Lipoprotein-X hyperlipidaemia in Chinese paediatric patients with liver graft-versus-host disease post-haematopoietic stem cell transplantation: two case reports

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Case reports

Case 1

An 8-year-old girl with severe aplastic anaemia and failed immunosuppressive therapy underwent a matched-sibling bone marrow transplantation. Neutrophils and platelets were engrafted 23 and 27 days after transplantation, respectively. Regeneration of marrow and full donor chimerism were demonstrated 30 days after transplantation. Progressive liver dysfunction and cholestasis were noted 5 weeks post-transplantation with peak alanine aminotransferase level of 878 IU/L (reference value, <35), aspartate aminotransferase level 966 IU/L (reference range, 10-40), gamma-glutamyltransferase level 2065 IU/L (reference range, 13-28), total bilirubin level 445 μmol/L (reference range, 10-24), and direct bilirubin level 430 μmol/L (reference range, 5-10). Cholesterol levels were also elevated with total cholesterol level of 23.1 mmol/L (reference value, <5.2), high-density lipoprotein-cholesterol (HDL-C) level 0.5 mmol/L (reference value, >1.6), and high triglycerides (TG) level 11.8 mmol/L (reference value, <1.7). Low-density lipoprotein cholesterol (LDL-C) level could not be calculated based on indirect quantitation with the Friedewald equation as per usual practice since TG level was >4.5 mmol/L; hence, it was measured directly and was normal at 0.2 mmol/L (reference value, <4.1).

Apolipoprotein (Apo) A1 level was low at 0.38 g/L (reference range, 1.2-2.0) and Apo B level was elevated to 1.88 g/L (reference range, 0.41-1.07). Lipoprotein electrophoresis showed chylomicron and very low–density lipoprotein bands, and an additional beta-lipoprotein band that had migrated to cathode was detected, compatible with lipoprotein-X (Lp-X) [Fig a]. There was no family history of hypercholesterolaemia and clinical examination did not reveal any xanthoma. With improvement of cholestasis, dyslipidaemia gradually resolved by 2 years post-transplant with expectant management (Fig b and Table).

Case 2

A 13-year-old boy with stage 4 right adrenal neuroblastoma and multiple nodal, bone and bone marrow metastases underwent chemotherapy (HKPHOSG-NB-07 N7 protocol), gross total tumour resection, and autologous cord blood transplantation followed by immunotherapy. Complete remission was achieved but he had spinal relapse 4.5 years later presenting with cord compression at the level of T5-T9 vertebrae warranting emergency laminectomy and spinal tumour excision. He then received one cycle of temozolomide and irinotecan followed by adjuvant radiotherapy 30 Gy/10 Fr to T5-T9 vertebrae and a haploidentical transplant with maternal TCRαβ-depleted and CD45RA-depleted grafts. Total lymphoid irradiation at 8 Gy, fludarabine 150 mg/m^2, thiotepa 10 mg/kg and melphalan 140 mg/m^2 were prescribed as conditioning. Neutrophils and platelets were engrafted 10 and 11 days after transplantation, respectively, with 99% donor chimerism evident in marrow 30 days after transplantation. His post-transplant course was complicated by severe acute graft-versus-host disease (GVHD) involving skin (grades 2-3), liver (grade 2, biopsy-proven) and gut (grade 4) requiring prolonged and heavy immunosuppression including prednisolone, cyclosporine, and mycophenolate mofetil. He also had disseminated nocardiosis complicated by left lower lobe necrotising pneumonia, parapneumonic effusion, hydropneumothorax and bronchopleural fistula. Prolonged courses of antimicrobials were required and included meropenem, levofloxacin, ceftriaxone, cotrimoxazole, linezolid and amikacin. Due to liver GVHD, the patient had grossly deranged liver function 8 months post-transplantation with peak alanine aminotransferase

