Hyperlipidemia Associated with Multiple Myeloma

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A 70-year-old woman with type IIb therapy-refractory hyperlipidemia was diagnosed as having IgA kappa type multiple myeloma. She had neither a family history nor any other disease known to accompany hyperlipidemia. The serum IgA concentration fell from 3.42 g/dl to 1.24 g/dl following chemotherapy with melphalan and prednisolone, and a concomitant decrease in both the serum cholesterol and triglyceride levels was observed. These serum lipids were positively correlated with the serum IgA concentration ($p < 0.001$) during the three cycles of chemotherapy. These findings suggest the involvement of the monoclonal protein of IgA in the development of hyperlipidemia in the present case.

(Internal Medicine 35: 337–340, 1996)

Key words: monoclonal IgA, lipoproteins, myeloma cell

Introduction

Multiple myeloma is characterized by an uncontrolled proliferation of plasma cells primarily in bone marrow that produce a monoclonal protein (M protein). Various clinical manifestations associated with M protein have been known to occur in patients with multiple myeloma. Among them are hyperviscosity syndrome, renal failure, cryoglobulinemia and coagulation abnormalities. In most patients with multiple myeloma, the serum lipid levels are either normal or decreased (1–3); however, there have been reports of multiple myeloma accompanied with hyperlipidemia (4–8). Although the M protein has been noted to play an important role in the development of hyperlipidemia in these cases (6–9), the mechanism is not completely understood. We describe a case of multiple myeloma accompanied with hyperlipidemia considered to have been caused by M protein.

Case Report

A 70-year-old woman was admitted to our hospital in August 1994 because of severe hyperlipidemia that had been refractory to the conventional therapy with anti-hyperlipidemic agents and low fat diet. Although she had been having a regular health check-up every year, no hyperlipidemia had been noted before she was found to have a high serum cholesterol level of 436 mg/dl in November 1992. In October 1992, she suffered from transient dysarthria, an episode that was suspected to be due to a transient ischemic attack (TIA) of the central nervous system. There was no history that suggested diabetes mellitus

and she did not drink alcoholic beverages. Family history was negative for hyperlipidemia, and the past history was unremarkable.

On physical examination she was 158 cm tall and weighed 55 kg. Her blood pressure was 160/60 mmHg and the pulse was 88/min. There were no xanthomas on the skin. The fundoscopic examination showed neither a marked sclerotic change of retinal arterioles nor dilatation of veins. No carotid bruit was audible and the thyroid was not enlarged. Both the respiratory and heart sounds were clear. There was no palpable mass in the abdomen, and the neurological examinations revealed no abnormalities. For the evaluation of the basal profile of serum lipids, the anti-hyperlipidemic agent was discontinued and she was placed on a regular diet containing fat of 60 g/day. Table 1 summarizes the laboratory findings on admission. Both the serum total cholesterol and triglyceride levels were elevated without an increase of chylomicrons in the analysis by lipoprotein electrophoresis and ultracentrifugation method. Although all the apoproteins measured were elevated, the plasma lipoprotein lipase concentration was found to be in the normal range. Both transaminases and alkaline phosphatase were within normal limits and there were no abnormalities in the thyroid function. The serum concentration of IgA was markedly increased and an M peak was detected at the position of β -globulin in the serum protein electrophoresis. This M protein was identified to be an IgA- κ by immunoelectrophoresis. Renal function was normal without Bence Jones protein in the urine. The bone marrow smear disclosed 19% plasma cells with a decrease in the erythroid series. There were no abnormalities in the systemic bone survey by X-ray examination. From these

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Received for publication June 5, 1995; Accepted for publication January 25, 1996

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Table 1. Laboratory Data on Admission

1. Peripheral blood		4. Lipoprotein electrophoresis	
White blood cell count	4,000/mm ³	α	49%
Neutrophil	62.5%	pre β	8%
Lymphocyte	32.5%	β	43%
Monocyte	2.5%	Chylomicron	0%
Eosinophil	2.5%	5. Lipoprotein analysis by ultracentrifugation	
Basophil	0.0%	HDL-cholesterol	195.9 mg/dl
Red blood cell count	287×10 ⁴ /mm ³	LDL-cholesterol	156.1 mg/dl
Hemoglobin	9.1 g/dl	VLDL-cholesterol	85.0 mg/dl
Hematocrit	27.2%	6. Apoproteins	
Platelet	22.9×10 ⁴ /mm ³	A-1	314 mg/dl
2. Blood chemistry		A-2	106 mg/dl
Total protein	8.01 g/dl	B	184 mg/dl
Albumin	52.0%	C-2	13.0 mg/dl
α_1 -Globulin	2.5%	C-3	27.0 mg/dl
α_2 -Globulin	8.2%	E	38.7 mg/dl
β -Globulin	32.0%	7. Lipoprotein lipase 257 ng/ml	
γ -Globulin	5.3%		
Total cholesterol	598 mg/dl		
Triglyceride	464 mg/dl		
HDL-cholesterol	147.3 mg/dl		
Fasting plasma glucose	76 mg/dl		
Urea nitrogen	21.0 mg/dl		
Creatinine	0.9 mg/dl		
Ca	9.2 mg/dl		
3. Immunoglobulins			
IgG	620 mg/dl		
IgA	3,420 mg/dl		
IgM	84 mg/dl		
IgD	<0.6 mg/dl		

HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low density lipoprotein.

findings, she was diagnosed as having stage IIA IgA- κ type multiple myeloma, with type IIb hyperlipidemia.

