Cutaneous Xanthoma in Association with Paraproteinemia in the Absence of Hyperlipidemia

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Abstract

In the present report we describe a patient with multiple myeloma and long-standing paraproteinemia who developed xanthoma in the absence of an elevation in plasma cholesterol or triglyceride concentrations. Studies demonstrated that our patient's monoclonal IgG antibody interacted with apoprotein B-100. The LDL-antibody complex isolated from our patient did not affect the degradation of LDL by human fibroblasts, indicating that while IgG derived from our patient interacted with LDL it did not alter the metabolism of this lipoprotein by the LDL receptor pathway. Since the LDL receptor pathway is the major route of LDL metabolism, this probably explains why our patient was not hyperlipidemic. In contrast to an absence of effect on the LDL receptor, our patient's LDL-antibody complex stimulated cholesterol esterification within macrophages indicating the uptake and degradation of the LDL-antibody complex. The LDL-antibody complex inhibited the degradation of acetyl LDL by macrophages (scavenger pathway), demonstrating that our patient's LDL-antibody complex was recognized as a modified LDL. Moreover, mixing Ig from our patient with normal LDL also resulted in the normal LDL increasing the esterification of cholesterol by macrophages. One can hypothesize that our patient's monoclonal IgG-LDL complex interacted with the macrophage scavenger receptor, thereby resulting in the occurrence of xanthoma in the absence of hyperlipidemia.

Introduction

Cutaneous xanthoma occurring in association with paraproteinemia is a well-documented clinical abnormality that is seen in patients with multiple myeloma, benign monoclonal gammapathies, and other reticular endothelial disorders (1–6). In many of these individuals the occurrence of xanthoma is associated with hyperlipidemia, but it should be recognized that cutaneous xanthoma in association with paraproteinemia can be observed in individuals whose plasma lipid levels are within the normal range (1, 3, 5, 7–9).

The association of paraproteinemia with hyperlipidemia could occur through a variety of mechanisms. In some cases the simultaneous occurrence of a familial disorder of lipid metabolism unrelated to paraproteinemia may be the basis for the hyperlipidemia (10). In other instances inhibition of heparin-induced lipoprotein lipase activity by an antibody has been observed, and this may be the underlying abnormality accounting for the hyperlipidemia (5, 11). It is more likely, however, that the majority of cases of hyperlipidemia that occur in association with paraproteinemia are secondary to the direct interaction of Ig with lipoproteins. Several studies have shown that Ig obtained from patients with reticular endothelial disorders interact with lipoproteins (4–6, 12–14). Furthermore, such interactions can result in alterations in lipoprotein metabolism. Baudet et al. have described the effect of IgA isolated from three patients with multiple myeloma, hyperlipidemia, and xanthomatosis on the metabolism of LDL in fibroblasts (15). These investigators observed that the IgA isolated from two of their patients blocked the LDL-induced feedback inhibition of cholesterol synthesis that is characteristically observed in fibroblasts incubated with LDL. This suggests that the antibody may have induced the hyperlipidemia by interfering with the metabolism of LDL by the LDL receptor pathway. Cortese et al. have described two patients with type III hyperlipidemia and xanthomatosis in association with myelomatosis whose LDL failed to bind to the LDL receptor of lymphocytes in vitro (16). They further showed in in vivo studies a greatly reduced fractional catabolic rate of IDL and a prolonged IDL[1] to LDL conversion time that was postulated to be due to inhibition of IDL binding to the LDL receptor. The results from these two studies support the concept that a direct interaction of Ig with lipoprotein may alter the metabolism of lipoproteins and thus result in the hyperlipidemia observed in some patients with paraproteinemia.

In contrast to the information available addressing the possible mechanisms by which paraproteinemia results in elevated lipid levels, studies of the pathophysiological basis for the xanthomas in the absence of hyperlipidemia in patients with paraproteinemia are few. In the present manuscript we describe a patient with elevated Ig who had numerous xanthomas for many years in the absence of hyperlipidemia. We also present results of in vitro studies that demonstrate that the interaction of this patient's Ig with LDL resulted in alterations of LDL metabolism that could account for his clinical manifestations.

