol to 16.2 mmol/l. Four cycles of chemotherapy with vincristine, adriblastin, and dexamethason were applied and stabilized the myeloma parameters without having an effect on the lipid levels (triglycerides 17.8 mmol/l and cholesterol 24 mmol/l). In contrast, three sessions of plasmapheresis in addition to a single dose of cyclophosphamide decreased the levels of triglycerides and cholesterol to 11.6, mmol/l, and 7.8 mmol/l, respectively, and promptly relieved the symptoms of hyperviscosity. Peripheral stem cells were collected, and two autologous stem cell transplantations were performed after melphalan conditioning in February and August 2002. Thereafter, lipid and IgA levels returned to normal with a concurrent resolution of the skin xanthomas until January 2003. However, because the paraprotein started to rise again in spring 2003, the patient underwent allogeneic stem cell transplantation from a human leukocyte antigen (HLA) identical brother, following a reduced intensity conditioning regiment in April 2003. Shortly thereafter, a rise in paraprotein and lipid levels, associated with hyperviscosity syndrome, was successfully treated with thalidomide and high doses of dexamethasone, as well as three sessions of plasmapheresis. The patient remained free of symptoms for 8 months before myeloma relapsed with bone lesions of the skull. Palliative radiation, bortezomib therapy, and three cycles of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE) were applied. Hyperviscosity syndrome necessitated biweekly plasmapheresis. In 2006, intractable bone pain developed, and posterior leucencephalopathy caused an incomplete left-sided paresis. After consultation with the patient and her family, no further therapeutic attempts were made, and the patient died. Permission to conduct necropsy was not granted, but post mortem DNA analysis of a bone marrow biopsy revealed a normal E3/E3 apolipoprotein E genotype.

Patients and methods

A PubMed search was carried out using the search terms “hyperlipidemia”, “hypertriglyceridemia” or “hypercholesterolemia”, “multiple myeloma”, and “paraproteinemia” or

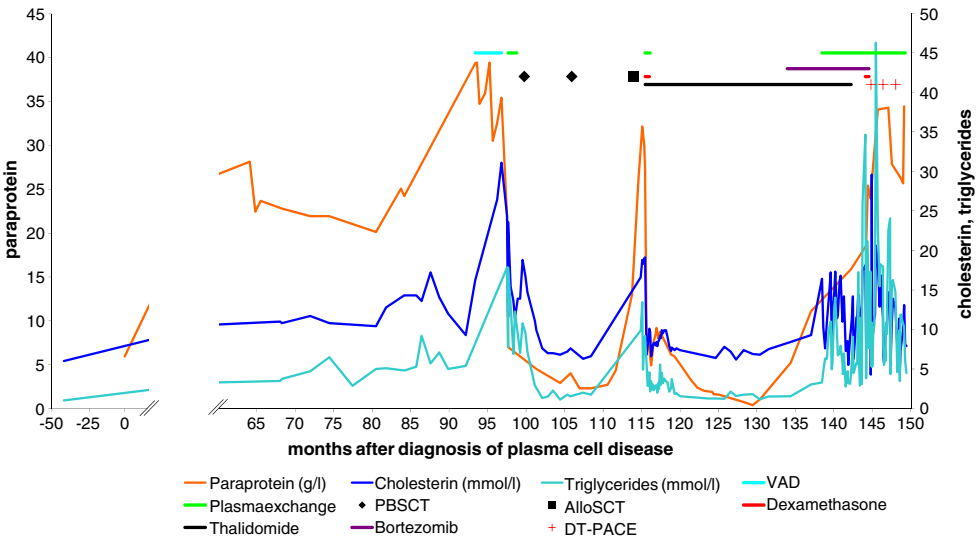

Fig. 1 Time course of events for our patient with HLM. Values for paraprotein, IgA, cholesterol and triglycerides are given, anti-myeloma treatments are indicated. *VAD* vincristine, adriblastin, dexamethasone; *DT-PACE* dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; *PBSCT* autologous peripheral blood stem cell transplant; *AlloSCT* allogeneic stem cell transplant

"paraprotein". Case reports published until June 2007 written in English, French, Spanish, German, Russian, and Czech fulfilling both of the following criteria were included: (1) paraproteinemia or an abnormal plasma cell clone in bone marrow or tissue biopsy; (2) hypertriglyceridemia >5 mmol/l or hypercholesterolemia >8.5 mmol/l. These high threshold values were chosen arbitrarily to exclude dyslipidemia of metabolic syndrome. Plasma cell disease was classified following international guidelines [29, 47] as monoclonal gammopathy of unknown significance (MGUS), multiple myeloma, or smoldering multiple myeloma. Since many reports lacked complete documentation of end organ damage, a plasma cell count of >30%, extensive bone marrow infiltration or pronounced atypia were also considered diagnostic for multiple myeloma. Complete remission (CR) for myeloma was defined as lack of any evidence of myeloma after treatment; partial remission (PR) required marked decrease of the paraprotein level. Similarly, CR required a normalization, and PR a marked improvement of lipid levels. Statistical analysis was carried out using Graphpad Prism® and included linear regression, Fisher's exact test, Mann-Whitney testing, and a survival analysis tool. Due to the fact that this meta-analysis contains incomplete data sets, *p* values have to be interpreted with caution.