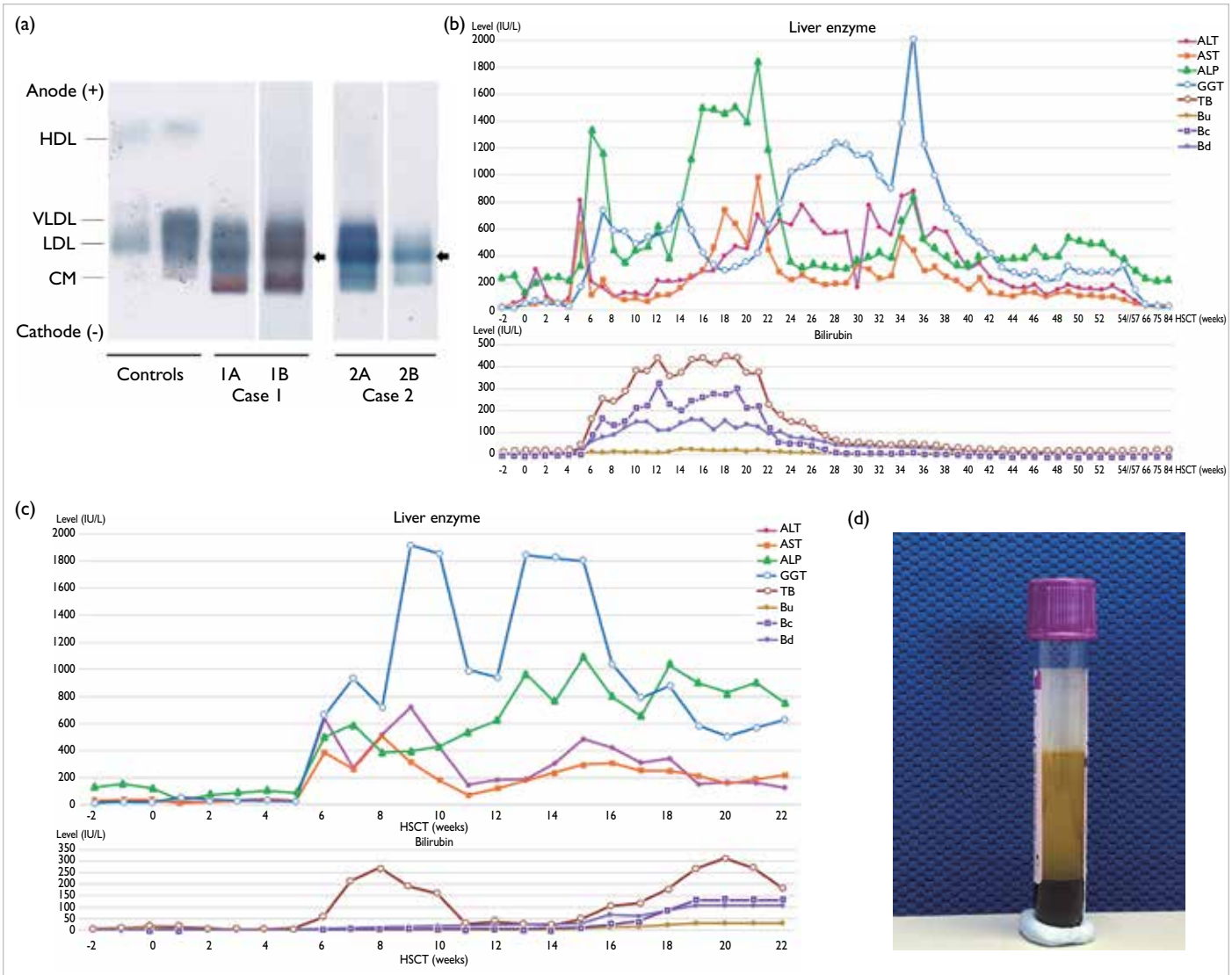

FIG. (a) Lipoprotein electrophoresis patterns of Cases 1 and 2. Lipoprotein species were separated by electrophoresis on agarose gel and subsequently stained with Sudan black. Lanes 1A and 1B belong to Case 1, with 1B sampled 7 days after 1A. Lanes 2A and 2B belong to Case 2, with 2B sampled 14 days after 2A. Other lanes belong to control samples and indicate the position of other lipoprotein species. Arrow indicates position of lipoprotein-X. (b) Trend of liver enzyme and bilirubin levels for Case 1. (c) Trend of liver enzyme and bilirubin levels for Case 2. (d) Lipemic and icteric peripheral blood sample from Case 2

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bc = conjugated bilirubin; Bd = delta bilirubin; Bu = unconjugated bilirubin; CM = chylomicron; GGT = gamma-glutamyltransferase; HDL = high-density lipoprotein; HSCT = haematopoietic stem cell transplantation; LDL = low-density lipoprotein; TB = total bilirubin; VLDL = very low–density lipoprotein

level of 720 IU/L, aspartate aminotransferase level 506 IU/L, and gamma-glutamyltransferase level 1916 IU/L. His worst cholestasis occurred 2 years post-transplantation with total bilirubin level of 312 μmol/L and direct bilirubin level 270 μmol/L (Fig c and Table). He was noted to have a lipemic blood sample (Fig d) at this time and lipid profile revealed total cholesterol level of 13.6 mmol/L, LDL-C (calculated) level 11.4 mmol/L, HDL-C level 0.2 mmol/L and TG level 4.2 mmol/L (Table). Physical examination did not show any xanthoma. With the clinical context of severe cholestasis, LDL-C was measured directly and revealed discordance