Case report. The patient is a 75-yr-old black male admitted for the evaluation of back pain and hypercalcemia. In 1967 he was noted on protein electrophoresis to have an IgG monoclonal spike (1.8 g). In 1974 the IgG monoclonal spike was again observed on protein electrophoresis (1.9 g). Bence-Jones proteins were not present in the urine and immunoelectrophoresis revealed a monoclonal IgG increase that was of the lambda

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1. *Abbreviations used in this paper:* IDL, intermediate density lipoprotein.

type. Repeat protein electrophoresis in 1978 demonstrated 1.9 g, in 1980, 2.1 g, and in 1984 just before admission, 4.4 g of gamma globulins. Bone marrow aspirations were normal in 1969, 1978, 1978, and 1980.

Xanthomata were first noted in the inguinal and periaxillary regions in 1972. The lesions were yellow nodules ~ 3 mm–1.5 cm in size (Fig. 1). The underlying skin also had a diffuse yellow coloration. Biopsy of a nodule in 1976 revealed fibrous tissue with a proliferation of histocytes and foam cells (Fig. 2). The size and number of lesions have remained relatively constant with time.

From 1969 to 1983 seven plasma cholesterol determinations were obtained that ranged from 152 to 285 mg/dl with an average of 221±15.6 (SEM). Five plasma triglyceride determinations ranged between 76 and 159 mg/dl with an average of 104±14.4. On several occasions the lipoprotein electrophoretic pattern was normal. The patient did not have any known relatives with either elevations in plasma lipid levels or xanthoma. The patient did not have a history of atherosclerotic vascular disease.

On physical examination vital signs were normal. The carotids were normal without bruits. The heartbeat was regular with a grade 2 over 6 systolic murmur at the second right intercostal space. On abdominal examination the liver was firm with a smooth edge and was 16 cm in span. A firm spleen was felt 3 cm below the left costal margin. No abdominal or femoral bruits were heard and femoral pulses were normal. Pulses in the distal extremities were also normal. The back was tender over the L-3 and L-4 region. Numerous yellow-orange nodules ~ 0.5–1 cm in size were present in the axillary and inguinal regions. Neurologic exam was unremarkable.

Routine laboratory studies were within normal limits except for a hematocrit of 27%, a platelet count of 95,000, and a white blood cell count of 1,700 with 37% neutrophils, 49% lymphocytes, 4% monocytes, 3% eosinophils, 1.5% basophils, and 5.3% large unstained cells. The serum creatinine level was 1.8 mg/dl, calcium 11.4 mg/dl, and the total protein 10.4 g/dl with an albumin of 3.4 g/dl. Immunoelectrophoresis revealed a monoclonal IgG of lambda type. Chest x ray and lumbar sacral spine films revealed diffuse osteopenia with multiple compression fractures in the lumbar and lower thoracic spine. Skeletel survey revealed multiple small lucencies in the pelvis and proximal femur. Bone marrow aspiration demonstrated that ~ 15% of the cellular elements were plasmacytoid with both primitive plasmacytoid lymphocytes and atypical binucleate plasma cells. The patient was begun on a protocol for the treatment of high tumor burden multiple myeloma.

Methods

20 ml of blood was obtained from the patient on several occasions. The plasma was separated by centrifugation and kept at room temperature until lipoproteins and circulating antibodies were separated by the methods described below, because initial studies demonstrated that the antibody precipitated in the cold. The effect of temperature on the Ig-lipoprotein complex is shown in Fig. 3. At ~ 7°C there is a rapid rise in optical density indicating protein precipitation. The plasma was passed over an ion exchange column (DE-52; Whatman Laboratory Products, Inc., Clifton, NJ) equilibrated with 0.0175 M sodium phosphate (pH 6.3). Elution with the same buffer resulted in the separation of two protein peaks, a fraction that contained Ig alone and a slower migrating fraction that contained both Ig and apo B-containing lipoproteins (Fig. 4). To quantitate the proportion of apoprotein B-con-

