

[ CASE REPORT ]

## Amyloid Polyneuropathy and Myocardial Amyloidosis 10 Years after Domino Liver Transplantation from a Patient with a *Transthyretin* Ser50Arg Mutation

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### Abstract:

A 54-year-old man with polycystic liver disease received a domino liver transplantation (DLT) from a patient of hereditary ATTR amyloidosis with the *transthyretin* Ser50Arg mutation. Ten years after transplantation, he felt a slight numbness in his toes, and cardiac amyloidosis was simultaneously suspected upon a heart function evaluation. Biopsy specimens from the myocardium revealed transthyretin amyloidosis with the Ser50Arg mutation. Oral tafamidis therapy has inhibited the progression of neurological and cardiovascular symptoms this far. We herein report this first case of amyloid polyneuropathy and myocardial amyloidosis after DLT from hereditary ATTR amyloidosis with a *transthyretin* Ser50Arg mutation and discuss similar cases of other mutations.

**Key words:** amyloid polyneuropathy, myocardial amyloidosis, domino liver transplantation, transthyretin, tafamidis

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### Introduction

Hereditary transthyretin (ATTR) amyloidosis (ATTRm) is an autosomal dominant systemic amyloidosis associated with multiorgan dysfunction involving the peripheral nerves, autonomic nervous system, cardiac muscle, and gastrointestinal tract. In systemic amyloidosis several precursor proteins, including the variant form of transthyretin (TTR), gelsolin, and apolipoprotein AI form amyloids with a fibrous structure, and amyloid deposition results in organ damage (1). ATTRm in the endemic foci of Japan often occurs in the 20s and 30s, and symptoms progress gradually, with an average survival duration of about 10 years in the absence of treatment (2). In contrast, gelsolin type amyloidosis has a good prognosis, and relatively older-onset patients are seen in the non-endemic area in Japan. The most frequent type of abnormal *transthyretin* (TTR) mutation in ATTRm is Val30Met (p.Val50Met), which results in sensory dominant neuro-

pathy, autonomic dysfunction, and cardiac dysfunction (3). In addition to the TTR Val30Met mutation, Glu42Gly (p.Glu62Gly), Gly47Glu (p.Gly67Glu), Ser50Arg (p.Ser70Arg), Ser50Ile (p.Ser70Ile), Glu54Gly (p.Glu74Gly), Leu55Pro (p.Leu75Pro), Val71Ala (p.Val91Ala), Tyr114Cys (p.Tyr134Cys), and many other mutations have been reported. Although the TTR Ser50Arg mutation is a rare variant, it results in the development of various symptoms of ATTRm and has a relatively young onset age (4, 5).

Tafamidis, which stabilizes the TTR tetramer and inhibits amyloid formation, is indicated in clinical practice (6). However, liver transplantation, which inhibits variant TTR production, was conducted as radical therapy in 2,136 cases from 1990 to December 2015 (7). Domino liver transplantation (DLT) is a particularly useful choice in Japan, as liver transplantations after brain death are infrequent.

While several reports have described recipients of DLT from ATTRm donors developing amyloid polyneuropathy, most patients exhibited the TTR Val30Met mutation. Others

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**Table 1. Nerve Conduction Study Findings of Left Extremities in This Patient.**

Nerve	Years from LT	DL (ms)	MCV (m/s)	CMAP(D/P) (mV)	F latency (ms)	SCV (ms)	SNAP ( $\mu$ V)
Median	9	3.7	49.0	5.7/4.0	30.6	54.5	17.8
	12	4.4	45.5	4.6/4.2	31.9	53.7	11.8
Ulnar	9	3.2	51.3	12.8/10.8	29.8	56.3	21.8
	12	3.2	45.6	10.6/8.7	31.5	50.6	17.0
Tibial	9	4.3	36.3	4.3/4.2	61.1		
	12	5.4	34.0	1.8/1.3	58.0		
Peroneal	9	5.2	36.9	2.9/2.3	58.7		
	12	5.4	34.8	0.8/0.9	-		
Sural	9					46.1	3.8
	12					42.6	3.3

LT: liver transplantation, DL: distal latency, MCV: motor conduction velocity, CMAP (D/P): compound motor action potential (distal/proximal), SCV: sensory conduction velocity, SNAP: sensory action potential

reported mutations include one Gly47Glu mutation, one Ser50Ile, one Glu54Gly, one Leu55Pro, and two Val71Ala and Tyr114Cys mutations each (8-18).