Results

Baseline characteristics and laboratory values A total of 52 additional cases of HLM published between 1937 and 2007 were identified (Table 1). The majority (85%) fulfilled the criteria of multiple myeloma; in addition, four cases (7.5%) were classified as smoldering myeloma and four cases as MGUS (Table 2). Overall, these patients differed from a large published myeloma cohort [35] by a predominance of IgA myeloma (53.3% vs 21%), while IgG (42% vs. 51.5%) light chain and nonsecreting myeloma (0% vs 3% and 20%, respectively) were underrepresented. In contrast, the distribution of kappa- and lambda myeloma was identical. HLM patients were slightly younger at diagnosis (57 years, range 21–74 vs 66 years old, range 20–92), and a slight male preponderance (30 cases vs. 23) was noted.

The median triglyceride value was 11.5 mmol/l (range 2.4–65.7) and the median cholesterol level 16.5 mmol/l (3.5–49.2). Cholesterol levels of patients with IgA myeloma were higher than with IgG myeloma (Fig. S1). A striking correlation between paraprotein and lipid concentrations was observed in our patient (R^2=0.84 and 0.74 for cholesterol and triglycerides, respectively, Fig. S2), in line with similar longitudinal data reported for 12 additional patients. Additional conditions aggravating hyperlipidemia were present in seven patients including nephrotic syndrome (four), diabetes mellitus (two), and hypothyroidism (one). The serum was reported to be milky, turbid, oily, or lipemic in 24 cases, sometimes with a creamy cap.

Clinical presentation Typically, symptoms of hyperlipidemia or xanthomas preceded the diagnosis of plasma cell disease in 21 and 22 cases, respectively, sometimes by more than 10 years (mean delay 4.1 and 3.6 years, respectively, Table S1). In other patients, plasma cell disease was diagnosed simultaneously (23 and four cases) or even before (five and three cases) the hyperlipidemic and xanthoma symptoms. Skin xanthomas were described in 37 of 53 patients (70%), typically, the palmar creases of the hands were involved, but the periorbital region, elbows, and knees were also concerned (Table S2). In general, xanthomas were painless; however, for five patients, painful lesions dominated