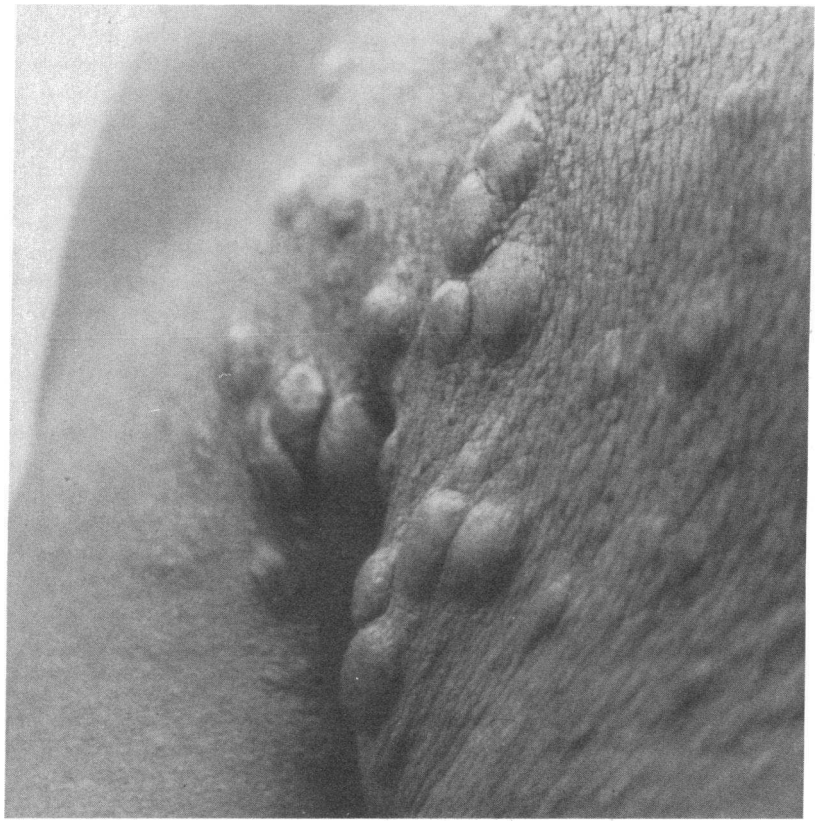

Figure 1. Xanthomata in the periaxillary region.

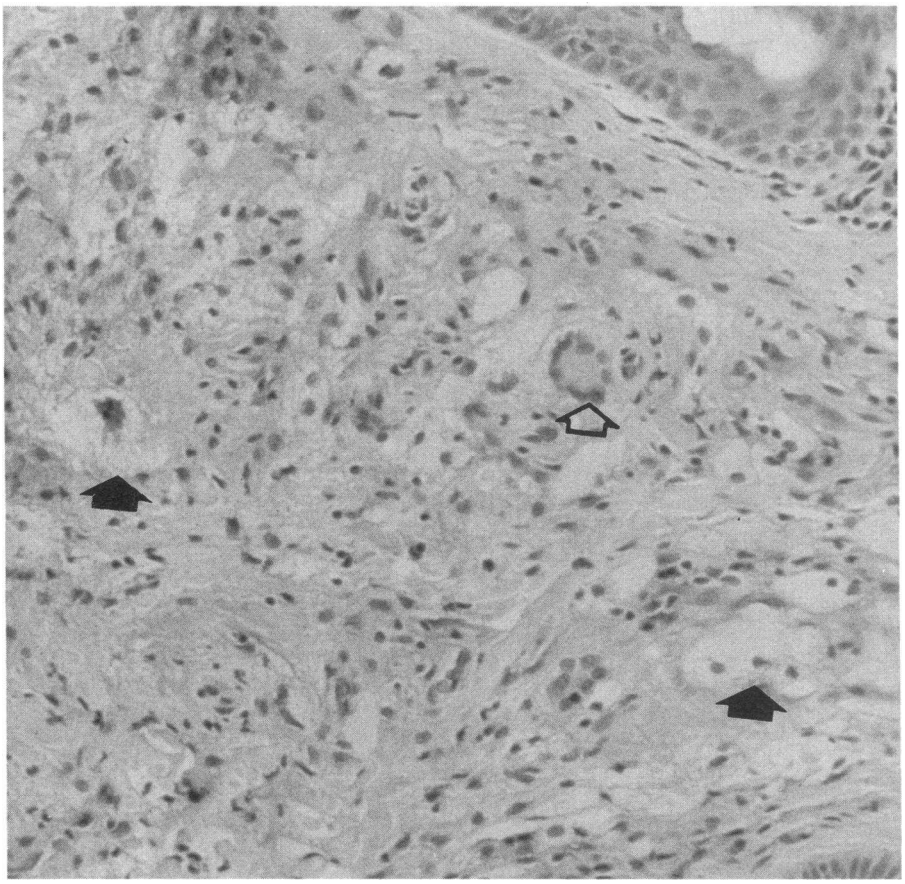

Figure 2. Light microscopy of xanthoma showing multinuclear histocytes (*open arrow*) and foam cells (*closed arrows*).

