Lipoprotein X hyperlipidemia in patients with liver graft-versus-host disease post-hematopoietic stem cell transplantation in Chinese children

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Abstract

Severe hypercholesterolemia mediated by graft-versus-host disease of liver in patients underwent allogeneic hematopoietic stem cell transplantation is a recognized yet overlooked phenomenon. Reports in literature is limited in both adult and pediatric population and none had been reported in Chinese children to date. As lipoprotein X hypercholesterolemia is due to regurgitation of cholesterol and bile salts into systemic circulation rather than overproduction by hepatocytes, usage of statins to downregulate cholesterol synthesis is not effective. Here we report 2 local cases to increase awareness of transplant physicians and endocrinologists of this association and avoid unnecessary and ineffective usage of statins.

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BRIEF REPORT

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Abbreviations

ALT	alanine aminotransferase
ALT	aspartate aminotransferase
Apo	apolipoprotein
GGT	gamma glutamyltransferase
GVHD	graft-versus-host disease
HDL-C	high density lipoprotein-cholesterol
HSCT	hematopoietic stem cell transplantation
LDL-C	low density lipoprotein-cholesterol
Lp-X	lipoprotein X
TC	total cholesterol
TG	triglycerides
VLDL	very low-density lipoprotein

MANUSCRIPT

ABSTRACT

Severe hypercholesterolemia mediated by graft-versus-host disease of liver in patients underwent allogeneic hematopoietic stem cell transplantation is a recognized yet overlooked phenomenon. Reports in literature is limited in both adult and pediatric population and none had been reported in Chinese children to date. As lipoprotein X hypercholesterolemia is due to regurgitation of cholesterol and bile salts into systemic circulation rather than overproduction by hepatocytes, usage of statins to downregulate cholesterol synthesis is not effective. Here we report 2 local cases to increase awareness of transplant physicians and endocrinologists of this association and avoid unnecessary and ineffective usage of statins.

Keywords (MeSH terms 2021): lipoprotein-X, hypercholesterolemia, hyperlipidemias, graft-versus-host disease, hematopoietic stem cell transplantation

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MAIN BODY TEXT

Introduction

Severe hypercholesterolemia mediated by graft-versus-host disease (GVHD) of the liver in patients underwent allogeneic hematopoietic stem cell transplantation (HSCT) is a recognized yet overlooked phenomenon. Reports in literature is limited in both adult (1-3) and pediatric population (4) and none has been reported in Chinese children to date. Here reports 2 cases of lipoprotein X (Lp-X) hypercholesterolemia due to liver GVHD post-HSCT in Hong Kong.

Case report

Case 1

An 8-year-old female patient with severe aplastic anaemia who failed immunosuppressive therapy with horse antithymocyte globulin and cyclosporin underwent 10/10 human leukocyte antigen-matched bone marrow transplantation with half-sibling elder brother. Neutrophil and platelet engrafted on D+23 and D+27 respectively. Regeneration marrow and full donor chimerism were demonstrated on D+30. She was noted to have progressive deranged liver function and cholestasis since post-transplant 5 weeks with peak alanine aminotransferase (ALT) 878 IU/L (<35), aspartate aminotransferase (AST) 966 IU/L (10-40), gamma glutamyltransferase (GGT) 2,065 IU/L (13-28), total bilirubin 445 μmol/L (10-24) and direct bilirubin 430 μmol/L (5-10) respectively. She was noted to have elevated cholesterol levels with total cholesterol (TC) 23.1 mmol/L (<5.2), high density lipoprotein-cholesterol (HDL-C) 0.5 mmol/L (>1.6) and high triglycerides (TG) 11.8 mmol/L (<1.7). Low density lipoprotein-cholesterol (LDL-C) could not be calculated based on indirect quantitation with Friedewald equation as TG was >4.5mmol/L as per usual practice and hence it was measured directly and found to be normal at 0.2 mmol/L (<4.1).

Apolipoprotein (Apo) A1 was low at 0.38 g/L (1.2-2.0) and ApoB was elevated 1.88 g/L (0.41-1.07). Lipoprotein electrophoresis showed chylomicron and very low-density lipoprotein (VLDL) bands, as well as an addition beta-lipoprotein band which migrated to cathode was detected, which was compatible with Lp-X **(Figure 1A)** . There was no family history of hypercholesterolemia and clinical exam did not show any xanthoma. Liver enzymes, bilirubin level and dyslipidemia gradually normalized by post-transplant 2 years by expectant management**(Figure 1B and Table 1)** .