Table 1 Fifty-three patients with HLM

Year of publication	Sex	Age[a]	Diagnosis[b]	Paraprotein g/l	TGL (mmol/l)	Cholesterol (mmol/l)	Reference	Atherosclerosis	Skin xanthomas
2009	F	43	MM (sMM)	IgA κ 34.4	34.7	31.1	This paper	no	yes, HKEFOP
2005	M	48	MM	IgG λ 72[d]	9.5	16.5	[9]	no	no
2005	M	72	MM	IgA κ 33.6	16.4	28.6	[8]	no	yes, HEF
1997	F	50	MM	IgA κ 26.1[d]	11.9	29.7	[45, 68]	no	yes, HKETF
1997	F	51	MGUS	IgG κ 23	5.5	14.6	[31]	no	yes, KFO
1996	F	70	MM	IgA κ 34[d]	5.2	15.5	[21]	TIA	no
1996	M	52	MGUS	IgG κ 22	6.2	6.2	[60]	no	yes, HEO
1995	F	61	MM	IgG ?	7.3	3.7	[67]	no	yes, TD
1992	F	58	MM	IgA κ[g]	20.5	18.5	[17]	no	yes, TF
1992	M	85	MM	IgG κ 49.9[d]	10.5	20.2	[1]	no	no
1991	F	42	sMM	IgM λ 12.3[d]	11.7	16.7	[25]	no	yes, H
1990	F	58	MM	IgA λ 63.6[d]	8.7	11.8	[18]	no	yes, HEO
1988	F	48	MM	IgA κ 6.5[d]	35.9	33.7	[16]	no	no
1987	F	49	MM (MGUS)	IgG λ 33.6[d]	7.7	13.3	[20]	no	yes, HO
1986	M	42	MM	IgG κ[c] 90	4.4	11	[53]	MI	no
1986	M	31	MGUS	IgA κ ?	2.4	23.3	[12]	MI	yes, E
1985	M	72	MM	IgA κ 27[d]	40.9	35.5	[32]	no	no
1982	M	52	MM	IgA κ 31[d]	26.3	34.1	[13]	PAD	yes, HKEFO
1982	M	50	MM	IgG κ 54[d]	10.9	5.6	[13]	no	yes, H
1982	F	58	MM	IgA λ 35[d]	12.4	49.2	[24]	no	yes, HKETFDP
1982	M	53	MM	IgG λ 5.7[d]	28.5	7.4	[48]	?	no
1979	M	50	MM	IgD λ 3.5[d]	27.1	n.a.	[49]	no	no
1979	F	57	MM	IgA λ 72.9	4.3	16.3	[15]	no	yes, HKEO
1978	M	64	MM	IgA λ 30	12.8	20.4	[64]	no	yes, HEO
1978	F	69	MM	IgG λ 30	8	10.6	[23]	no	no
1978	F	69	MM	IgG κ 28[d]	12.7	20.4	[63]	no	yes, HD
1975	M	59	sMM	IgA λ 34[d]	26.3	32.4	[27, 37]	PAD	yes, ET
1975	M	31	MM	IgG κ 18[d]	4.9	14.8	[66]	MI	yes, O
1975	F	57	MM	IgG λ ?	2.6	12.6	[39]	no	yes, HTFO
1975	M	60	MM	IgA κ 7[d]	6.8	11.4	[52]	no	yes, HKET
1972	M	60	MM	IgG λ 56[e]	11.3	n.a.	[22]	MI, PAD	no
1972	F	n.a.	MM	IgG ? 120[f]	12.7	31.6	[10]	no	yes, HETOP
1972	F	41	MGUS	IgG κ 28.4[d]	5.3	7.3	[33]	no	yes, TFO
1971	M	60	MM	IgG ?	3.6	8.6	[56]	no	yes, O
1970	M	49	MM	IgG λ 38[d]	7.3	9.7	[42, 43]	no	yes, HTFD
1970	M	50	sMM	IgA ?	n.a.	14.3	[46]	SCD	no
1968	F	42	MM	IgA ? 58[d]	22.6	41.4	[30]	no	yes, EFDP
1968	M	59	MM	IgA ?	16.3	3.5	[62]	no	no
1967	M	57	MM	IgA κ 45.6	16.3	25.6	[5, 6]	MI	yes, HTOD
1967	M	62	MM	IgA κ 92[f]	20.8	29	[2, 5]	PAD	yes, E
1967	M	41	MM	IgA ? 18.5[d]	9.3	18.5	[54]	no	no
1966	F	56	MM	IgG λ ?	11.6	25.9	[11]	no	yes, HETFP
1965	M	52	MM	n.a. ?	n.a.	8.7	[58]	no	yes, O
1965	F	68	MM	IgA ? 25.8[e]	28.5	45.8	[55]	MI	yes, KE
1964	M	46	MM	β-2 ?	n.a.	30.8	[44]	MI	yes, HEP
1964	M	56	sMM	γ-type ?	n.a.	8.4	[40]	no	yes, FO
1963	F	53	MM	γ-type ?	n.a.	9.8	[28]	no	no
1961	M	59	MM	γ-type ?	n.a.	13.9	[19]	no	yes, TFO

Table 1 (continued)

Year of publication	Sex	Age[a]	Diagnosis[b]	Paraprotein g/l	TGL (mmol/l)	Cholesterol (mmol/l)	Reference	Atherosclerosis	Skin xanthomas
1960	F	65	MM	IgA ?	n.a.	21.5	[3, 26, 36]	MI	yes, HTOD
1960	M	n.a.	MM	IgA ?	n.a.	24.1	[3, 26]	?	yes, n.s.
1952	F	50	MM	β-2 ?	8.2	15	[65]	?	no
1950	M	55	MM	n.a. ?	65.7	23.3	[7]	MI	yes, OD
1937	M	50	MM	n.a. ?	n.a.	9.2	[14]	CVI	no

MM multiple myeloma, *sMM* smoldering type multiple myeloma, *MGUS* monoclonal gammopathy of unknown significance, *n.a.* not available, *MI* myocardial infarction, *SCD* sudden cardiac death, *CVI* cerebrovascular insult, *PAD* peripheral arterial disease, *H* hands (palmar surface or palmar creases), *K* knee, *E* elbow, *T* trunk, *F* flexor folds, *O* periorbital, *D* diffuse skin involvement, *P* relation to pressure points (rings and brassiere)

[a] Age at which the first diagnosis of plasma cell disease was made

[b] If different from final diagnosis, initial hematological diagnosis is given in brackets

[c] Biclonal myeloma, light chain lambda type was also found

[d] Concentration of class of antibody (IgA, IgG or IgM)

[e] Protein concentration of electrophoresis fraction (b or g) containing paraprotein