taining lipoproteins the plasma from this patient was passed over a protein A column, which removes all detectable IgG. Only 15% of the apoprotein B loaded on the column passed through, suggesting that the majority of the apoprotein B-containing lipoproteins are bound to IgG. Immunological analysis of the proportion of IgG and apoprotein B present in the circulating complex indicated a molar apoprotein B/IgG ratio of 0.95 and 1.04 on two separate analyses (apoprotein B, 515,000 mol wt). These data are consistent with the circulating complex containing equimolar quantities of apoprotein B and IgG.

Human fibroblasts were obtained from the University of California Tissue Culture facility and were grown in Eagle's MEM containing 10% FCS to near confluence then transferred to a medium containing 10% lipoprotein-deficient serum for 48 h. Lipoprotein-deficient serum was prepared from the plasma of normal fasting subjects by ultracentrifugation at a density of 1.24 g/ml (17). LDL was isolated from the plasma of normal fasting subjects by ultracentrifugation between densities 1.019 and 1.063 g/ml (17). The LDL was radiolabeled with ^{125}I using the monochloride method of McFarlane (18). The degradation of ^{125}I-labeled LDL by the fibroblasts was determined by incubating at 37°C for 5 h with 2.5 μg of ^{125}I-LDL in 1 ml of Eagle's MEM containing 10% lipoprotein-deficient serum. At the end of the incubation the medium was removed and treated with cold 25% TCA. After centrifugation the supernatant fluid was extracted with hydrogen peroxide and chloroform to remove free radioiodide. The radioactivity was measured in a portion of the aqueous phase to determine ^{125}I-labeled degradation products released into the medium. Plates without cells were incubated under the same conditions to control for the spontaneous breakdown of labeled LDL (19).

Mouse peritoneal macrophages were harvested from unstimulated Swiss male mice (25–30 g) by the procedure of Goldstein et al. (20). The incorporation of [^3H]oleate-albumin into cholesteryl esters was determined in monolayers of macrophages that were incubated fro 5 h at 37°C in 0.6 ml of DME containing 0.2 mM [^3H]oleate. At the end of the incubation the cells and the medium were extracted with methanol

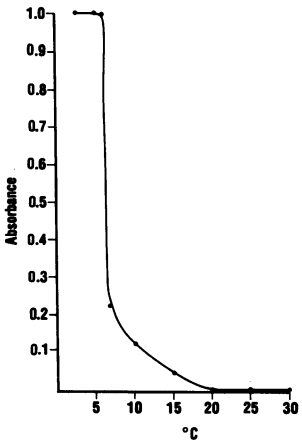

Figure 3. Temperature precipitation. The patient's plasma was cooled at 1°C/min. At ~ 7°C visible flocculation became evident, measured as a sharp increase in absorbance at 535 nm.

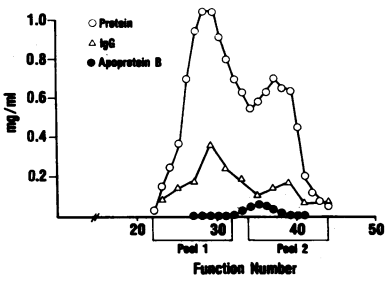

Figure 4. Elution pattern of the patient's plasma on a DE-52 ion exchange column under the conditions described in Methods.

and the cholesteryl [^{3}H]oleate isolated by TLC on layers of silicic acid on glass plates (Merck, Darmstadt, FRG) developed in hexane/diethyl ether/acetic acid (83:16:1, vol/vol/vol). The spots corresponding to standards of cholesteryl esters were cut from the plate and counted in a liquid scintillation counter (19).

