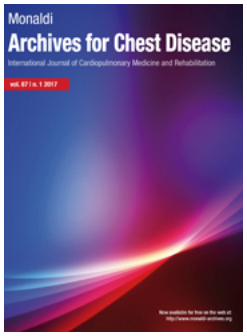

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Kholaif N, Batha L, Elmahi I, et al. **Transplantation of heterozygous familial hypercholesterolemia living donor liver resulting in early myocardial infarction: a possible dangerous link.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2907

Transplantation of heterozygous familial hypercholesterolemia living donor liver resulting in early myocardial infarction: a possible dangerous link

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Contributions: NK, began the project, wrote, reviewed the manuscript and the figures, looked for and carefully examined the references and approved the final manuscript; LB, IE, MA, AA, wrote, reviewed and approved the final manuscript, looked for and carefully examined the references and approved the final manuscript; SA, interpreted and commented the clinical data and imaging, wrote, reviewed and approved the final manuscript; SA, collected clinical data, wrote, reviewed the manuscript and the figures, and approved the final manuscript; NA, commented clinical data and imaging wrote, reviewed and approved the final manuscript; DA, collected clinical data, wrote, reviewed and approved the final manuscript.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study was approved by the office of research affairs and the Ethical Committee of our Institution (approval number: RAC 2191111).

Patient consent for publication: obtained.

Funding: this project did not receive funding from any source

Availability of data and materials: data and materials are available from the corresponding author upon request.

Abstract

Living donor liver transplantation (LDLT) is a lifesaving procedure that is often curative for several liver diseases. Familial hypercholesterolemia (FH) is a metabolic disease that results from an autosomal dominant mutation in the low-density lipoprotein receptor; yet, young patients with FH can live years without detection. Herein, we report a case of a patient who developed early myocardial infarction (MI) after having a transplant from a donor with undetected heterozygous FH. This was a 67-year-old female with non-alcoholic steatohepatitis-related liver cirrhosis, free from coronary artery disease, who underwent LDLT from her daughter, a 45-year-old female with no past medical history. One year post-transplant, she presented with an acute MI with a large atherosclerotic burden. Genetic analysis confirmed heterozygous FH in the donor but not in the recipient. This case emphasizes the importance of incorporating a thorough clinical history and lipid profile into pre-transplant testing for both the recipient and donor, as well as aggressive lipid-lowering therapy post-transplantation to avoid cardiovascular complications.

Key words: living donor liver transplant, familial hypercholesterolemia, non-alcoholic steatohepatitis, myocardial infraction

Introduction

Liver transplantation is a lifesaving procedure for severe liver disease, but donor shortages and rising demand has not been matched by an equivalent increase in deceased donor organs, leading to longer waiting times and higher mortality rates for those on the list which have necessitated the use of Living donor liver transplantation (LDLT) [1]. The selection criteria for LDLT remains an indispensable part of the process, owing to the fact that it is a procedure of high risk complications on both donors and recipients. The donor evaluation process is ever-evolving, in addition to a carful history and physical exam, a full metabolic panel is now routinely requested. Imaging modalities like echocardiography and coronary evaluation including performing an angiogram is being implemented in routine practice. Focusing not only on the donor's graft; but also ensuring the donor's operation can be performed in a safe manner with good long-term outcomes [2]. Even though LDLT is now becoming a routine procedure, it is still accompanied by a number of challenges that are usually overlooked due to the increased demand and donor shortage. If a donor has undiagnosed Familial Hypercholesterolemia (FH) or another metabolic disorder, it could be unwittingly passed on to the recipient, potentially leading to cardiovascular complications post-transplant. Therefore, careful screening for metabolic and genetic diseases is an essential part of the donor evaluation process to mitigate these risks [3]. In this case report, we are specifically interested in the possibility of metabolic disease transmission, especially FH, which is not very common in the literature, but is still possible. FH is a common hereditary metabolic condition caused by an autosomal dominant low-density lipoprotein (LDL) receptor (R) mutation. Due to the delayed clearance, total cholesterol (TC) and serum LDL cholesterol (LDL-C) levels increase; resulting in excess deposition of cholesterol in skin, tendons, and arterial walls, eventually leading to progressive atherosclerosis and premature coronary heart disease [4,5]. In this context, we report our experience with a patient who developed myocardial infarction (MI) after undergoing a LDLT from a donor with undetected heterozygous FH.

Case Report

Pre-transplant

We present the clinical course of a 67-year-old female with a medical history of type II diabetes mellitus, hypertension, chronic kidney disease, bronchial asthma, and non-alcoholic steatohepatitis-related liver cirrhosis. She was not known to have cardiovascular disease (CVD) but had recurrent encephalopathy and gastrointestinal bleeding, leading to consideration for liver transplantation. The patient's liver donor was her 45-year-old daughter, who had no prior medical issues. Table 1 displays the pre-transplant laboratory results for both the patient and the liver donor.