[f] Total protein concentration in serum

[g] IgA 16-fold upper limit of normal

the clinical picture. In five cases (including ours), xanthomas developed preferentially below pressure points, for instance in the region below the rings of the fingers or the brassiere. Skin biopsies were performed in 21 cases and showed uniformly foam cells, sometimes together with a lymphocytic infiltrate. Immunoglobulin deposition was detected in one skin biopsy and one surgical sample of an artery, four skin biopsies tested negative for immunoglobulins. Hyperviscosity syndrome occurs in 2–6% of myeloma patients [41], but developed in 14 HLM patients (26%) causing symptoms of bleeding in five patients including two with retinal hemorrhage, ischemia of the lower limbs (two) or abdominal organs (three). Mental changes were noted in eight patients including symptoms of confusion, headache, dizziness, ataxia, nausea, and prolonged unconsciousness. In 14 patients, plasmapheresis was performed, 11 for documented hyperviscosity, and an additional three for unclear reasons.

Atherosclerosis was common among HLM patients (Table S3) affecting more than a fourth of all patients (15 out of 50 cases with sufficient data). Typically, the coronary arteries were involved (ten patients) followed by lower limbs (four cases) and cerebral arteries (two cases). In contrast to a predominance of atherosclerosis among cases published before 1975 (14 out of 25 patients), it was much less often observed within the last 30 years (four out of 25).

Treatment Anti-myeloma chemotherapy was applied in 33 patients (Table S4), two of which (including the present case) were treated by autologous and allogeneic bone marrow transplantation. In 14 patients, a partial or complete response, typically for a limited time period was documented. In all of these patients, the lipid levels markedly improved or even normalized. Anti-myeloma treatment of six patients with skin xanthomas induced complete normalization and marked improvement of skin symptoms in two patients, respectively. Pharmacological treatment of hyperlipidemia was reported in 19 patients (Table S5). Most commonly, fibrates were used (total 13 cases, 11 with sufficient data) resulting in lipid normalization in one and an improvement in seven patients. Other drugs also resulted at best in a partial response (two out of five for statins, three out of five for niacine, two out of

Table 2 Characteristics of 53 patients with HLM. Median values and 95% confidence intervals are given

	HLM	Usual myeloma [35]
Male Female	n=30 (57%) n=23 (43%)	Slight male predominance
Median age at diagnosis	55.3 years±3.1	
Multiple myeloma Smoldering myeloma	57.0 years±3 53 years±6.3	66 years
MGUS	49 years±7.8	
IgG	n=19 (42.2%)	51.5%
IgA	n=24 (53.3%)*	21%
IgM	n=1 (2.2%)	0.5%
IgD	n=1 (2.2%)	2%
Kappa	n=20 (57.1%)[a]	66.6%
Lambda	n=15 (42.9%)	33.4%

* p=0.0006, significant difference compared to normal myeloma cohort. Please note that in meta-analysis with incomplete data, p values have to be interpreted with extreme caution

[a] not significant.

six for cholestyramin/cholestipol, and three out of four for probucol).

Outcome Both, progression of myeloma and atypical hyperlipidemia determined the outcome of the disease. Twenty-five patients died, 11 of them because of myeloma complications including infections (seven), renal failure (three), and progression of myeloma (one). The causes of death for 12 of the remaining patients were myocardial infarction (five), sudden cardiac death (one), heart failure (three), hyperviscosity syndrome (two), and pancreatitis (one). A Kaplan–Meier estimation of median overall survival of multiple myeloma patients with HLM (28 months) was slightly shorter than in patients with normal multiple myeloma (30 months). Median survival of patients with smoldering myeloma or MGUS tended to be longer.

Pathophysiology The mechanisms leading to hyperlipidemia in patients with HLM are not known. In general, hyperlipidemia might either be due to an increased lipid synthesis or decreased lipid degradation. The half-life of lipids was tested experimentally in six cases, four times in vivo using labeled lipids, and twice in tissue culture. Uniformly, a prolonged half-life for lipids was demonstrated suggesting decreased lipid degradation as the mechanism causing hyperlipidemia. Physical binding of paraprotein and lipoprotein was demonstrated in 24 of 32 cases tested (Table 3). Co-migration in electrophoresis (14/19) and ultracentrifugation (12/18) were frequently employed to demonstrate complex formation. Binding activity was found to be within the Fab fragment of the antibody in all four cases tested. In five cases, the paraprotein was purified and a complex of lipoproteins and paraprotein was reconstituted with normal serum, suggesting that properties of the paraprotein and not the lipoprotein were responsible for the formation of this abnormal complex. In contrast, in 12 of the 28 patients tested, evidence against complex formation was found in at least one assay (Table 3). Sometimes, different assays yielded contradictory results within a single patient. Moreover, in a minority of patients, no association of paraprotein and lipoprotein could be documented at all and different pathophysiological mechanisms were suggested: In some cases, lipolytic activity in the serum after injection of heparin was found to be low (Table 3). In two patients, the paraprotein had an affinity to heparin, which is an essential co-factor for lipases. In another case, blocking of the LDL receptor by the paraprotein inhibited lipid degradation.