The degradation of acetylated LDL was determined in mouse peritoneal macrophages. LDL was acetylated with acetic anhydride as described by Basu et al. and the acetyl LDL was radiolabeled with ^{125}I using the monochloride method of McFarlane (18, 21). The degradation of the ^{125}I-labeled acetyl LDL was determined as described above for labeled LDL. In addition the ^{125}I-labeled acetyl LDL was used to determine if our patient's antibody bound to acetyl LDL. Serum was incubated overnight at 4°C with ^{125}I-labeled acetyl LDL followed by the addition of protein A beads (protein A:IgGsorb from the Enzyme Center, Inc., Malden, MA). After a 1-h incubation the labeled acetyl LDL bound to antibody were separated by centrifugation, washed several times by centrifugation, and counted.

Purified apoproteins, antibodies to these apoproteins, and lipoproteins were prepared as described in an earlier publication (22). Chylomicrons were obtained from a patient with primary lipoprotein lipase deficiency.

Statistical significance was determined by a two-tailed t test.

Results

Our initial studies demonstrated that the Ig obtained from our patient formed a precipitin line with apoprotein B-100 and did not react with apoprotein A-I, A-II, C, or E. The Ig-lipoprotein complex in our patient's plasma was absorbed on protein A agrose, then disassociated by treatment with 3 M thiocyanate, dialyzed against 0.15 M NaCl, 1 M Na EDTA, pH 7, and the protein composition of the lipoprotein determined using antibodies directed against apoprotein A-I, A-II, B-100, C, and E. The only apoprotein present in the Ig lipoprotein complex isolated from our patient's fasting plasma was apoprotein B-100, confirming that our patient's Ig was directed against apoprotein B-100. Additionally, based on the absence of other apoproteins, these results suggest that the major lipoprotein complexed with the antibody in the circulation of our patient is LDL. These results together suggest that our patient's Ig binds to apoprotein B-100 which is associated with LDL.

The interaction of our patient's Ig with apoprotein B-containing lipoproteins isolated from normals is shown in Fig. 5. As is apparent from the figure, our patient's Ig bound with high affinity to LDL and with much less affinity to VLDL and chylomicrons, which also contain apoprotein B. This suggests that the epitope of apoprotein B to which the Ig binds is less accessible when associated with VLDL or chylomicrons. The Ig bound poorly or not at all to the density 1.063–1.21 lipoprotein fraction. Similarly, serum that did not contain lipoproteins (d > 1.21) did not form a precipitant line with our patient's Ig.

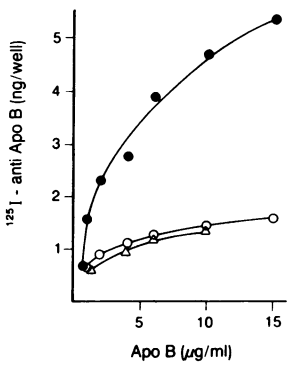

Figure 5. Microtiter wells were coated with 100 μl (10 μg/ml) of purified patient's IgG solution overnight. After blocking with PBS-BSA, lipoproteins were added in 100 μl at the apoprotein B concentrations indicated and incubated for 4 h at 4°C. ^{125}I-labeled rabbit antihuman IgG B polyclonal antibody (~ 6 × 10^5 cpm) was then added and incubated overnight at 4°C. After rinsing and slicing the microtiter wells were counted in a gamma counter. •, LDL; ○, VLDL; △, chylomicron.

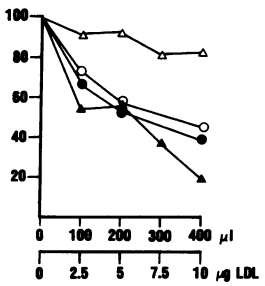

Figure 6. Degradation of ^{125}I-LDL by human fibroblasts. Each dish contained 1 ml of Eagle's MEM containing 10% lipoprotein-deficient serum (4 mg protein/ml), 2.5 μg of ^{125}I-LDL, and either the indicated amount of normal LDL (○), the indicated volume of our patient's Ig-LDL complex (▲) the indicated volume of our patient's Ig (30.5 μg/ml) (△), or the indicated volume of our patient's Ig plus the indicated amount of normal LDL (●). There was 100 μg/ml of apoprotein B and 30.5 μg/ml of IgG in the Ig-LDL complex. Y axis is ^{125}I-LDL degradation % of control. The 100% value for degradation of ^{125}I-LDL in the absence of competing compounds was 1.02 μg/5 h per mg cell protein.

