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CASE REPORT: CLINICAL CASE

# Early Progression of Aortic Stenosis Associated With Iatrogenic Variant Transthyretin Amyloidosis After Domino Liver Transplantation

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## ABSTRACT

We report a 65-year-old man who underwent aortic valve replacement because of severe aortic stenosis associated with de novo iatrogenic variant transthyretin amyloidosis derived from a liver graft extracted from a patient with hereditary transthyretin amyloidosis 9 years after the domino liver transplantation. (**Level of Difficulty: Advanced.**)
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Domino liver transplantation (DLT) has been used to alleviate the shortage of liver allografts for patients with liver failure who would not have survived without such a procedure (1). The explanted liver from a patient with hereditary transthyretin amyloidosis, which has normal functions except for secretion of variant transthyretin into the blood stream, is sometimes used for another patient with liver failure because of the shortage of liver grafts for transplantation. However, DLT using the liver grafts extracted from patients with hereditary transthyretin amyloidosis is associated with a risk of de novo iatrogenic variant transthyretin amyloidosis (1). We herein describe a 65-year-old man who developed severe aortic stenosis (AS) associated with de novo iatrogenic variant transthyretin amyloidosis derived from a liver graft extracted from a patient with hereditary transthyretin amyloidosis 9 years after the DLT.

### LEARNING OBJECTIVES

- To understand that de novo iatrogenic variant transthyretin amyloidosis can cause progression of aortic valve stenosis.
- To understand that careful follow-up echocardiographic examinations are required in patients undergoing domino liver transplantation with transthyretin amyloidosis.

## HISTORY OF PRESENTATION

A 65-year-old man was admitted to our hospital because of a progressively worsening dyspnea on exertion.

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**ABBREVIATIONS AND ACRONYMS**

**AS** = aortic stenosis

**DLT** = domino liver transplantation

**LV** = left ventricular

**PG** = pressure gradient

## MEDICAL HISTORY

At the age of 56 years, he had undergone DLT for nonviral liver cirrhosis. He received a liver graft extracted from a 29-year-old man with early-onset hereditary transthyretin Val30Met (p.Val50Met) amyloidosis, who had developed polyneuropathy and autonomic disturbances without cardiac involvement at 28 years of age. Transthoracic echocardiography before the DLT showed no cardiac abnormality with intact aortic valve findings. Four years after the DLT, he underwent an operation for an incisional hernia. At that time, transthoracic echocardiography showed moderate AS (Videos 1, 2, and 3). The aortic valve area, the peak velocity, and the mean pressure gradient (PG) measurements were 1.1 $cm^2$, 3.9 m/s, and 33.7 mm Hg, respectively (**Figure 1A**). Other echocardiographic data at that time were as follows: left ventricular (LV) diastolic diameter, 36.4 mm; LV systolic diameter, 20.2 mm; interventricular septal thickness, 13.3 mm; posterior LV wall thickness, 13.0 mm; LV ejection fraction, 67.9%; E/A, 0.74; and E/e', 12.0. After the examination, his aortic valve was checked annually by echocardiography. At the age of 63 years, he developed distal paresthesia and hypoesthesia in the lower extremities without autonomic symptoms or gastrointestinal symptoms. Histopathologic examination of a gastric mucosal biopsy specimen showed transthyretin amyloid deposits, and he was diagnosed with iatrogenic variant transthyretin amyloidosis. At the age of 64 years, he began treatment with oral tafamidis, a transthyretin tetramer stabilizer which has inhibitory effects on the progression of transthyretin amyloidosis. We found no progression of his neurologic findings after the administration of tafamidis. He was also prescribed tacrolimus, mycophenolate mofetil, sitagliptin phosphate hydrate, ezetimibe, rosuvastatin calcium, and ursodeoxycholic acid.

## DIFFERENTIAL DIAGNOSIS

Rapidly progressive aortic stenosis, infectious endocarditis, pulmonary thromboembolism, and acute coronary syndrome were considered.

## INVESTIGATIONS

On admission, first-degree atrioventricular block was observed by electrocardiogram. His blood pressure was 110/60 mm Hg, pulse was 70 beats/min. Transthoracic echocardiography showed severe AS with severe calcification (Videos 4, 5, and 6). The aortic valve area, the peak velocity, and the mean PG measurements were 0.8 $cm^2$, 4.0 m/s, and 38.0 mm Hg, respectively (**Figure 1B**). Other preoperative echocardiographic data were as follows: LV diastolic diameter, 35.8 mm; LV systolic diameter, 25.6 mm; interventricular septal thickness, 14.2 mm; posterior LV wall thickness, 14.4 mm; LV ejection fraction, 65.9%; E/A, 0.5; and E/e', 11.7. Although interventricular septal thickness in diastole increased to 15.3 mm, $^{99m}$Tc-pyrophosphate scintigraphy showed negative myocardial uptake (**Figure 2**). Cardiac magnetic resonance imaging did not show a typical late gadolinium enhancement pattern (**Figure 3**). His renal function was normal (blood urea nitrogen, 19.7 mg/dl; creatinine, 0.59 mg/dl; and estimated glomerular filtration rate, 90 ml/min/1.73 $m^2$). His brain natriuretic peptide level was 51.4 pg/ml, and troponin T level was 0.0214 ng/ml.