Case 2

A 13-year old boy with stage 4 neuroblastoma of right adrenal with multiple nodal, bone and bone marrow metastases underwent chemotherapy (HKPHOSG-NB-07 N7 protocol), gross total tumour resection, autologous cord blood transplantation with VAMP conditioning followed by immunotherapy (5 cycles of dinutuximab with alternating cycles of sargramostim and aldesleukin and inter-cycle isotretinoin). Complete remission was achieved but he had spinal relapse 4.5 years after treatment presented with cord compression at T5-T9 level warranting emergency laminectomy and spinal tumour excision. He then received one cycle of temozolomide and irinotecan followed by adjuvant radiotherapy 30Gy/10Fr to T5-T9 vertebrae and haploidentical transplant with maternal TCRαβ/CD45RA depleted graft. Total lymphoid irradiation 8Gy, fludarabine 150mg/m^2, thiotepa 10mg/kg and melphalan 140mg/m^2 were employed as conditioning. Neutrophil and platelet engrafted on D+10 and D+11 respectively with 99% donor chimerism in D+30 marrow. Post-transplant course was complicated with severe acute GVHD involving skin (grade 2-3), liver (grade 2, biopsy-proven) and gut (grade 4) requiring prolonged and heavy immunosuppression including prednisolone, cyclosporine, and mycophenolate mofetil. He also suffered from disseminated Nocardia infection complicated with left lower lobe necrotizing pneumonia, parapneumonic effusion, hydropneumothorax and bronchopleural fistula requiring prolonged course of antimicrobials including meropenem, levofloxacin,

ceftriaxone, cotrimoxazole, linezolid and amikacin. Due to liver GVHD, patient had grossly deranged liver function with peak ALT 720 IU/L, AST 506 IU/L, GGT 1,916 IU/L at 8 months post-transplant. His worst cholestasis occurred as post-transplant 2 years with total bilirubin 312 μmol/L and direct bilirubin 270 μmol/L **(Figure 1C and Table 1)** . He was noted to have lipemic blood sample **(Figure 1D)** at post-transplant 2 years and lipid profile done revealed TC 13.6 mmol/L, LDL-C (calculated) 11.4 mmol/L, HDL-C 0.2 mmol/L, non-HDLC 13.4 mmol/L and TG 4.2 mmol/L **(Table 1)** . Physical exam did not show any xanthoma. With the clinical context of severe cholestasis, LDL-C was measured directly and it showed discordance between the measured and calculated LDL-C values (measured 1.7 mmol/L versus calculated 11.4 mmol/L). Low ApoA (0.52 g/L) and elevated ApoB (1.7 g/L) levels were revealed. Trace chylomicron band, Lp-X band and faint lipoprotein Y bands were detected in lipoprotein electrophoresis **(Figure 1D)** . Patient had neuroblastoma relapse and is currently undergoing palliative care.

Discussion

GVHD of the liver is one of the known complications of allogeneic HSCT characterized by elevation of hepatic enzymes, cholestasis, severe hypercholesterolemia and hypertriglyceridemia (in excess of 1,000 mg/dL). In contrast to hypercholesterolemia contributed by medications such as cyclosporine (5, 6), sirolimus (7, 8), mycophenolate and glucocorticoids (9) which are usually below 7.8 mmol/L (300 mg/dL) and medicated by LDL-C, hypercholesterolemia caused by GVHD of liver is mediated by cholestasis. In general, there are 2 sources of cholesterol in the body - dietary cholesterol absorption from the intestine and de novo synthesis of cholesterol, which mainly takes place in the liver. Liver is the primary site of cholesterol biosynthesis and storage and is also the principal site of sterol elimination by converting cholesterol to bile acids and removing free cholesterol as neutral sterols via biliary excretion (10, 11). In patients with cholestasis related to liver GVHD, the impaired bile flow in cholestasis results in accumulation of cholesterol and bile salts, and hence elevated LDL-C. On the other hand, Lp-X is another major cause of hyperlipidaemia in cholestasis, during which bile constituents are refluxed from the bile ducts or hepatocytes into the blood stream. Lp-X particles are formed when bile lipoprotein enters the blood stream and incorporates triglycerides, ApoC and esterified cholesterol. Unlike LDL-C, Lp-X does not contain apolipoprotein B, which is the most important ligand to the hepatic LDL-C receptor. Therefore, Lp-X could not internalized into the hepatocyte (10, 11) . As Lp-X hypercholesterolemia is not due to overproduction by hepatocytes, usage of statin drugs to downregulate cholesterol synthesis is not effective (4). Indeed, since LP-X does not contain apolipoprotein B, which is the major component of LDL and one of the most important factors in the pathogenesis of atherosclerotic plaques. Therefore, it is not atherogenic (12). However, Lp-X could be associated with hyperviscosity syndrome (13) and that plasma exchange or apheresis might be indicated (14). Both of our cases reported here did not have complications of hypercholesterolemia include exanthemata, retinal thromboembolism and pulmonary cholesteroloma. They were also not associated with hyperviscosity syndrome requiring plasma exchange or apheresis.