We herein report the case of a patient who received DLT from an ATTRm patient with the *TTR* Ser50Arg mutation and presented with cardiac amyloidosis and polyneuropathy 10 years after DLT.

### Case Report

A 66-year-old man was admitted to our hospital. His mother and elder sister had polycystic kidney disease, and his elder sister had polycystic liver disease as well. More than one maternal relative had had polycystic liver disease and had died of stroke. He presented with hematuria in his 30s and was diagnosed with polycystic kidney disease. He had started undergoing dialysis in his 40s, and polycystic liver disease had subsequently been diagnosed. At 54 years of age, his abdominal distension as a result of liver cysts rapidly worsened, and his nutritional state also deteriorated. He was added to the liver transplantation waiting list, and DLT from a 50-year-old ATTRm patient with a *TTR* Ser50Arg mutation was conducted. The donor had developed autonomic dysfunction, including diarrhea and orthostatic hypotension, at 46 years of age, followed by polyneuropathy and ventricular wall hypertrophy. However, the donor's cardiac and liver functions were normal.

Six and nine years after DLT, our patient visited the neurology department for peripheral neuropathy tests, but a neurological examinations and nerve conduction studies (NCS) demonstrated no signs of neuropathy (Table 1). Ten years after DLT (at 64 years of age), he noticed a slight numbness in his toes. He also had unruptured cerebral aneurysms and decided to undergo a clipping operation. He was referred to the cardiology department for a heart function evaluation before the operation. Echocardiography demonstrated left ventricular hypertrophy, left atrial wall thickness, leaflet thickness, and pericardial effusion (Figure A).  $^{99m}$ Tc-PYP scintigraphy showed diffuse accumulation enhancement in the left

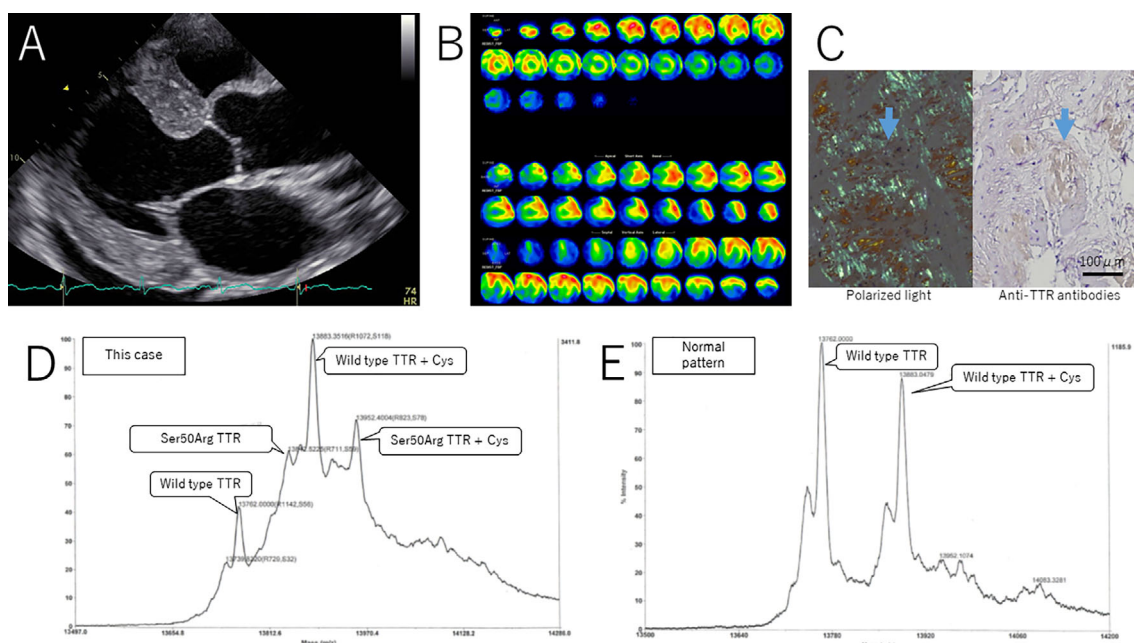
ventricular myocardium (Figure B). Cardiac amyloidosis was suspected, at which time he visited the neurology department for a reevaluation of neuropathy.