## MANAGEMENT

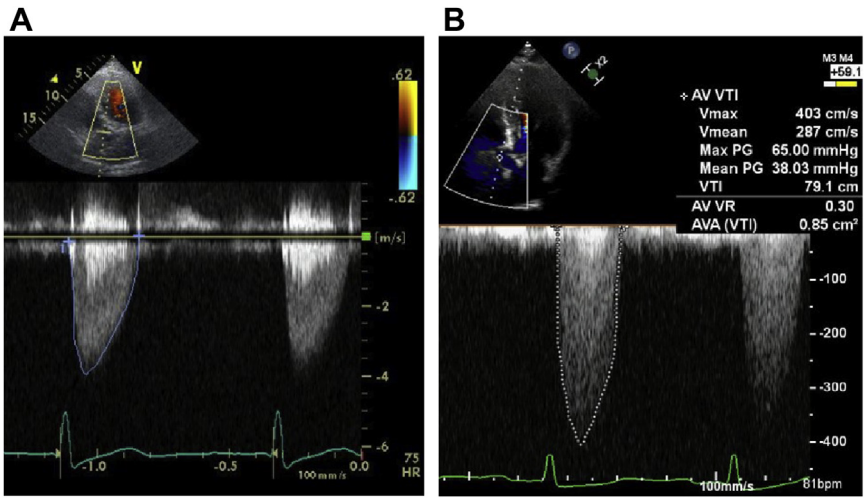
We performed aortic valve replacement using a bioprosthetic valve with no complications. Three leaflets of the aortic valve were severely calcified, and no fusion was present between the leaflets.

To investigate whether amyloid infiltration was associated with AS in this patient, we performed histopathologic examinations of the removed aortic valve. We found Congo red-positive severe amyloid deposits (**Figures 4A and 4B**), which were derived from transthyretin (**Figure 4C**). In addition, we analyzed the composition ratios of wild-type and variant Val30Met (p.Val50Met) transthyretin in valvular amyloid deposits by means of laser microdissection and liquid chromatography/tandem mass spectrometry according to the previous report (2). Those mass spectrometric analyses revealed that those valvular amyloid deposits were derived mainly from variant transthyretin secreted from the liver graft extracted from the patient with hereditary transthyretin amyloidosis (**Figure 5**).

## DISCUSSION

An explanted liver from a patient with hereditary transthyretin amyloidosis has been used for another patient with severe liver cirrhosis in a DLT procedure because the liver functions in patients with hereditary transthyretin amyloidosis are intact except for secretion of variant transthyretin into the blood stream (1). However, DLT recipients are reportedly at risk of iatrogenic variant transthyretin amyloidosis because of the introduction of transthyretin amyloid

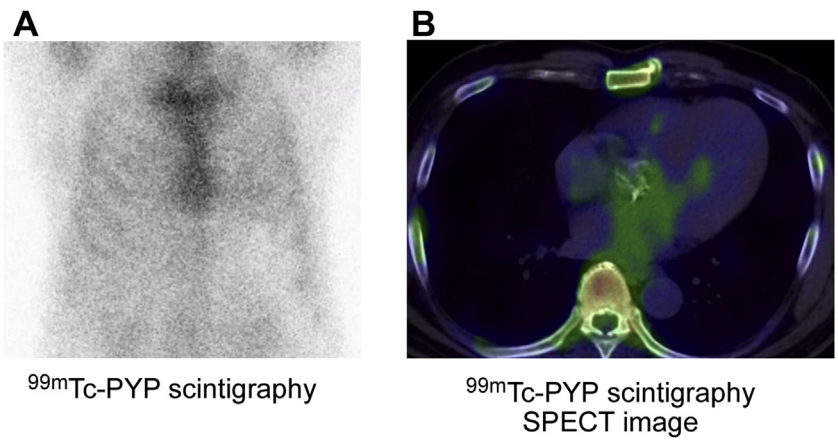
**FIGURE 1 Transthoracic Echocardiography**




**(A)** Transthoracic echocardiography at the time of the operation for the incisional hernia showed that the aortic valve area (AVA), the peak velocity, and the mean pressure gradient (PG) were 1.1 $cm^2$, 3.9 m/s, and 33.7 mm Hg, respectively. **(B)** Transthoracic echocardiography at the time of the operation for the aortic stenosis showed that the AVA, the peak velocity, and the mean PG were 0.8 $cm^2$, 4.0 m/s, and 38.0 mm Hg, respectively.