We next determined the effect of our patient's serum on the degradation of ^{125}I-labeled LDL by fibroblasts. As shown in Fig. 6, the Ig-LDL complex obtained from our patient inhibited the degradation of labeled LDL to a similar degree as LDL obtained from normal subjects. Additionally, the combining of normal LDL and our patient's Ig also resulted in the inhibition of the degradation of labeled LDL, whereas Ig alone had no effect on labeled LDL degradation. These studies indicate that the LDL-Ig complex obtained from our patient reacts with the LDL receptor in a manner similar to that of normal uncomplexed LDL, i.e., that complex formation does not interfere with the receptor binding site.

The effect of our patient's Ig and his Ig-lipoprotein complex on the formation of cholesterol esters in mouse peritoneal macrophages was determined next (Fig. 7). The incorporation of oleate into cholesterol esters is a sensitive index of the delivery of cholesterol to macrophages and has been shown to be increased in a variety of circumstances that result in the increased uptake of cholesterol by macrophages (23, 24). The Ig-lipoprotein complex isolated from our patient resulted in an increase in the incorporation of [^{3}H]oleate into cholesterol esters. Similarly, normal LDL mixed with our patient's Ig resulted in an increase in cholesterol ester formation. These results indicate that our patient's Ig-LDL complex results in an increased delivery of cholesterol to the macrophage.

The macrophage is known to possess a scavenger receptor reactive with chemically modified LDL such as acetyl LDL (20, 23). This receptor is distinct from that which catabolizes native unmodified LDL. To determine whether our patient's complex interacted with the scavenger receptor, the effect of our patient's Ig lipoprotein complex on the degradation of acetyl ^{125}I-labeled LDL by macrophages was determined (Fig. 8). Our patient's Ig-lipoprotein complex inhibited the degradation of acetyl LDL by macrophages. In a single experiment normal LDL mixed with our patient's Ig also inhibits degradation of acetyl LDL by macrophages. In contrast, normal LDL or Ig alone had no major effect on the degradation of acetyl LDL. To determine the potential interaction of our patient's Ig with acetyl LDL, ^{125}I-labeled acetyl LDL or ^{125}I-labeled LDL

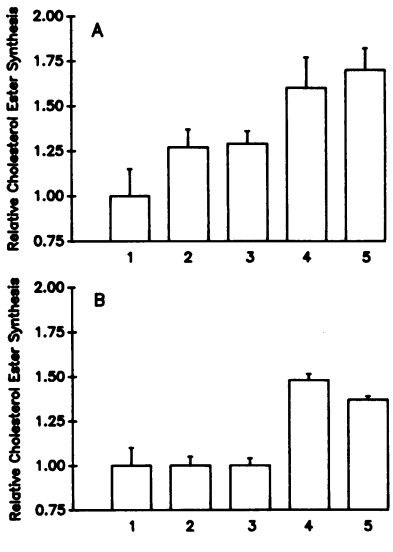

Figure 7. Formation of cholesterol esters in macrophages. Each monolayer received 0.6 ml of DME containing 0.2 mM [H^3]oleate, 2.4 mg/ml albumin and, as indicated, the following additions: (*1*) 100 μl of saline; (*2*) 100 μl of patient's Ig; (*3*) 5 μg of normal LDL; (*4*) 100 μl of patient's Ig-LDL complex; or (*5*) 100 μl of patient's Ig and 5 μg of normal LDL. The data are presented as mean±SEM and the results are expressed as the relative cholesterol ester synthesized with the saline sample equal to 1. In *A*, $n = 3$ for all conditions and in *B*, $n = 4$ for all conditions. (*A*) 1 vs. 2 NS, 1 vs. 3 $P < 0.1$, 1 vs. 4 $P < 0.05$, 1 vs. 5 $P < 0.02$, 2 vs. 3 NS, 2 vs. 4 $P < 0.1$, 2 vs. 5 $P < 0.05$, 3 vs. 4 $P < 0.1$, 3 vs. 5 $P < 0.05$, 4 vs. 5 NS. (*B*) 1 vs. 2 NS, 1 vs. 3 NS, 1 vs. 4 $P < 0.01$, 1 vs. 5 $P < 0.01$, 2 vs. 3 NS, 2 vs. 4 $P < 0.01$, 2 vs. 5 $P < 0.01$, 3 vs. 4 $P < 0.01$, 3 vs. 5 $P < 0.01$, 4 vs. 5 NS.