Discussion

Summarizing the available data for all reported cases of HLM, the typical clinical presentation is characterized by IgA myeloma, hyperlipidemia, and skin xanthomas of palmar creases, hands and knees, and hyperviscosity which may dominate the clinical picture. HLM can be associated

Table 3 Summary of experiments describing the mechanism of hyperlipidemia in HLM. Patients with evidence for complex formation have higher cholesterol concentrations ($p=0.014$) than patients with evidence against complex formation

	Complex formation of paraprotein and lipoprotein	
Criteria	Found	Not found
Co-migration in electrophoresis	14	5
Ultracentrifugation	12	6
Gel filtration	4	2
Low speed centrifugation	5	1
Immunodiffusion	5	3
Other[a]	5	4
	Evidence in at least one assay	
	For complex formation	Against complex formation
All	24 (32 tested)	12 (32 tested)
Excluding electrophoresis	18 (25 tested)	10 (25 tested)
	Post heparin lipolytic activity	
Post heparin lipase activity	Reduced 4[b]	Normal 3
	Specific activity of paraprotein	
Anti-Heparin	2	
Anti-LDL receptor	1	

[a] Other assays included LDL sepharose, native western blot, immunoprecipitation, immunoflourescence, immunofixation, immunoelectrophoresis, and rocket electrophoresis

[b] In most cases lipoprotein lipase activity; in one case, hepatic triglyceride lipase activity was measured

with artherosclerosis; however, since it was less frequently diagnosed in recent years, we believe that overall better treatment and prophylaxis may delay the onset of atherosclerosis. The best therapy for HLM has not been defined; in most patients, pharmacological lipid-lowering therapy was largely ineffective. In contrast, even partially successful anti-myeloma chemotherapy resulted in clear improvement of the lipid levels. In some cases, lipid values were conveniently used as disease marker for HLM. The effect of anti-myeloma chemotherapy on xanthomas was less impressive. Most likely, reversing xanthomas requires a prolonged period with normal or near normal lipid and paraprotein levels which was not achieved in most patients.

HLM is considered to be an exceedingly rare clinical entity. Indeed, in a large study, only 6% of 300 myeloma patients tested had cholesterol levels above 7.76 mmol/l including 1% above 12.9 mmol/l [34]. In the same study, 2% of 131 patients tested had triglyceride levels >3.4 mmol/l, all of these values were elevated above 5.7 mmol/l. However, the most common lipid abnormality of multiple myeloma seems to be a low cholesterol level: in 26% of the 300 patients the cholesterol levels were below 3.9 mmol/l; and 13% had cholesterol levels below 0.57 mmol/l [34]. Nevertheless, since lipid levels were only reported in a subgroup of myeloma patients, lipid abnormalities might be an underdiagnosed condition.

The mechanisms leading to hyperlipidemia are not entirely clarified. In two-thirds of the patients tested, a complex between paraprotein and lipoprotein was demonstrated. In these cases, the antibody seems to cover the lipoprotein, preventing steric access of lipases and reducing lipid degradation. The epitopes recognized by the antibody are largely unknown; in some cases, the paraprotein was able to bind lipoproteins derived from a wide range of species (fish to mammals, HDLs to VLDLs), suggesting unspecific binding to universal components of lipoproteins. For other paraproteins, the substrate range was more specific. The affinity of the paraprotein to its lipoprotein target is most likely week: in most cases, hyperlipidemia occurred while the paraprotein concentration was high and resolution required lowering, but not disappearance of the paraprotein. For unknown reasons, the pathological process leading to hyperlipidemia seems to be better supported by IgA than by IgG molecules. In a minority of patients, complexes between paraprotein and lipoproteins were not detected despite considerable experimental efforts. On the one hand, a week or transient interaction might have evaded detection, on the other hand, a different mechanism might be responsible for hyperlipidemia in these patients. An inhibition of lipoprotein lipases, possibly via an affinity towards the co-factor heparin was proposed, as well as blocking of the cellular LDL receptor.

Complexes of lipoprotein and paraprotein might be more common than appreciated. In some of the myeloma patients with hypocholesterolemia, an affinity of paraprotein towards lipoprotein was also demonstrated [38, 51, 57, 61]. It has been speculated that the paraprotein opsonises the lipoprotein followed by degradation by macrophages [50]. In one of these studies, the serum of 20 patients with detectable affinity of paraproteins to lipoproteins had significantly lower total lipid values then the sera of 38 patients without this activity [51]. It remains mysterious as to what features of the antibody are increasing or decreasing the degradation of the lipoproteins in hyperlipidemic versus hypolipidemic myeloma.