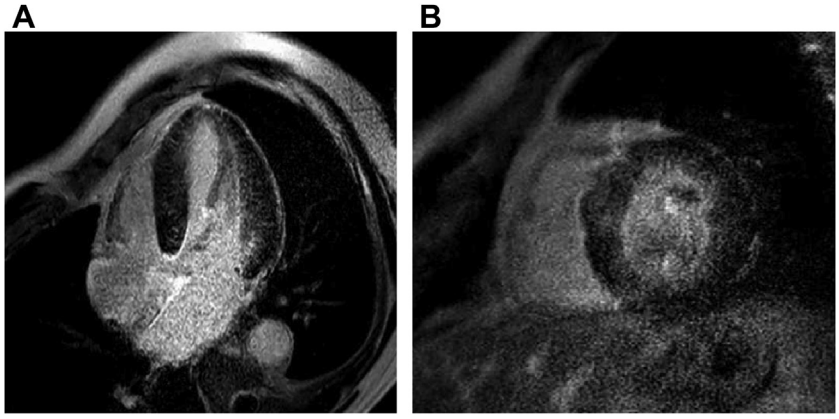
produced by the donor liver (1). Amyloid deposition in the tissue may start soon after DLT, and iatrogenic amyloid neuropathy may affect up to 8% to 24% of DLT recipients (3,4). The present case developed iatrogenic variant transthyretin amyloid neuropathy 7 years after the DLT using a liver graft extracted from a patient with hereditary transthyretin amyloidosis. AS also developed simultaneously at that time; however, because the grade of stenosis was moderate, follow-up echocardiographic examination was carefully performed. After only 2 years, the AS had worsened to severe. Although the main

**FIGURE 2 Cardiac Imaging**




Cardiac images in a patient with severe aortic valvular stenosis 9 years after the domino liver transplantation using a liver graft extracted from a patient with hereditary transthyretin Val30Met (p.Val50Met) amyloidosis. **(A)** 99m Tc-PYP planar image. **(B)** 99m Tc-PYP SPECT image. PYP = pyrophosphate; SPECT = single-photon emission computerized tomography.

**FIGURE 3 Late Gadolinium Enhancement Images of Cardiac Magnetic Resonance**



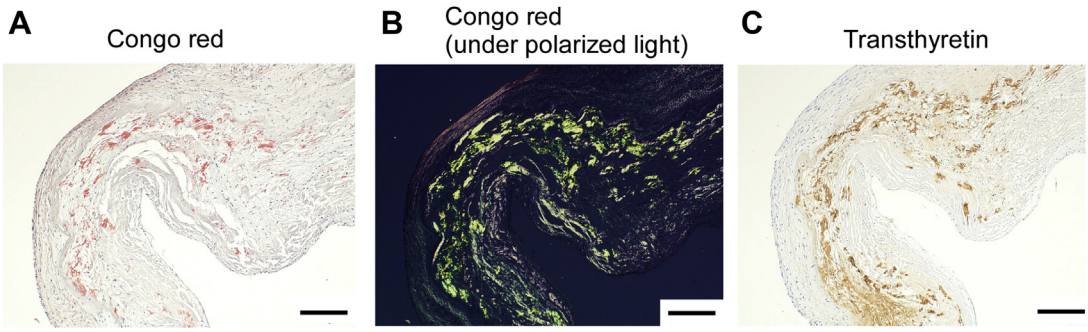

**(A)** Four-chamber view. **(B)** Short-axis view.

cause of the AS was calcification of the leaflets, the amyloidosis was at least partly related to the progression of AS because amyloid deposition was found in the leaflets.

Co-existence of AS and "occult" age-related non-hereditary cardiac wild-type transthyretin amyloidosis was reportedly associated with a poor outcome (5); however, whether a causative relationship exists between AS and non-hereditary wild-type transthyretin amyloidosis remains unclear (6). Some reports have described aortic valve replacement in patients with cardiac amyloidosis; however, focal deposition of amyloid was rarely found in the aortic valve leaflet (7). One necropsy study indicated valvular amyloid deposits were found in 74% of stenotic aortic valves; they failed to identify amyloid proteins in those cases except for one case, in which amyloid was derived from apolipoprotein AI (8). In the present report, we successfully indicated that severe variant transthyretin amyloid deposits were associated with severe iatrogenic AS in the second recipient of DLT using the liver graft extracted from the patient with hereditary transthyretin Val30Met (p.Val50Met) amyloidosis by means of histopathologic and mass spectrometric analyses.