was incubated overnight at 4°C with our patient's serum and the interaction determined as described in Methods. Similar to our observations for LDL described above, our patient's Ig was able to bind to acetyl LDL. Circulating antibody was reactive to a nearly equivalent extent with both native and acetyl LDL. The ratio of apoprotein B precipitated under equivalent conditions was 1.3 (native LDL/acetyl LDL). As shown in Fig. 8, this did not affect the degradation of acetyl LDL by macrophages, which is analogous to the results shown in Fig. 6 where our patient's Ig alone did not affect LDL degradation in fibroblasts. These results indicate that the Ig-LDL complex interacts with the acetyl LDL receptor of macrophages and thereby interferes with the interiorization of labeled acetyl LDL.

Discussion

Numerous studies have demonstrated that Ig can interact with apoproteins and lipoproteins (4–6, 12–14). In a few instances these interactions have been shown to alter the metabolism of lipoproteins. Baudet et al. have demonstrated that an IgA isolated from patients with multiple myeloma, hyperlipidemia, and xanthomas blocked the binding of LDL to the LDL receptor of fibroblasts (15). Similarly, Cortese et al. have demonstrated that the LDL from two patients with multiple myeloma, type III hyperlipidemia, and xanthomas did not bind to the LDL receptor of lymphocytes (16). Thus, the interactions of Ig with lipoproteins can result in an alteration of lipoprotein metabolism. It is likely that the interference by antibody of LDL metabolism by the LDL receptor pathway, the major pathway of LDL metabolism (25), would significantly affect plasma lipid levels and could account for the hyperlipidemia in these patients.

In the present manuscript we describe a patient who had numerous xanthomata for more than a decade in association with paraproteinemia. Over this period of time numerous plasma cholesterol and triglyceride measurements were obtained that did not demonstrate the presence of hyperlipidemia. The mechanism by which xanthoma occur in association with paraproteinemia in the absence of hyperlipidemia to our knowledge has only been explored in a single study. In 1981 Groszak et al. reported, based on in vivo turn over studies, that there was an increased rate of clearance of VLDL triglyceride and chylomicrons in a patient with normolipidemic xanthomatosis associated with benign monoclonal gammapathy (9). These authors postulated that an enhanced tissue uptake and increased lipolysis due to the interaction of antibody with triglyceride-rich lipoproteins could possibly be the underlying mechanism accounting for the xanthoma.

In the present report we have observed that the monoclonal IgG antibody isolated from our patient interacted with apoprotein B-100. Additionally, the Ig-lipoprotein complex isolated from our patient reacted only with antibodies directed against apoprotein B-100 and not antibodies directed against other apoproteins, indicating that the Ig binds to apoprotein B-100 in LDL form. Direct formation of an antibody antigen complex between circulating antibody in this patient and both native and acetyl LDL was also demonstrated. However, the LDL-antibody complex isolated from our patient inhibited the degradation of LDL to a similar degree as normal LDL, which indicates that the LDL-antibody complex interacts normally with the LDL receptor of fibroblasts. Additionally, mixing Ig from our patient with normal LDL also did not affect the degradation of LDL by fibroblasts. These observations indicate that while IgG derived from our patient interacted with LDL it did not alter the metabolism of this lipoprotein by the LDL receptor pathway. Because the LDL receptor pathway is the major pathway of LDL metabolism this observation probably explains why our patient was not hyperlipidemic (25).