In many aspects, patients with HLM mimic the disease familial dysbetalipoproteinemia (FD). Patients suffering from this condition also have elevated cholesterol and triglyceride levels and develop similar skin xanthomas [59]. Lipid electrophoresis demonstrates a typical broad beta peak in FD patients. Even though documentation was incomplete, at least 15 reported patients with HLM revealed a similar electrophoretic pattern. However, FD is not known to be associated with multiple myeloma and responds promptly to lipid-lowering therapy. The genotype E2/E2 or rare mutations of the apolipoprotein E (ApoE) gene are responsible for FD. ApoE is present on LDLs and serves as a co-receptor for the LDL receptor. The affinity of the ApoE2 allele to its receptor is 100-fold weaker, causing a reduced uptake of LDL and, consequently, accumulation of lipoproteins. However, only a fraction of patients with this genotype develops hyperlipidemia, typically in association with other diseases such as diabetes mellitus or hypothyroidism. The ApoE genotype was tested in nine patients with HLM, two were homozygous for E2, and five heterozygous. In contrast, the frequencies for the E2/E2 and E2/E3 genotypes in the normal population are 1% and 10%, respectively. It is tempting to speculate that covering of the lipoproteins with antibodies in the setting of a partially or completely deficient LDL co-receptor causes hyperlipidemia. However, in the two patients (including ours) that were of the E3/E3 genotype, other so far unrecognized pathogenetic mechanisms must be responsible for hyperlipidemia.

In summary, the association of multiple myeloma and hyperlipidemia is a rare but clinically relevant and scientifically fascinating condition. Since many features of the disease remain unresolved, further work with systematic biochemical experiments in a larger series of patients is needed. These biochemical data in combination with clinical and genetic data might clarify the mechanism of this association.