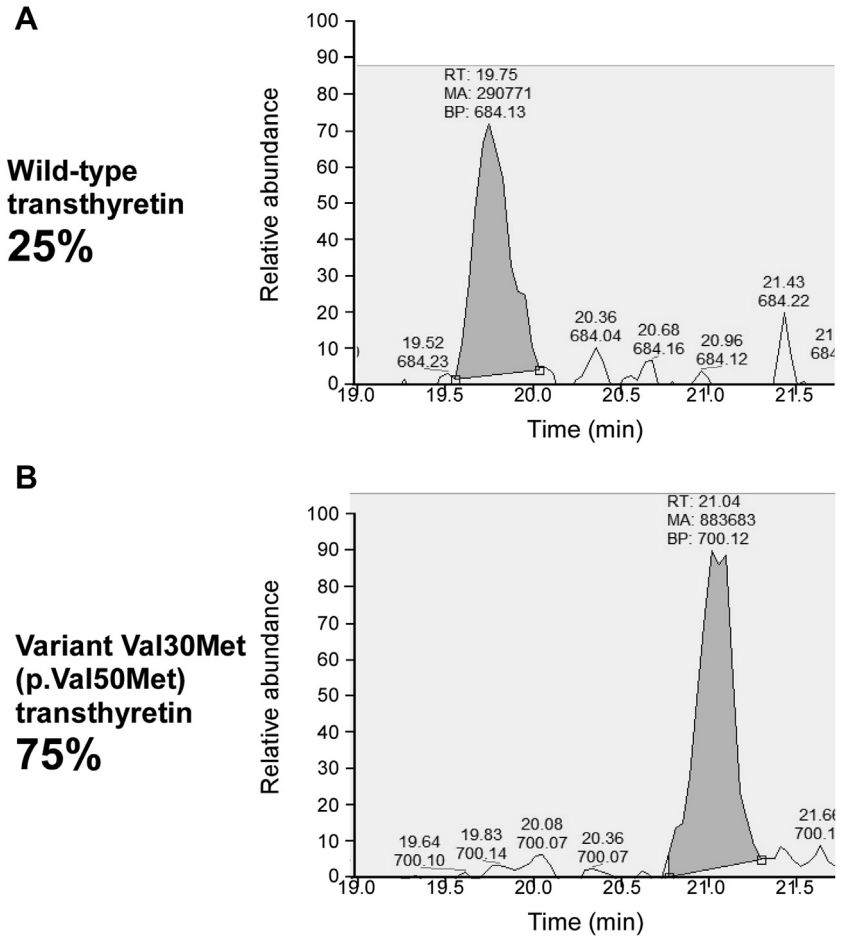
Oxidative stress, inflammation, and extracellular remodeling have been suggested to be associated with the transthyretin amyloidogenic process (9).

**FIGURE 4 Valvular Transthyretin Amyloid Deposits**




Valvular transthyretin amyloid deposits in a patient with severe aortic valvular stenosis 9 years after the domino liver transplantation using a liver graft extracted from a patient with hereditary transthyretin Val30Met (p.Val50Met) amyloidosis. **(A)** Congo red staining. **(B)** Congo red staining viewed under polarized light microscopy. **(C)** Immunohistochemical staining using polyclonal rabbit anti-human transthyretin antibodies (1:400 dilution, Agilent, Santa Clara, California) (Scale bars: 200 μm).

**FIGURE 5** Mass Spectrometric Analysis




Peaks of **(A)** wild-type and **(B)** variant Val30Met (p.Val50Met) transthyretin analyzed by laser microdissection and liquid chromatography/tandem mass spectrometry transthyretin. Composition ratios of **(A)** wild-type and **(B)** variant Val30Met (p.Val50Met) transthyretin in valvular amyloid deposits were 25% and 75%, respectively.

Moreover, these mechanisms are speculated to accelerate the pathophysiology of AS (10).

In summary, relatively rapid progression of AS was observed in a non-elderly patient who underwent DLT with a graft that was explanted from a patient with hereditary transthyretin Val30Met (p.Val50Met) amyloidosis. This suggests that careful follow-up echocardiographic examination should be performed in patients undergoing DLT with transthyretin amyloidosis.

## FOLLOW-UP

The patient's postoperative course was uneventful and his symptoms have improved.

## CONCLUSIONS

We report a patient with severe AS associated with de novo iatrogenic variant transthyretin amyloidosis derived from a liver graft extracted from a patient with hereditary transthyretin amyloidosis 9 years after the DLT. Careful follow-up echocardiographic examination should be performed in patients undergoing DLT with transthyretin amyloidosis.

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**KEY WORDS** aortic valve replacement, domino liver transplantation, transthyretin amyloidosis

**APPENDIX** For supplemental videos, please see the online version of this paper.