As reported in literature, hypercholesterolemia secondary to intra-hepatic cholestasis caused by liver GVHD can appear at any time between 2 months to 2 years post-HSCT. The condition could be easily diagnosed by demonstrating discordance between calculated and directly measured LDL-C levels, as well as lipoprotein electrophoresis. With the resolution of cholestasis, Lp-X would also resolve with no specific treatment.

Conclusion

To conclude, severe hypercholesterolemia mediated by Lp-X in post-HSCT patients with liver GVHD is a recognized yet overlooked phenomenon. Transplant physicians and endocrinologists should have increased awareness of this association and avoid unnecessary and ineffective usage of statins.

Disclosure

All authors have disclosed no conflicts of interest.

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Illustrations

Table 1 Table showing lipid profiles for patients 1 and 2

Figure 1A Pictures showing lipoprotein electrophoresis patterns of patients 1 and 2.

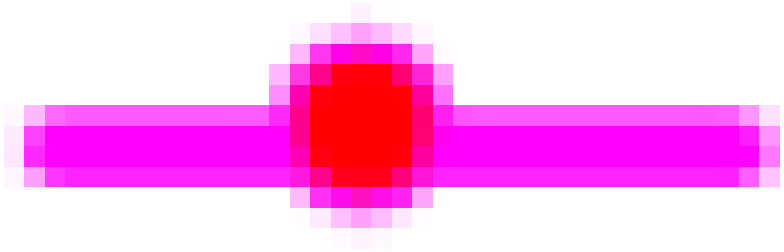
Lipoprotein species were separated through electrophoresis on agarose gel and subsequently stained with Sudan black. Lanes 1A and 1B belonged to case 1, with 1B sampled 7 days after 1A. Lanes 2A and 2B belonged to case 2, with 2B sampled 14 days after 2A. Other lanes belonged to control samples to indicate position of other lipoprotein species. Filled arrow head indicated position of Lp-X.

Figure 1B Figure illustrating trends of liver enzymes and bilirubin level for patient 1

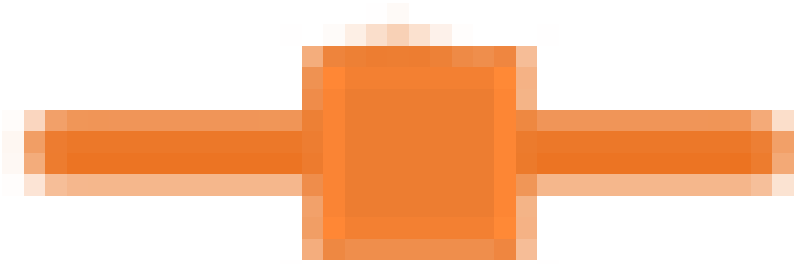
Figure 1C Figure illustrating trends of liver enzymes and bilirubin level for patient 2

Figure 1D Picture showing lipemic and icteric peripheral blood sample collected from patient 2

Legend for Figures 1B and 1C



Alanine aminotransferase (ALT)