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References

1. Ansari Z (1992) Hyperlipidemia in monoclonal gammopathy. N Y State J Med 92(11):496–497
2. Aubert L et al (1967) Clinical and cytologic study of a 2nd case of xanthomatous IgA myeloma with circulating anti-lipoprotein antibodies. Sem Hop 43(48):3014–3021
3. Beaumont JL (1969) Gamma globulins and hyperlipemia. Hyperlipemia caused by autoantibodies. Ann Biol Clin 27(10):611–635
4. Beaumont JL, Beaumont V (1977) Autoimmune hyperlipidemia. Atherosclerosis 26(4):405–418. doi:10.1016/0021-9150(77)90111-3
5. Beaumont JL et al (1970) Myeloma anti-lipoprotein autoantibodies. Comparative study of 2 types anti-Lp P.G. IgA and anti-Lp A.S. IgG. Ann Biol Clin 28(5):387–399
6. Beaumont JL, Jacotot B, Beaumont V (1967) Hyperlipidemia caused by auto-antibodies. A cause of atherosclerosis. Presse Med 75(46):2315–2320
7. Brehmer W, Lubbers P (1950) Generalized xanthomatosis with affection of the bone and diffuse plasma cell proliferation in the bone-marrow in essential hyperlipemia. Virchows Arch 318 (3):394–431. doi:10.1007/BF00952334
8. Burnside NJ et al (2005) Type III hyperlipoproteinemia with xanthomas and multiple myeloma. J Am Acad Dermatol 53(5, Suppl 1):S281–S284. doi:10.1016/j.jaad.2005.04.009
9. Chee L et al (2005) Acquired myeloma-associated type III hyperlipidaemia treated by nonmyeloablative HLA-identical sibling allogeneic stem cell transplant using a donor with essential thrombocythaemia (ET): evidence of engraftment without manifestation of ET in recipient. Bone Marrow Transplant 35 (12):1213–1214. doi:10.1038/sj.bmt.1704973
10. Cloarec M, Etienne J, Debray J (1972) Association of myeloma and hyperlipidemia with xanthomatous eruption. Sem Hop 48 (52):3459–3466
11. Cohen L et al (1966) Familial xanthomatosis and hyperlipidemia, and myelmatosis. Am J Med 40(2):299–317. doi:10.1016/0002-9343(66)90111-2
12. Corsini A et al (1986) Autoantibodies to the low density lipoprotein receptor in a subject affected by severe hypercholesterolemia. J Clin Invest 78(4):940–946. doi:10.1172/JCI112684
13. Cortese C et al (1982) Myelomatosis with type III hyperlipoproteinemia: clinical and metabolic studies. N Engl J Med 307(2):79–83
14. Cremer J (1937) Retikulose mit Leberxanthomatose. Zentralbl Allg Pathol 68(8):289–298
15. Descamps J, Miled A, Goudemand J (1979) Monoclonal myelomatous IgA with antilipoprotein antibody activity of Ra specificity (author's transl). Nouv Rev Fr Hematol 21(2):171–183
16. Dieuzeide G, Pire R, Simian S (1988) Myeloma type IgAk, hyperlipidemia and hyperviscosity syndrome. Medicina 48(1):54–58
17. Dvoretskii LI et al (1992) A combination of myelomatous disease with generalized xanthomatosis. Ter Arkh 64(7):114–115
18. Feussner G, von Hodenberg E, Ziegler R (1990) Atypical type III hyperlipoproteinemia in a patient with Ig A myelomatosis. Klin Wochenschr 68(10):526–532. doi:10.1007/BF01648250
19. Frame B, Pachter MR, Nixon RK (1961) Myelomatosis with xanthomatosis. Ann Intern Med 54:134–141
20. Friedman SJ, Martin TW (1987) Xanthoma striatum palmare associated with multiple myeloma. J Am Acad Dermatol 16 (6):1272–1274. doi:10.1016/S0190-9622(87)80039-7
21. Fukudome K et al (1996) Hyperlipidemia associated with multiple myeloma. Intern Med 35(4):337–340. doi:10.2169/internalmedicine.35.337
22. Glueck HI, MacKenzie MR, Glueck CJ (1972) Crystalline IgG protein in multiple myeloma: identification effects on coagulation and on lipoprotein metabolism. J Lab Clin Med 79(5):731–744
23. Gudiol F, Ariza J, Callis M (1978) Hyperlipemia and multiple myeloma. Report of a case. Rev Clin Esp 149(3):303–305
24. Hagiyama M et al (1982) Polymorphic type of xanthomatosis in association with IgA myeloma. J Dermatol 9(5):347–354
25. Hambrecht R et al (1991) Type III hyperlipoproteinemia in monoclonal IgM gammopathy. Dtsch Med Wochenschr 116 (45):1710–1714. doi:10.1055/s-2008-1063808
26. Heremans J (1960) Les globulines sériques dy système gamma. Éditions Arscia S.A., Bruxelles, pp 227–232
27. Ho KJ et al (1976) Cholesterol dynamics in autoimmune hyperlipidemia. J Lab Clin Med 88(5):769–779
28. Hollan SR, Solti V (1964) Grape cell plasmacytoma associated with lipaemia and dynamic changes in the serum protein pattern. Acta Med Acad Sci Hung 20:249–261
29. International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121(5):749–757. doi:10.1046/j.1365-2141.2003.04355.x
30. James W 3 rd, Harland WR (1968) Plasma cell disease and xanthomatosis. Trans Am Clin Climatol Assoc 79:115–123
31. Johnston JD, Lumb PJ, Wierzbicki AS (1997) Hyperlipidaemia in association with benign paraproteinaemia. Ann Clin Biochem 34 (Pt 6):697–699
32. Kilgore LL et al (1985) Immune complex hyperlipidemia induced by an apolipoprotein-reactive immunoglobulin A paraprotein from a patient with multiple myeloma. Characterization of this immunoglobulin. J Clin Invest 76(1):225–232. doi:10.1172/JCI111951
33. Kodama H, Nakagawa S, Tanioku K (1972) Plane xanthomatosis with antilipoprotein autoantibody. Arch Dermatol 105(5):722–727. doi:10.1001/archderm.105.5.722
34. Kyle RA (1975) Multiple myeloma: review of 869 cases. Mayo Clin Proc 50(1):29–40
35. Kyle RA et al (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78(1):21–33. doi:10.4065/78.1.21
36. Lennard-Jones JE (1960) Myelomatosis with lipaemia and xanthomata. BMJ 5175:781–783. doi:10.1136/bmj.1.5175.781
37. Lewis LA et al (1975) Autoimmune hyperlipidemia in a patient. Atherosclerotic course and chaning immunoglobulin pattern during 21 years of study. Am J Med 59(2):208–218. doi:10.1016/0002-9343(75)90355-1
38. Lewis LA, Page IH (1954) Serum proteins and lipoproteins in multiple myelomatosis. Am J Med 17(5):670–673. doi:10.1016/0002-9343(54)90026-1
39. Marien KJ, Smeenk G (1975) Plane xanthomata associated with multiple myeloma and hyperlipoproteinaemia. Br J Dermatol 93 (4):407–415. doi:10.1111/j.1365-2133.1975.tb06514.x
40. McKenzie AW (1964) Plane xanthoma, hypercholesterolaemia and myelomatosis. Proc R Soc Med 57:889–890
41. Mehta J, Singhal S (2003) Hyperviscosity syndrome in plasma cell dyscrasias. Semin Thromb Hemost 29(5):467–471. doi:10.1055/s-2003-44554
42. Moschella SL (1970) Plane xanthomatosis associated with myelomatosis. Arch Dermatol 101(6):683–687. doi:10.1001/archderm.101.6.683
43. Moschella SL (1970) Xanthomatosis, associated with multiple myeloma. Arch Dermatol 102(1):121–123. doi:10.1001/archderm.102.1.121b
44. Neufeld AH, Morton HS, Halpenny GW (1964) Myelomatosis with xanthomatosis multiforme. Can Med Assoc J 91:374–380