During her pre-transplant cardiac work-up, the patient had a normal left ventricular (LV) ejection fraction (EF) > 55% and normal valves.

On October 2020, a coronary angiogram revealed mild atherosclerotic plaques but no obstructive coronary artery disease, as shown in Figure 1A.

Transplant and initial follow-up

On May 20, 2021, the patient underwent LDLT, receiving the right lobe of her daughter's liver. The postoperative course was uneventful. On June 18, 2021, the patient's post-transplant laboratory results showed normal liver enzymes, but her lipid profile revealed elevated LDL levels (8 mmol/L). This elevation was thought to be related to the immunosuppressive therapy received post-transplant, thus, no lipid lowering therapy was initiated.

Post-transplant event

On January 18, 2022, the patient presented with right-sided chest pain for one week, associated with vomiting and decreased oral intake. An electrocardiogram showed occasional premature ventricular contractions, and significantly elevated high-sensitivity cardiac troponin T of 1280 ng/L (range; <14). A lipid profile was done, showing elevated LDL levels (4.6 mmol/L). Echocardiography revealed mildly reduced LV systolic function (EF 40-45%) with akinesis of the anterior, lateral, and mid-inferolateral walls. The patient was adherent to her transplant medications at that time which included tacrolimus, low dose prednisone, mycophenolate mofetil, lisinopril, Trimethoprim sulfamethoxazole and valganciclovir. She was then admitted

with non-ST elevation MI. The patient was started on Atorvastatin 40 mg in addition to Ezetimibe 10 mg, metoprolol tartrate 25mg oral twice daily and was loaded with dual antiplatelets followed by regular doses of aspirin, and clopidogrel. Intravenous heparin was also initiated as per protocol.

A coronary angiography on January 19, 2022 showed severe stenosis in the mid-left anterior descending (LAD) artery and the first obtuse marginal branch (OM 1), as shown in Figure 1B. Optical coherence tomography (OCT) to LAD showed a ruptured plaque with white thrombus in the mid segment with severe luminal narrowing in the mid to distal LAD and scattered areas of severe fibrofatty atheroma, as presented in Figure 1C.

Percutaneous coronary intervention (PCI) to LAD was performed using 3 drug-eluting stents. A staged PCI to OM 1 was done on January 24, 2022, with a drug-eluting stent deployed directly to the OM 1 lesion.

Further inquiry into the liver donor's history revealed a family history of premature coronary artery disease (both father and brother died from early coronary artery disease). The donor was healthy during pre-transplant assessment, but her LDL pre-transplant was 5.74 mmol/L on February 17, 2020. The Dutch criteria for FH was applied and scored 4, which is designated as “possible FH” [6]. Furthermore, genetic analysis was done for both daughter and mother. The patient (mother) had a normal LDL receptor while the daughter had a pathological LDLR variant of c2416dup p.(Val806Glyfs*11), making her positive for FH [7].

Long-term follow-up

The patient's follow-up lipid profile on October 17, 2022, still showed elevated LDL levels, and she experienced on-off stabbing chest pain not related to exertion. Evolocumab (PCSK9 inhibitor) was added to her treatment regimen.

On January 13, 2023, the patient underwent further PCI to distal LAD and OM 1, after which she reported no further chest pain. A follow-up lipid profile on March 26, 2023, showed significant improvement, with LDL levels reduced to 0.67 mmol/L. A summary of patient’s fluctuating LDL levels across the treatment events is shown in Figure 2.

Discussion

Literature suggests that the transmission of FH is not very common, however, it can still occur. Very few reported cases provide evidence that disease can be transferred from a liver donor with FH to the recipient. For example, one case reported in 2014 involved a 58-year-old patient with autoimmune hepatitis and no history CVD. This patient received a liver transplant from a 24-year-old patient, who later died because of an ischemic cerebral vascular event. The transplanted patient showed increased LDL levels post-transplant, but no CVD. Another reported case in 2014 discusses a liver transplant done for a 57-year-old patient with alcoholic cirrhosis. The donor was a 59-year-old man who also died due to CVD. The recipient in this case also had increased LDL levels post-transplant but no signs of CVD [8].