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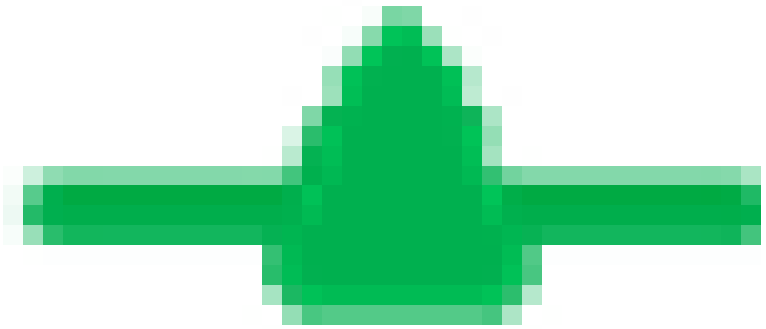
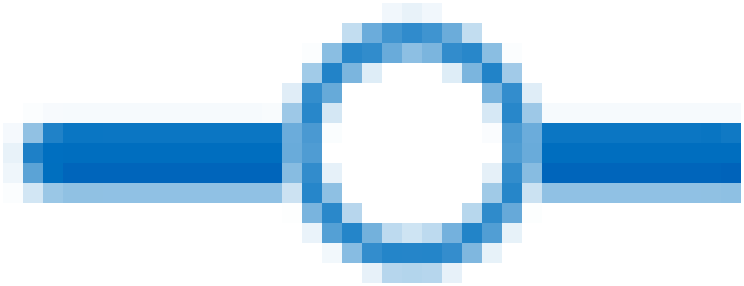
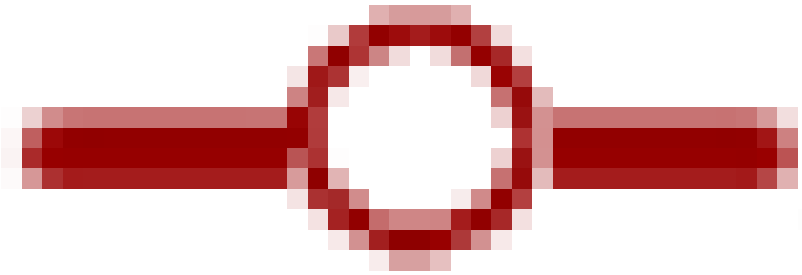


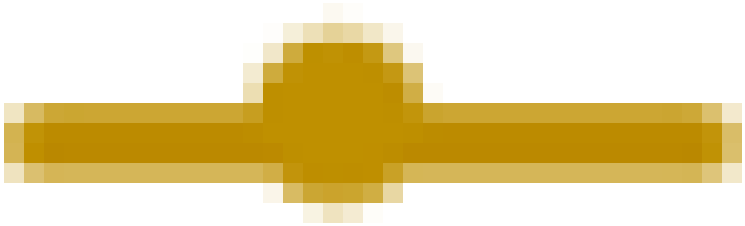
Alkaline phosphatase (ALP)



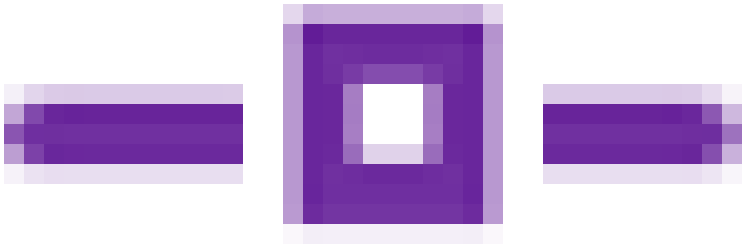
Gamma glutamyltransferase (GGT)



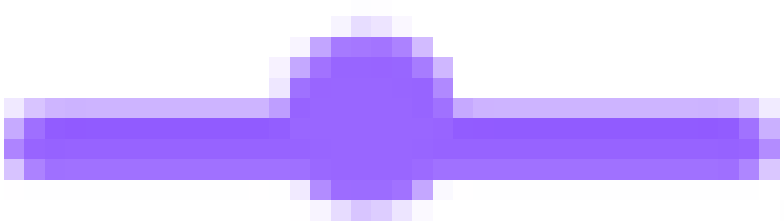
Total bilirubin (TB)