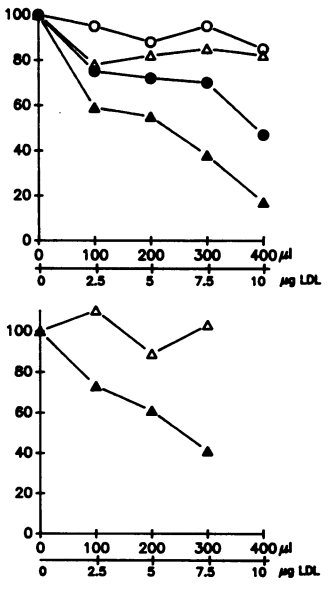

Figure 8. Degradation of ^{125}I-acetyl LDL by mouse peritoneal macrophages. Each dish contained 1 ml of DME containing 10% lipoprotein-deficient serum (4 mg protein/ml), 2.5 μg of ^{125}I-acetyl LDL, and either the indicated amount of normal LDL (4 mg protein/ml) (○), the indicated volume of our patient's Ig-LDL complex (▲), the indicated volume of our patient's Ig (△), or the indicated volume of our patient's Ig plus the indicated amount of normal LDL (●). There was 60 μg/ml of apoprotein B in the Ig-LDL complex, with the proportion of apoprotein B to Ig as in Fig. 6. *Y* axis is ^{125}I-acetyl-LDL degradation % of control. The 100% value for degradation of ^{125}I-acetyl-LDL in the absence of competing compounds was 2.97 μg/5 h per mg protein. The top and bottom panels represent separate experiments carried out at different times. Each point is the mean of duplicate samples.

This property is the opposite of that previously reported for circulating anti-LDL-Ig, presumably because in the present case the epitope on apo B-100 recognized is not located at or adjacent to the receptor binding site.

In contrast to the absence of an affect on the LDL receptor pathway we found that our patient's LDL-antibody complex delivered cholesterol to macrophages. When mouse peritoneal macrophages are incubated with human LDL they do not take up or degrade a great deal of the native lipoprotein (20, 23, 26). However, LDL that is treated with acetic anhydride, which acetylates the amino group of lysine, does bind to mouse peritoneal macrophages (20, 23). These distinct binding sites for acetyl LDL are of high affinity and saturable, and lead to the internalization of LDL through endocytosis (scavenger pathway of LDL metabolism) (20, 22). Within the cell the LDL is digested in lysosomes with the release of cholesterol which is rapidly reesterified (23). Acetyl LDL does not bind to the LDL receptor on fibroblasts (20, 23). The LDL antibody complex from our patient stimulated cholesterol esterification within macrophages, indicating the uptake and degradation of the LDL antibody complex by macrophages (Fig. 7). Additionally, as shown in Fig. 8 the LDL-antibody complex from our patient also inhibited the degradation of ^{125}I-acetyl LDL by macrophages, demonstrating that our patient's LDL-antibody complex was recognized as a modified LDL by the acetyl LDL receptor on macrophages (scavenger pathway). Moreover, mixing Ig from our patient with normal LDL results in the normal LDL also increasing the esterification of cholesterol in macrophages (Fig. 7) and in a single experiment, inhibiting the degradation of ^{125}I-acetyl LDL by macrophages (Fig. 8). These observations indicate that the monoclonal IgG from our patient is capable of binding with LDL in a manner such that the LDL-antibody complex is recognized by the acetyl LDL receptor of macrophages.

Our observations indicate that our patient's LDL-Ig complex is taken up by macrophages to a greater extent than normal LDL, and this could account for the occurrence of xanthoma in the absence of hyperlipidemia. The mechanism of uptake of our patient's LDL-Ig complex by macrophages has not been definitely demonstrated in these studies, but our results do indicate that the LDL-Ig complex is recognized by the acetyl-LDL receptor. This raises the possibility that the increased uptake is due to the interaction of the LDL-Ig complex with the acetyl-LDL receptor, but clearly other potential avenues of uptake could be operative. Our patient did not have any clinically apparent atherosclerotic vascular disease despite the long duration of extensive cutaneous xanthoma, and this raises the possibility that the uptake of LDL by macrophages does not by itself lead to an increased occurrence of vascular disease.

In summary, this study presents evidence that the interaction of antibody with LDL can increase the uptake of LDL by macrophages and thereby perhaps result in the clinical syndrome of xanthomatosis in association with paraproteinemia in the absence of hyperlipidemia.

Acknowledgments

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