Case Studies

A patient with new-onset hypercholesterolemia

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Background

Hypercholesterolemia is a common health problem with increasing prevalence in many countries.1 A comprehensive evaluation of patients presenting with lipid disorders is warranted to obtain a definite diagnosis and apply the most appropriate treatment. Hypercholesterolemia is sometimes attributed to secondary causes, such as diabetes mellitus, hypothyroidism, cholestasis, chronic kidney disease, and nephrotic syndrome.2 Herein we describe a case of new-onset hypercholesterolemia attributed to underlying malignancy associated with nephrotic syndrome.

Case report

A 46-year-old woman visited the Outpatient Lipid Clinic of our university hospital due to recent-onset hypercholesterolemia (total cholesterol [TC] of 390 mg/dL). The patient had normal lipid levels in previous laboratory tests. She was asymptomatic, had no family history of hypercholesterolemia or coronary heart disease, her menstruation circle was normal, and she had not changed her dietary habits recently. She was receiving no medications. On physical examination, she had a body mass index of 27 kg/m², her blood pressure was 120/80 mm Hg, and there were no xanthomas, xanthelasmas or arcus cornea. The only abnormal finding was a mild pitting bilateral edema in the lower extremities. A fasting blood sample showed elevated levels of TC (387 mg/dL), high-density lipoprotein cholesterol (HDL-C) (93 mg/dL), and low-density lipoprotein cholesterol (LDL-C) (259 mg/dL), whereas triglyceride levels were moderately increased (177 mg/dL).

Further laboratory work-up excluded hypothyroidism (thyroid stimulating hormone 2.91 μIU/L; reference range, 0.5–4.8 and free thyroxine 0.74 ng/dL; reference range 0.7–1.85), diabetes mellitus (fasting plasma glucose 88 mg/dL; reference range, 70–125), cholestasis (total bilirubin 0.3 mg/dL; reference range, 0.1–1 and alkaline phosphatase 77 IU/L; reference range 30–125) and chronic kidney disease (serum creatinine 0.8 mg/dL; reference range, 0.6–1.2, with estimated glomerular filtration rate of 90 ml/min/1.73 m²). However, an elevated erythrocyte sedimentation rate (64 mm in the first hour) was found. Furthermore, urinary dipstick was positive for proteinuria, which was confirmed with a 24-hour urine collection (5.7 g). Serum albumin concentration was low at 2.3 g/dL (reference range 3.4–5.0). The presence of marked proteinuria, low serum albumin, and hypercholesterolemia established the diagnosis of nephrotic syndrome. The patient underwent kidney biopsy, which showed amyloid deposits in the glomeruli (Fig. 1).

A serum protein electrophoresis revealed the presence of monoclonal immunoglobulin A (IgA; 1190 mg/dL; reference range, 0–165). The patient’s bone marrow examination disclosed >20% plasma cells. Thus, the final diagnosis was IgA type multiple myeloma. The patient was treated with six cycles of chemotherapy with vincristin, adriamycine, and dexamethasone. Chemotherapy was well tolerated without serious gastrointestinal side effects, anorexia, or weight loss. Proteinuria eventually subsided, and subsequent improvement in the patient’s lipid profile was observed (TC, 266 mg/dL, HDL-C, 61 mg/dL, TG, 150 mg/dL, and LDL-C, 175 mg/dL).

Conflicts of interest: The authors have no conflicts of interest.
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Diagnosis of nephrotic syndrome. Nephrotic syndrome bile acids, whereas an imbalance between apolipoproteins dysregulate cholesterol biosynthesis and catabolism to common causes of secondary dyslipidemia. The patient clinical approach was, therefore, to search for possible genetic disorder that could explain dyslipidemia. The patient described here presented with recent-onset hypercholesterolemia, a personal and family medical history free of early vascular disease, and no clinical signs of a hypercholesterolemia is usually attributable to lifestyle factors combined with an underlying polygenic predisposition, but it may also have an entirely genetic cause. However, secondary causes should always be considered.

The patient described here presented with recent-onset hypercholesterolemia, a personal and family medical history free of early vascular disease, and no clinical signs of a genetic disorder that could explain dyslipidemia. The next step in our evaluation was the differential diagnosis of nephrotic syndrome.

Hypercholesterolemia in nephrotic syndrome is associated with a marked increase of very low-density lipoprotein (VLDL) synthesis and reductions of hepatic LDL receptor and HDL scavenger receptor class B type I activity, thus leading to limited hepatic uptake of plasma lipoprotein cholesterol.

Furthermore, alterations in several liver enzymes dysregulate cholesterol biosynthesis and catabolism to bile acids, whereas an imbalance between apolipoproteins C-II and C-III may contribute to inhibition of lipoprotein lipase and impaired lipoprotein catabolism.

The patient underwent kidney biopsy, which demonstrated the presence of amyloidosis (Fig. 1). Amyloidosis may be primary or secondary due to chronic inflammation (eg, rheumatoid arthritis) and sometimes is associated with multiple myeloma. The absence of chronic inflammation and the elevated erythrocyte sedimentation rate directed diagnostic evaluation to multiple myeloma, which was subsequently confirmed by an abnormal serum protein electrophoresis consistent with a monoclonal IgA protein. This led to a bone marrow biopsy.