TABLE. Lipid profile for Cases 1 and 2

	Case 1	Case 2	Reference value
Total cholesterol, mmol/L	23.1	13.6	<5.2
Triglycerides, mmol/L	11.8	4.2	<1.7
HDL-C, mmol/L	0.5	0.2	>1.6
LDL-C (calculated), mmol/L	17.2	11.4	<4.1
LDL-C (direct), mmol/L	0.2	1.7	<4.1
Apo A1, g/L	0.38	0.52	1.2-2.0
Apo B, g/L	1.88	1.7	0.41-1.07

Abbreviations: Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

between the measured and the calculated value (1.7 mmol/L vs 11.4 mmol/L). Low Apo A1 (0.52 g/L) and elevated Apo B (1.7 g/L) levels were revealed. Trace chylomicron band, Lp-X band and faint lipoprotein Y bands were detected on lipoprotein electrophoresis (Fig d).

Discussion

Liver GVHD is a known complication of allogeneic haematopoietic stem cell transplantation. It is characterised by elevation of hepatic enzymes, cholestasis, severe hypercholesterolaemia and hypertriglyceridaemia (in excess of 1000 mg/dL). In contrast to drug-mediated hypercholesterolaemia (cyclosporine, sirolimus, mycophenolate and glucocorticoids) when cholesterol level is usually <7.8 mmol/L (300 mg/dL) and mediated by LDL-C, hypercholesterolaemia caused by liver GVHD is mediated by cholestasis. In general, there are two main sources that contribute to the liver cholesterol pool, namely de novo (endogenous) cholesterol that is mainly synthesised in the liver, and dietary cholesterol (exogenous). Liver is the primary site of cholesterol biosynthesis and storage. It is also the principal site of sterol elimination by converting cholesterol to bile acids and removing free cholesterol as neutral sterols via biliary excretion.[1,2] In liver GVHD-related cholestasis, impaired bile flow results in accumulation of cholesterol and bile salts, and hence elevated LDL-C level. Lipoprotein-X is another major cause of hyperlipidaemia in cholestasis when bile constituents reflux from the bile ducts or hepatocytes to the blood stream. Lipoprotein-X particles are formed when bile lipoprotein enters the blood stream and incorporates TG, Apo C and esterified cholesterol. Unlike LDL-C, Lp-X does not contain Apo B, the most important ligand to the hepatic LDL-C receptor. Therefore, Lp-X cannot be internalised into hepatocytes. Since Lp-X hypercholesterolaemia is not due to overproduction by hepatocytes, use of medications such as statins to downregulate cholesterol synthesis is ineffective.[3] In addition, since Lp-X does not contain Apo B, which is the major component of LDL and one of the most important factors in the pathogenesis of atherosclerotic plaques, it is not atherogenic.[4] Neither of our cases reported here had any complications of hypercholesterolaemia including exanthemata, retinal thromboembolism and pulmonary cholesteroloma. Nonetheless Lp-X may be associated with hyperviscosity syndrome and plasma exchange or apheresis may be indicated.[5]

As reported in the literature, hypercholesterolaemia secondary to intrahepatic cholestasis caused by liver GVHD can appear at any time between 2 months and 2 years after haematopoietic stem cell transplantation. The condition can be easily diagnosed by demonstrating discordance between calculated and directly measured LDL-C level, as well as lipoprotein electrophoresis. With the resolution of cholestasis, Lp-X will resolve with no specific treatment.

To conclude, severe hypercholesterolaemia mediated by Lp-X in post-haematopoietic stem cell transplantation patients with liver GVHD is a recognised yet overlooked phenomenon. Reports in the literature are limited for both adult and paediatric populations. To the best of our knowledge, this is the first report in Chinese children. Transplant physicians and endocrinologists should have an increased awareness of this association and avoid unnecessary and ineffective use of statins.

Author contributions

Concept or design: WYK Chan, JYL Tung.
Acquisition of data: WYK Chan, ECY Law, TK Ling, FCK Wong, JYL Tung.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: WYK Chan.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

Patients were treated in accordance with the Declaration of Helsinki. Consents for treatment, procedures and publication were obtained.

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