To add to that, two other cases did not show overt CVD upon long-term follow-up in Domino liver transplant from FH patients, despite increased postoperative cholesterol levels. The first was in 2001, which was about a 46-year-old patient with Hepatocellular Carcinoma (HCC) and Hepatitis B virus (HBV) related cirrhosis who received a liver transplant from a 25-year-old patient with homozygous familiar hypercholesterolemia (HoFH). 7 years post-transplant, the patient had elevated total cholesterol levels (8.8 mmol/L) which was not accompanied by any apparent signs of ischemic heart disease [9]. Another case in 2007 was about a 60 year-old with HCC and HBV related cirrhosis, transplanted from a 17-year-old patient with HoFH. The follow-up for the first 10 months of the recipient was free of overt CVD with total cholesterol levels of 7.8 mmol/L [10]. Of note, in these cases no angiogram or imaging studies were done to document the absence of occult coronary artery disease. In these cases, it is not possible to role out coronary artery disease. The short-term follow-up in most of these cases, and the lack of controls limits our ability to conclude that there was no increase in cardiovascular risk. In addition, statins were initiated which are known to reduce cardiovascular events [11]. Our patient had mild atherosclerosis and diabetes both risk factors for future development of coronary artery disease, yet the early development of myocardial infarction with a high atherosclerotic burden, strongly disfavors the notion of transplanting patients with this mutation. It is certainly interesting that although the donor was born with this mutation, at the time where she donated her liver she did not suffer from apparent coronary artery disease, while the recipient developed a MI in less than a year following transplantation. Therefore, unrecognized

donor transmission of FH may contribute to an increased risk of CVD in recipients. Larger cohorts, with a design to elucidate coronary artery disease and ideally randomized controlled trials are needed to better understand the true cardiovascular risks associated with these procedures in this patient population

Future direction

To better understand the physiology of transplanted livers with LDLR mutation, the recently developed Golden Syrian knockout Hamster [12], which has a lipid profile more similar to humans than other small mammals, can provide insights into how transplanted livers with this mutation behave and the various factors that contribute to the progression of cardiovascular disease in this novel population.

Conclusions

Our patient developed a myocardial infarction less then a year after receiving a LDLT from her daughter who was HeFH (proved by genetic testing). It is important to further study how the transmission of FH differs according to the recipient/donor disease type, as the recipient baseline risk and need for immunosuppressive therapy can contribute to earlier and more severe cardiac complications. Therefore, despite time limitation and urgent need for a transplant, detailed clinical history and lipid panel studies must be strictly incorporated into pre-transplant testing for both donors and recipients. Genetic testing in borderline cases could be potentially an important tool to aid in decision-making. More research in this area is needed to validate this approach. Our case is a call for caution, highlighting the risks of transplanting organs from donors with potential metabolic conditions like familial hypercholesterolemia (FH) to vulnerable recipients, which may lead to grave complications.

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Table 1. Pre-transplant labs for both recipient (mother) and donor (daughter).

LABs	Recipient (Mother)	Donor (Daughter)	Normal Range
Blood Group	O+	O+	
White blood cell count	6.36 10^9/L	7.6 10^9/L	3.9 - 11
Hemoglobin	111 g/L	127 g/L	110 - 160
Platelet	135 10^9/L	319 10^9/L	155 - 435
Creatinine	73 umol/L	68 umol/L	46 - 96
Albumin	23 g/L	43 g/L	28 - 46
Total bilirubin	11 umol/L	4 umol/L	0 - 21
Alanine transaminase (ALT)	27 U/L	23 U/L	10 - 45
Aspartate aminotransferase (AST)	39.8 U/L	20 U/L	10 - 45
Alkaline phosphatase	174 U/L	75 U/L	46 - 122
Total Cholesterol (T Chol.)	3.1 mmol/L	6.9 mmol/L	5.2 - 6.2
High Density Lipoprotein (HDL)	1.24 mmol/L	1.15 mmol/L	1.04 - 1.55
Low Density Lipoprotein (LDL)	1.83 mmol/L	5.7 mmol/L	2.59 - 4.92
Triglycerides (TG)	0.95 mmol/L	0.67 mmol/L	1.69 - 5.65