After the establishment of the diagnosis, she was given standard intermittent pulse chemotherapy with 10 mg of melphalan and 60 mg of prednisolone for 5 days every 6 weeks. The serum concentration of IgA gradually decreased following the chemotherapy with the concomitant decreases in both the total cholesterol (T-Cho) and triglyceride (TG) levels (Fig. 1). Figure 2 shows the relationship of the IgA concentration with the serum total cholesterol and triglyceride levels. Positive correlations were found between the IgA and the serum lipids during the three cycles of the chemotherapy ($p < 0.001$). The plasma cells decreased from 19% to 7% in the bone marrow following the therapy and neither a loss of appetite nor change in the body weight was observed. In addition, she had no fever that suggested an infection secondary to suppressed immune system throughout the therapy. After the third cycle, she was discharged and continued to receive intermittent chemotherapy in the outpatient clinic.

Figure 1. Time course of the serum concentrations of IgA, total cholesterol and triglyceride. Arrows indicate the chemotherapy with melphalan and prednisolone. MP: melphalan and prednisolone, T-Cho: total cholesterol, TG: triglyceride.

Figure 2. Relationships of the IgA concentration with the total cholesterol (A) and triglyceride (B) during the three cycles of chemotherapy. Linear regression analysis was used to assess the correlations between the IgA and serum lipids. T-Cho: total cholesterol, TG: triglyceride.

Discussion

Multiple myeloma represents a malignant proliferation of plasma cells producing M protein, occasionally resulting in various disorders such as hyperviscosity syndrome and cryoglobulinemia. Hyperlipidemia is a rare complication observed in patients with multiple myeloma; however, several cases have been described following the report by Waldenström (4) of multiple myeloma accompanied with hyperlipidemia. These reports suggested that the M protein in serum of the patients played an important role in the development of hyperlipidemia (5–9). In the present case, the elevated IgA concentration fell following the three cycles of chemotherapy

to a level less than a half of that before treatment (Fig. 1). Both the serum cholesterol and triglyceride concentrations concomitantly decreased without any other treatment for hyperlipidemia. In addition, significant correlations were observed between the IgA and these serum lipid concentrations during the chemotherapy (Fig. 2). These findings indicate involvement of the M protein of IgA produced by the myeloma cells in the development of hyperlipidemia in the present case.

Hyperlipidemia was also reported to develop in patients with systemic lupus erythematosus or idiopathic thrombocytopenic purpura (10, 11). Efforts have so far been made to clarify the mechanisms of this rare disorder that occurred in patients with multiple myeloma as well as autoimmune diseases. In the cases of myeloma, the mechanism to cause hyperlipidemia is considered to be a binding of the M protein to either the low-density lipoprotein (LDL) receptor or lipoproteins, resulting in a decrease of the receptor-mediated clearance of the lipoproteins (7–9). In fact, Kilgore et al showed that the Fab fragment cleaved from monoclonal IgA of a myeloma patient had binding activity to LDL *in vitro* (7). It may be of interest to note the absence of skin xanthoma and severe atherosclerotic disease in the present case considering the mechanism for hyperlipidemia since there have been reports of possible involvement of the M-protein-lipoprotein complex in the formation of xanthomas or atherosclerotic lesions (1, 12), whereas, the relatively short history of hyperlipidemia may also simply be an explanation for the absence of these lesions in the present case.

Kihara et al reported the presence of an auto-antibody against lipoprotein lipase which lowered the metabolic rate of chylomicrons in a patient with idiopathic thrombocytopenic purpura (11). In the present case, the increases in the serum levels of LDL, very low density lipoprotein (VLDL) and high-density lipoprotein (HDL) were accompanied with increases in the apoproteins of A-1, A-2, B, C-2, C-3 and E; whereas, the serum chylomicrons were not elevated. Taken together with the findings that the plasma lipoprotein lipase concentration was in the normal range, an impairment of the receptor-mediated clearance of lipoproteins by the monoclonal IgA may have caused hyperlipidemia in the present case, although the precise mechanism remains to be elucidated.

In summary, we report a case of multiple myeloma accompanied with hyperlipidemia that improved following chemotherapy. The close relationship between the serum IgA and lipid levels suggests the involvement of monoclonal IgA in the development of hyperlipidemia in this case.

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