

Severe hypercholesterolemia in a patient with chronic graft-versus-host disease of the liver

Abstract

With the advances in bone marrow transplantation, and the increased number of patients undergoing this procedure yearly, new complications of transplant are starting to occur more frequently. Severe hypercholesterolemia (cholesterol level above 1000 mg/dl) following graft-versus-host disease (GVHD) has been reported in eight patients so far. We hereby report a case of severe hypercholesterolemia developing in a patient with acute myelogenous leukemia after undergoing bone marrow transplant and having graft versus host disease complication. The patient underwent plasmapheresis with subsequent improvement in her cholesterol and lipid profile.

Keywords: Severe Hypercholesterolemia; Lipoprotein X; Graft versus host disease of the liver; Hyperviscosity syndrome

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Abbreviations: LDL Cholesterol, low density lipoprotein cholesterol; HDL Cholesterol, high density lipoprotein cholesterol; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; GGT, gamma-glutamyltransferase; TSH, thyroid stimulating hormone; Hb/Hct, hemoglobin/hematocrit; INR, international normalized ratio

Introduction

Hypercholesterolemia is a very common condition which occurs in several parts of the world however severe hypercholesterolemia with a cholesterol level above 1000 mg/dl is an extremely rare event and there are only few conditions that may lead to this.

Familial hypercholesterolemia (FH), known to be as the most important cause of severe hypercholesterolemia, is a genetic disease characterized by elevated LDL-Cholesterol (LDL-C), mainly caused by an autosomal dominant condition due to mutations in the LDLR gene that normally encodes the LDL receptor protein, leading to its decreased function and decreased LDL cholesterol clearance from the blood. This leads to elevated levels of total cholesterol and LDL cholesterol. The severe form occurs in individuals who inherit the gene mutation from both parents, making them genetically homozygous or compound heterozygous leading to tendinous xanthomas (waxy deposits of cholesterol in tendons), xanthelasmas (cholesterol deposits in the eyelids) and corneal arcus (cholesterol deposit around the cornea of the eye).¹⁻³ This is also known to be a common cause of premature cardiovascular disease due to atherosclerotic plaque deposition in the coronary arteries, where myocardial infarction was documented as early as 18 months of age in patients with homozygous familial hypercholesterolemia.⁴

Allogeneic hematopoietic stem cell transplantation is an increasingly common treatment for certain malignant and nonmalignant disorders.⁵⁻⁷ However, one of its major complications is the graft-versus-host disease (GVHD) of the liver which can occur in up to 40% of recipients from HLA matched related donors.⁸ Chronic GVHD involving the liver leads to lobular hepatitis, chronic persistent

hepatitis in addition to intra hepatic cholestasis due to thickening of basement membrane of the ducts. This leads to a cholestatic pattern and disproportionate elevation in alkaline phosphatase with regards to the serum aminotransferases and an elevation in the serum bilirubin.^{8,9} Hypercholesterolemia is an observed metabolic abnormality that occurs in 1% of patients after graft-versus-host disease (GVHD).⁵ This manifestation has been postulated to be the result of GVHD itself or due the usage of drugs such as calcineurin inhibitors, mycophenolate, cyclosporine and glucocorticoids which are normally utilized after the transplant.¹⁰⁻¹³ However these drugs are only known to lead to a mild increase in cholesterol level reaching around 300 mg/dL.¹² Cholestasis on the other hand may lead to an increase in total serum cholesterol reaching above 1000 mg/dL.¹⁴ This phenomenon which is thought to be mediated by Lipoprotein X, was first reported in the pediatric population.¹⁵ Lipoprotein X unlike regular alpha and beta lipoproteins is up regulated in cholestasis, does not stain with lipid stains, and does not turn the plasma lipemic.¹⁶ Lipoprotein X is an abnormal lipoprotein particle within the low-density lipoprotein (LDL) that is rich in free cholesterol and phospholipids.¹⁷

Severe hypercholesterolemia in such patients has been reported to be either asymptomatic, or to cause symptoms such as solitary pulmonary cholesteroloma, xanthelasmas, and more importantly hyperviscosity syndrome.¹⁸ Up to our knowledge severe hypercholesterolemia has only been reported in eight cases in patients with GVHD of the liver.¹⁹ Hereby we report another cause of severe hypercholesterolemia in a patient with graft versus host disease developing after allogeneic stem cell transplant.