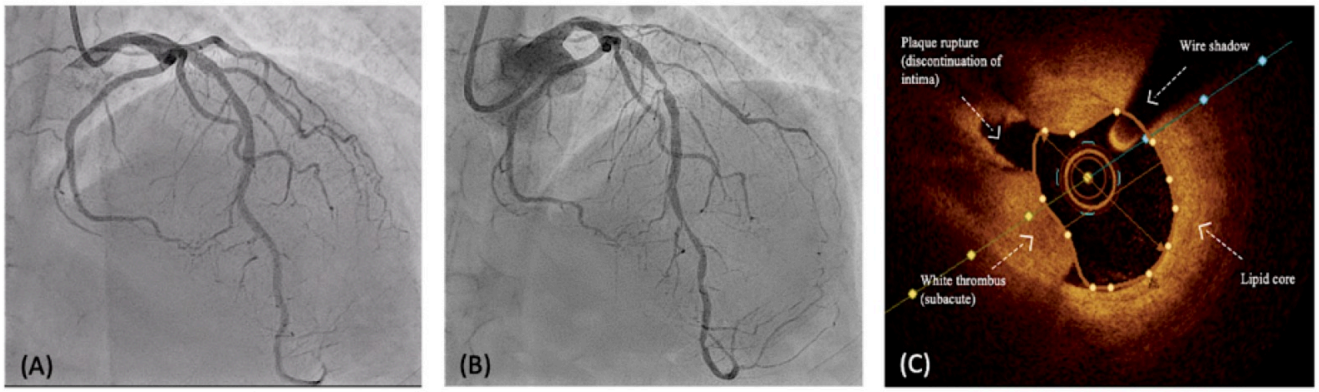

Figure 1. A) Pre-transplant angiogram, anterior-posterior view with cranial angulation of the left coronary system, showing mild irregularities but no obstructive lesions; B) post-transplant angiogram of the left coronary system, revealing subtotal occlusion and plaque rupture in the mid LAD, along with significant lesions in the distal artery; C) post-transplant optical coherence tomography (OCT) of the mid Left anterior descending artery, exhibiting a ruptured plaque with white thrombus in the mid segment, severe luminal narrowing, and scattered areas of severe fibrofatty atheroma.

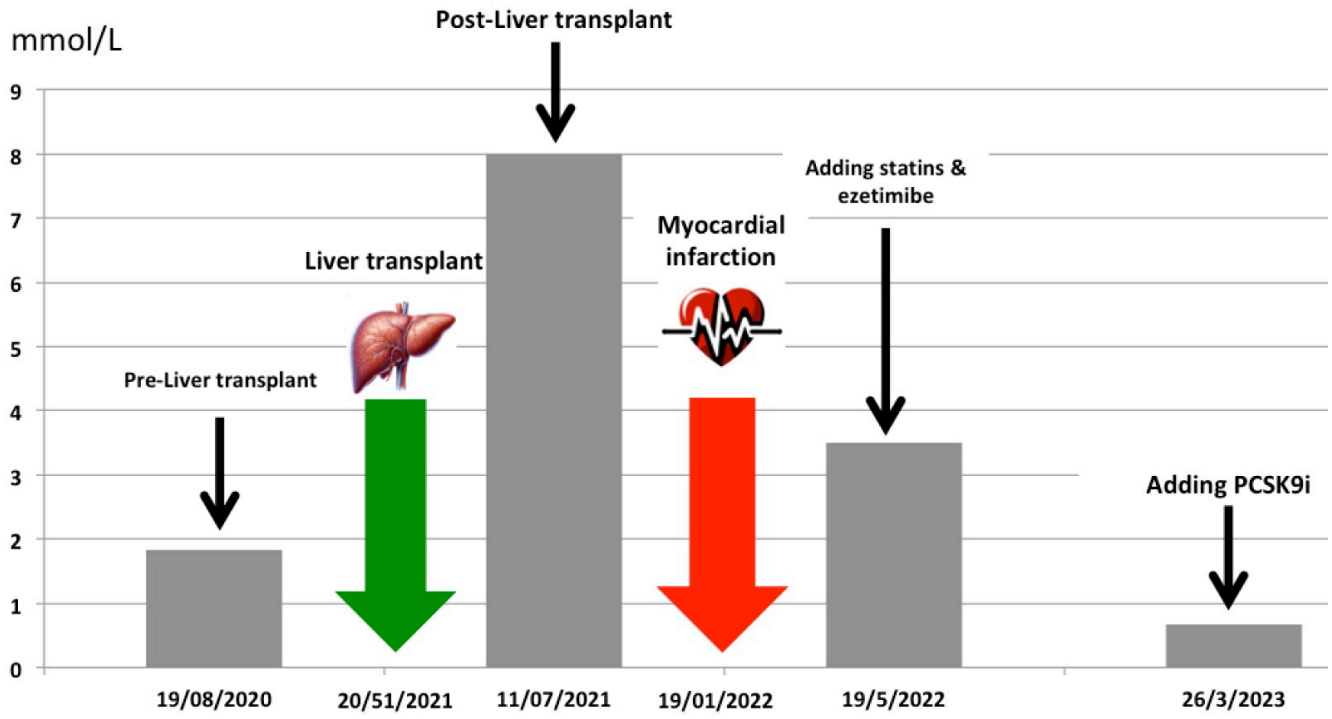

Figure 2. A graph that displays the patient's LDL levels over various treatment events. The X-axis represents dates, while the Y-axis represents LDL levels in mmol/L. Arrows show relevant events taking place at the time of the test. Statin: atorvastatin 40 mg daily, Ezetimibe 10 mg daily, and PCSK9i: (Proprotein convertase subtilisin/kexin type 9 serine protease) Evolucumab 140 mg once every two weeks.