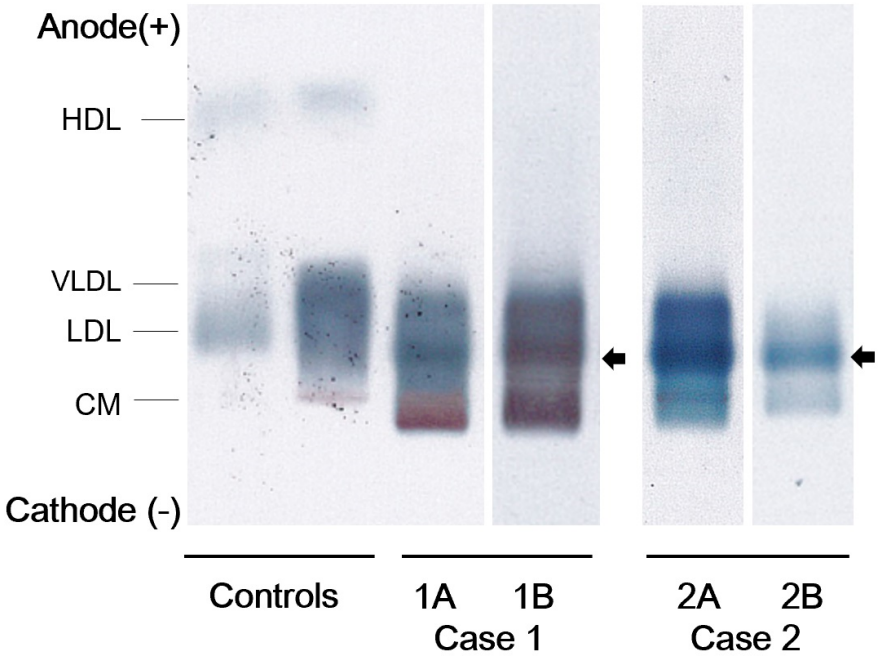
Unconjugated bilirubin (Bu)

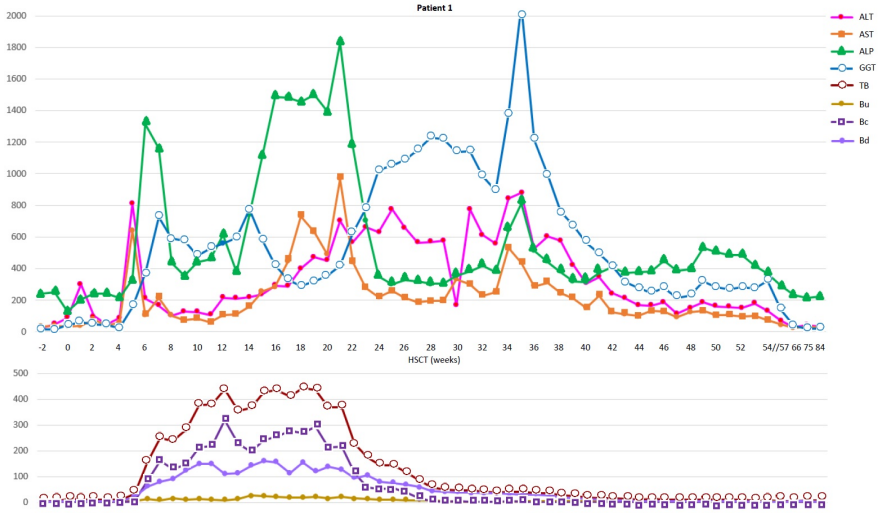


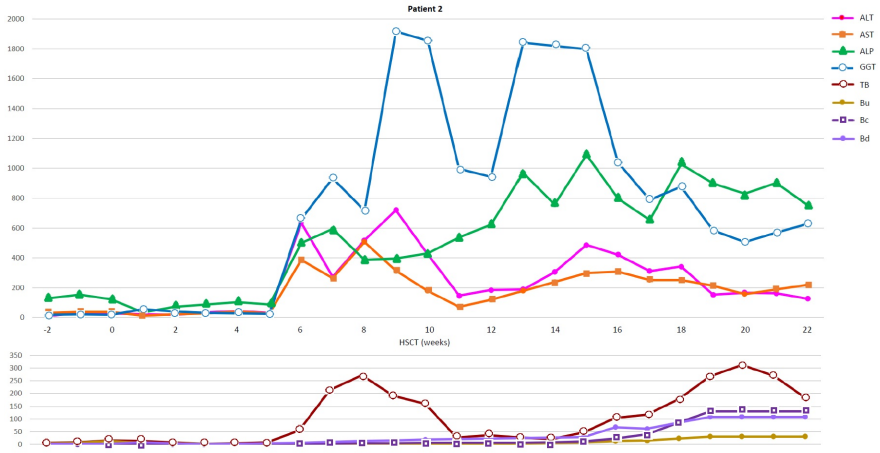
Conjugated bilirubin (Bc)