Case report

A 50-year old lady with history of acute myelogenous leukemia (AML) who underwent allogeneic hematopoietic stem cell transplantation (brother) in January 2013, developed graft versus host disease (GVHD) which was further confirmed by liver biopsy, with associated cholestasis in May 2013, and was maintained since then on cyclosporin and steroids. Then the patient had a relapse in July 2013 after which she underwent donor lymphocyte infusion followed by

Vidaza (azacitidine) therapy. After the 4th cycle of azacitidine therapy the patient developed jaundice with worsened cholestasis where liver function tests done in September 2013 showed a cholestatic pattern with a markedly increased Gamma- Glutamyl Transferase (GGT) of 1747, alkaline phosphatase (ALK) of 457 and bilirubin Total and Direct of 14.9 and 12.1 respectively. The patient's lipid profile was taken in November 2013 and she was found to have a total Cholesterol of 1787 mg/dl, LDL of 1590 mg/dl, HDL of 42 mg/dl and triglycerides of 788 mg/dl. Her only known previous measurement of lipid profile was done in January 2013 prior to BMT and at that time she had a total cholesterol of 132 mg/dl, LDL of 70 mg/dl, HDL of 30 mg/dl and triglycerides of 161 mg/dl. Patient was a non-smoker and non-alcoholic. Medications included insulin glargine and lispro, folic acid, amlodipine, valacyclovir, cyclosporine and prednisone with a total dose of 10 mg daily. Physical examination did not show any xanthomata, xanthelasma or corneal arcus. Past medical history included steroid-induced diabetes, dyslipidemia, acute myelogenous leukemia status post allogeneic bone marrow transplant complicated by graft versus host disease. Family history was negative for dyslipidemia, diabetes or hypertension. Since patient's severe hypercholesterolemia was attributed to the severe cholestasis which may lead to a hyperviscosity syndrome, viscosity level was taken and it was elevated with a level of 3.29 (Normal range between 1.6 and 2). Plasmapheresis was done in January 2014 and this led to a significant drop in total cholesterol and LDL level (Table 1). Patient since then presented for plasmapheresis every 6 weeks with the aim of preventing the development of hyperviscosity syndrome that may be induced from the extremely high cholesterol level.

Discussion

The patient described above was not directly tested for the presence of Lipoprotein X by agarose gel electrophoresis. However, the blood viscosity that was measured turned out to be elevated. These points towards the presence of hyperviscosity syndrome that is most likely mediated by the elevated Lipoprotein X.

To explore the etiology of the hypercholesterolemia, other diseases had to be ruled out first. Prior to the transplant, the cholesterol levels were normal in this patient, which excluded congenital disorders of lipid metabolism.²⁰ Although the patient was on medications that have been shown to cause lipid dysregulations, the disease process was most likely mediated by Lipoprotein X in this case since the level of cholesterol elevation was extreme and not mild as normally induced by medications intake. Thyroid function tests were also taken to exclude thyroid abnormality that may be related to lipid dysregulations and they turned out to be normal as well.²¹

As previously stated, the severe rise in cholesterol may be asymptomatic, or it may lead to the manifestations of hypercholesterolemia or the hyperviscosity syndrome.¹⁸ Our patient had hyperviscosity as evident by the lab test that was taken; however, she did not report any of the associated hyperviscosity symptoms. In addition, the patient was observed to have pseudohyponatremia. Pseudohyponatremia was uncommonly reported in cases with cholestasis resulting from GVHD or other causes such as drug induced cholestasis.²² This laboratory artifact may be induced by hyperlipoproteinemias including Lipoprotein X, and observed by indirect potentiometry. In fact, laboratory sodium analysis assumes that plasma water content is constant. In severe hyperlipidemia, the increase in lipid fraction of the plasma displaces serum water with a

resulting decrease in serum water fraction, and falsely depresses the serum sodium reading.²³ Direct potentiometry would only be able to reveal the accurate sodium concentration in this case.^{23,24}

As for the treatment of this condition, it should be instituted in order to prevent the acute and long-term complications of hyperlipidemia. Plasmapheresis was utilized successfully to alleviate the symptoms and decrease the levels of cholesterol.^{13,14} In other cases, patients passed away due to other complications of GVHD and no treatment was tried. In one case, immunosuppressive therapy guided towards relief of GVHD led to the improvement of the cholesterol levels without any other specific interventions.⁶ In our patient plasmapheresis was instituted due to the high viscosity level. Although statins are known to reduce LDL cholesterol level, their use in patients with GVHD affecting the liver is definitely not desirable since statins are excreted in bile and in those patients with cholestatic liver disease bile clearance is reduced and this may lead to their accumulation to toxic levels with all their associated side effects manifestation.^{25,26}

Conclusion

The occurrence of this condition, although rare, should prompt the measurement of cholesterol levels before the transplant, and after the occurrence of GVHD symptoms. It is suggested that a repeated blood level should be checked at the earliest sign of graft-versus-host disease affecting the liver and should be done regularly weekly until resolution or clearance of disease occurs with the development of stable cholesterol levels. It is currently unsure when to start treatment for this condition, but in case LDL was elevated or hyperviscosity was documented then treatment by plasmapheresis may be effective and essential.

Acknowledgments

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Conflict of interest

The author declares there is no conflict of interest.

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