45. Nozaki S et al (1997) Autoimmune hyperlipidemia with inhibitory monoclonal antibodies against low density lipoprotein binding to fibroblasts in a case with multiple myeloma. Intern Med 36 (12):920–925. doi:10.2169/internalmedicine.36.920
46. Ozer FL et al (1970) Monoclonal gammopathy with hyperlipidemia. Am J Med 49(6):841–844. doi:10.1016/S0002-9343(70)80066-3
47. Rajkumar SV et al (2001) Thalidomide for previously untreated indolent or smoldering multiple myeloma. Leukemia 15(8):1274–1276. doi:10.1038/sj.leu.2402183
48. Reckless JP et al (1982) Studies of a variant very low-density lipoprotein with an acquired deficiency of apolipoprotein C-II. Clin Sci 62(1):93–100
49. Richard JL et al (1979) Important hyperlipidemia associated with IgD myeloma (author's transl). Nouv Presse Med 8(19):1603
50. Riesen W, Noseda G (1975) Antibodies against lipoproteins in man. Occurrence and biological significance. Klin Wochenschr 53 (8):353–361. doi:10.1007/BF01468673
51. Riesen W, Noseda G, Butler R (1972) Anti-lipoprotein activity of human monoclonal immunoglobulins. Vox Sang 22(5):420–431. doi:10.1111/j.1423-0410.1972.tb03989.x
52. Roberts-Thomson PJ et al (1975) Polymeric IgA myeloma, hyperlipidaemia and xanthomatosis: a further case and review. Postgrad Med J 51(591):44–51. doi:10.1136/pgmj.51.591.44
53. Rodriguez Fuchs C et al (1986) Unusual multiple myeloma: biclonal gammopathy associated with hyperlipidemia. Sangre 31 (3):360–366
54. Rosen S et al (1967) Multiple myeloma and the nephrotic syndrome. A biochemical and morphologic study. Am J Clin Pathol 47(5):567–579
55. Savin RC (1965) Hyperglobulinemic purpura terminating in myeloma, hyperlipemia, and xanthomatosis. Arch Dermatol 92 (6):679–686. doi:10.1001/archderm.92.6.679
56. Sawkar LA (1971) Familial xanthelasma, hyperlipidemia and multiple myeloma. J Assoc Physicians India 19(4):329–334
57. Schless GL (1958) Serum cholesterol-globulin complex in multiple myeloma. Am J Med Sci 235(5):562–565. doi:10.1097/00000441-195805000-00009 passim
58. Schuller Perez A et al (1965) A case of multiple myeloma with generalized herpes, hyperlipemia and xanthomatosis. Rev Clin Esp 98(6):412–415
59. Smelt AH, de Beer F (2004) Apolipoprotein E and familial dysbetalipoproteinemia: clinical, biochemical, and genetic aspects. Semin Vasc Med 4(3):249–257. doi:10.1055/s-2004-861492
60. Spagnuolo V et al (1996) Dyslipoproteinemia and monoclonal gammopathy: a case report. Ann Ital Med Int 11(3):204–207
61. Spain DM et al (1956) The degree of coronary and aortic atherosclerosis in necropsied cases of multiple myeloma. Am J Med Sci 231(2):165–167. doi:10.1097/00000441-195623120-00007
62. Spikes JL Jr, Cohen L, Djordjevich J (1968) The identification of a myeloma serum factor which alters serum beta lipoproteins. Clin Chim Acta 20(3):413–421. doi:10.1016/0009-8981(68)90298-2
63. Taylor JS et al (1978) Plane xanthoma and multiple myeloma with lipoprotein–paraprotein complexing. Arch Dermatol 114(3):425–431. doi:10.1001/archderm.114.3.425
64. Valek J et al (1978) An unusual case of hyperlipoproteinemia type III manifestation. Vnitr Lek 24(5):496–501
65. Waldenstrom J (1952) Abnormal proteins in myeloma. Adv Intern Med 5:398–440
66. Wilson DE et al (1975) Multiple myeloma, cryoglobulinemia and xanthomatosis. Distinct clinical and biochemical syndromes in two patients. Am J Med 59(5):721–729. doi:10.1016/0002-9343(75)90233-8
67. Yim H et al (1995) Xanthoma of the liver in a patient with multiple myeloma associated with hyperlipidemia. A case report. J Korean Med Sci 10(6):453–456
68. Yokoyama K, Shinohara N, Wada K (1988) Osseous xanthomatosis and a pathologic fracture in a patient with hyperlipidemia. A case report. Clin Orthop Relat Res 236:307–310