Delta bilirubin (Bd)







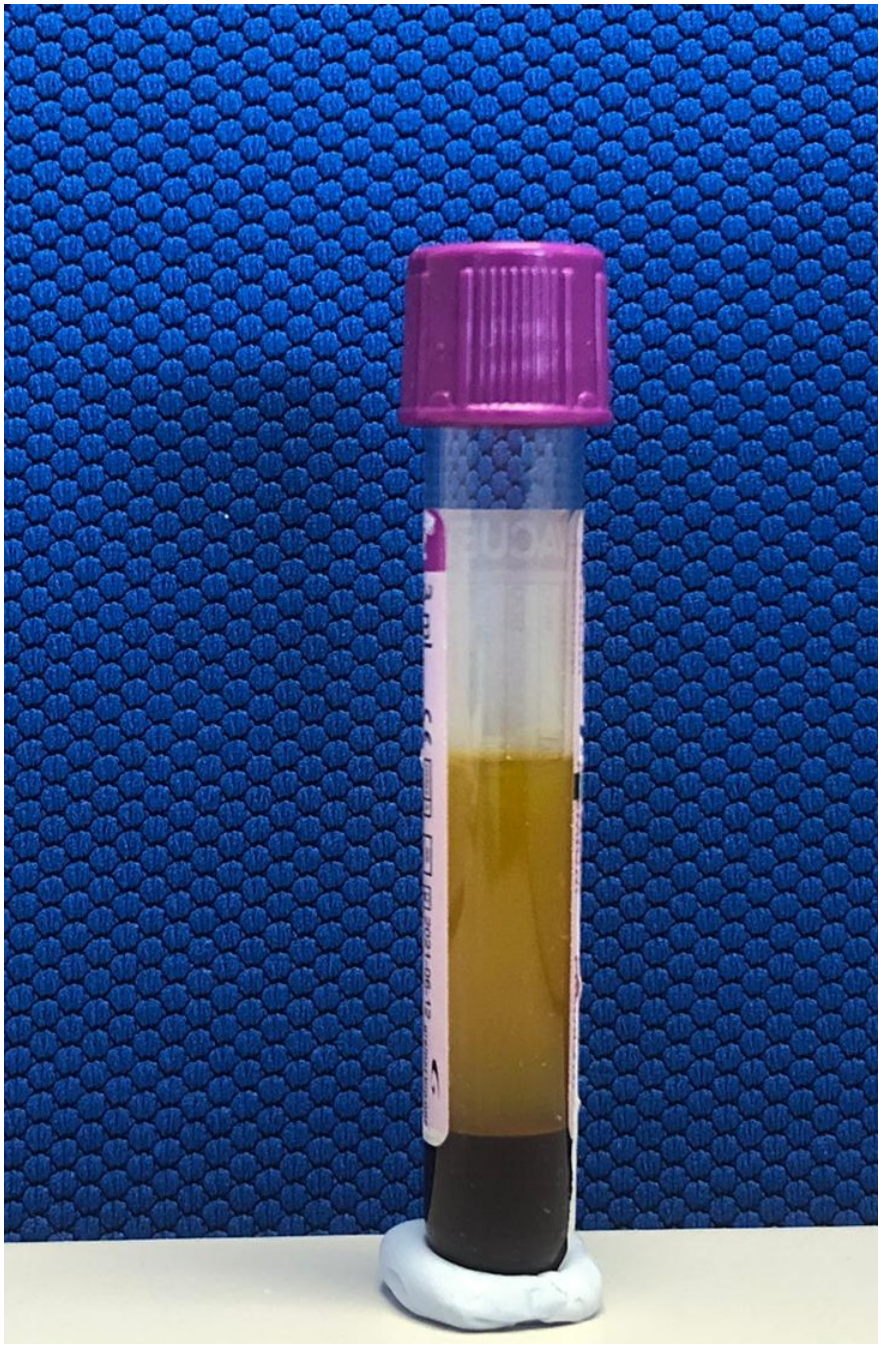


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Table 1.docx available at https://authorea.com/users/359981/articles/710383-lipoprotein-x-hyperlipidemia-in-patients-with-liver-graft-versus-host-disease-post-hematopoietic-stem-cell-transplantation-in-chinese-children