Multiple myeloma represents a malignant proliferation of plasma cells that usually produce a monoclonal protein. Approximately 12% to 15% of patients with multiple myeloma develop amyloidosis during the course of the disease. As is the case with many malignancies, multiple myeloma is usually accompanied with normal or low serum lipid levels. Physicians should always be concerned about an underlying malignancy when a patient presents with hypcholesterolemia.

However, myeloma-associated hyperlipidemia has been previously described (Table 1). Monoclonal protein has been speculated to cause hyperlipidemia in all cases in the literature. Monoclonal protein may bind to either to the LDL receptor or lipoproteins, thus leading to decreased receptor-mediated clearance of chylomicron remnants, intermediate-density lipoprotein (IDL), and LDL. Specifically, Fukudome et al described a patient with severe hyperlipidemia (TC, 598 mg/dL, triglycerides, 464 mg/dL, and HDL-C, 147 mg/dL) refractory to hypolipidemic therapy who was diagnosed with IgA myeloma. There was a close relationship between the serum IgA and lipid levels, whereas 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 this patient.

A similar case of a patient with IgA myeloma and more severe dyslipidemia (TC, 1370 mg/dL and triglycerides, 3620 mg/dL) has also been described. The strong propensity of this patient’s IgA to form stable complexes in a specific manner with VLDL, IDL, and LDL seems to be the underlying mechanism of myeloma-induced dyslipidemia in this case.

A woman who presented with a pathologic fracture of the neck of the left femur due to an osseous xanthoma was diagnosed with IgA multiple myeloma, which was also associated with severe hyperlipidemia (TC, 1150 mg/dL, triglycerides, 1060 mg/dL). Analysis of the patient’s IgA revealed that it inhibited the binding of LDL to LDL receptors. VLDL from this patient also contained IgA, suggesting an interference between IgA and VLDL metabolism as the cause of severe hypercholesterolemia and hypertriglyceridemia.

In vivo kinetic studies in two men with myeloma-associated type III hyperlipidemia demonstrated a greatly reduced fractional catabolic rate of IDL and a greatly prolonged IDL-to-LDL conversion time compared to controls. In vitro studies of LDL from both patients failed to bind to the LDL receptor of normal blood lymphocytes in contrast to LDL from subjects with familial type III hyperlipoproteinemia. In one patient immunoglobulin was associated with IDL and LDL. Therefore, hyperlipidemia reflected impaired IDL metabolism, probably secondary to the binding of immunoglobulin to lipoproteins. A similar impairment of receptor-mediated LDL catabolism did not
result in elevated plasma LDL concentration because of the low IDL-to-LDL conversion rate.\textsuperscript{12}

Another possible underlying mechanism could be monoclonal protein binding to lipoprotein lipase leading to impaired catabolism of triglyceride-rich lipoproteins.\textsuperscript{13} To our knowledge, this is the first time that multiple myeloma-associated hypercholesterolemia was induced by renal amyloidosis and subsequent nephrotic syndrome. Although lipid abnormalities have been previously described in patients with secondary renal amyloidosis there was no clear indication that multiple myeloma was among the underlying causes in those cases.\textsuperscript{14}

Multiple myeloma-associated hyperlipidemia is often refractory to lipid-lowering medications and subsides with treatment for multiple myeloma,\textsuperscript{10} as was the case with our patient. The improvement of patient’s lipid profile and the reversal of proteinuria following chemotherapy supports the causal relationship among multiple myeloma, nephrotic syndrome, and hypercholesterolemia. It should be noted that the improvement in dyslipidemia after chemotherapy did not appear to be a function of anorexia, nausea, and weight loss because these adverse effects were not observed.

We conclude that physicians should always investigate secondary causes of newly diagnosed hypercholesterolemia as this may be an early manifestation of a serious underlying disease, such as multiple myeloma.

### References


### Table 1  Reported cases of multiple myeloma-associated hyperlipidemia

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Baseline lipid profile</th>
<th>Possible underlying mechanism</th>
<th>Post-treatment lipid profile</th>
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<tbody>
<tr>
<td>Kilgore et al\textsuperscript{11}</td>
<td>TC, 1370 mg/dL; triglycerides, 3620 mg/dL</td>
<td>Strong propensity of patient’s IgA to form stable complexes in a specific manner with VLDL, IDL, and LDL</td>
<td>TC, 150 mg/dL; triglycerides, 457 mg/dL</td>
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<tr>
<td>Fukudome et al\textsuperscript{10}</td>
<td>TC, 598 mg/dL; triglycerides, 464 mg/dL; HDL-C, 147 mg/dL</td>
<td>Impairment of the receptor-mediated clearance of lipoproteins by the monoclonal IgA</td>
<td>TC, 350 mg/dL; triglycerides, 300 mg/dL</td>
</tr>
<tr>
<td>Nozaki et al\textsuperscript{9}</td>
<td>TC, 1150 mg/dL; triglycerides, 1060 mg/dL; HDL-C, 48 mg/dL</td>
<td>Inhibition of LDL binding to LDL receptors and interference of the VLDL metabolism by the monoclonal IgA</td>
<td>Improvement</td>
</tr>
<tr>
<td>Cortese et al\textsuperscript{12}</td>
<td>Type III hyperlipoproteinemia</td>
<td>Impaired metabolism of IDL, probably secondary to the binding of immunoglobulin to the lipoproteins</td>
<td>N/A</td>
</tr>
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HDL-C, high-density lipoprotein cholesterol; IgA, immunoglobulin A; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; N/A, not available; TC, total cholesterol; VLDL=very low density lipoprotein.