On a physical examination, a subcutaneously fixed superficial artery on the right arm was observed, but no findings of cardiac tamponade, including paradoxical pulse, heart sound attenuation, or jugular venous distention, were observed. A neurological examination revealed a decreased deep tendon reflex in the upper and lower extremities and abnormal sensation in the left lower extremity, but no muscle weakness, thermal hypoalgesia, hypopallesthesia, or orthostatic hypotension were observed. Autonomic dysfunction was screened by the Japanese version of scales for outcomes in Parkinson's disease - autonomic questionnaire; there were no subjective signs of problems.

A blood examination detected mild hepatic dysfunction and renal dysfunction equivalent to dialysis. Blood glucose and vitamin B<sub>12</sub> levels were within normal limits, and major autoantibodies were absent. A *TTR* gene mutation was not detected in a whole-genome sequence of the patient's peripheral blood. NCS revealed decreased motor conduction velocity, compound motor action potential, and sensory nerve action potential in the left lower limb, and F wave latencies in the upper and lower extremities were delayed, but these findings did not meet the criteria of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Table 1). The coefficient of variation of the R-R intervals in the electrocardiogram was 1.87% (normal range >2.0%). A metaiodobenzylguanidine scan was not conducted.

A myocardial biopsy revealed TTR-type amyloidosis. The positive image of this specimen in polarized light examination matched that of anti-TTR antibodies, but not those of anti-AA, anti-IGLC $\kappa$ , or anti-IGLC $\gamma$  antibodies (Figure C). These findings corresponded to TTR-type amyloidosis. Expectedly, Ser50Arg TTR was found in the patient's serum (Figure D).

As the symptoms of neuropathy were relatively mild, a nerve biopsy was not conducted. Based on the clinical course and examination results, including the myocardial bi-



**Figure.** Laboratory findings of echocardiography, <sup>99m</sup>Tc-PYP scintigraphy, myocardial biopsy and mass spectroscopy of TTR protein. **A:** Echocardiography demonstrated left ventricular hypertrophy, left atrial wall thickness, leaflet thickness, and pericardial effusion. **B:** <sup>99m</sup>Tc-PYP scintigraphy showed diffuse accumulation enhancement in the left ventricular myocardium. **C:** Myocardial biopsy findings. The positive image of this specimen in polarized light examination (left) matched that of anti-TTR antibodies (right). **D:** Ser50Arg TTR was found in mass spectroscopy of TTR protein.

opsy, causes of neuropathy other than ATTRm were unlikely. It was suggested that this patient had developed iatrogenic ATTRm a long time after DLT. In addition, as there was no accompanying osteolesion, dialysis amyloidosis was unlikely in this patient.

Based on the diagnosis and with the patient's consent, we started tafamidis to inhibit symptom progression. While only a relatively short time has passed since starting treatment, there has been no deterioration of the neurological or cardiovascular symptoms in this patient over the past two years.

## Discussion

Previous cases in which patients developed ATTRm after DLT showed *TTR* Val30Met, Gly47Glu, Ser50Ile, Glu54Gly, Leu55Pro, Val71Ala, or Tyr114Cys mutations; this is the first report of a case with a Ser50Arg mutation (Table 2). The ATTRm with *TTR* Ser50Arg mutation was characterized by neuropathic pain, walking disabilities, weight loss, diarrhea, orthostatic hypotension, and cardiomyopathy (5, 19).

A previous report described a patient with cadaveric DLT in Japan; the authors of that patient's report had observed no *de novo* ATTRm cases among recipients of DLT but cautioned that careful attention to the development of ATTRm in the future was needed (20). Confirming this prediction, a number of cases of ATTRm after DLT were reported, starting in 2005 (Table 2) (8-18).

Of the 1,112 DLT cases (7), more than 10 have developed

ATTRm. The average duration from DLT to the onset of polyneuropathy was 7.4 years (to the extent that it was confirmed, 3-11 years). The present case showed a relatively long duration to development compared with other cases. However, the period to develop ATTRm was shorter than previously considered. ATTRm was previously suspected to develop 20 to 30 years after DLT (21), but this was not entirely true. Liver transplantation, including DLT, is an effective choice for radical therapy for ATTRm, but the recipient's risk of developing iatrogenic ATTRm in the future should be considered. Tafamidis, a TTR tetramer stabilizer, or diflunisal (22), immunotherapy (23), gene conversion therapy (24), and RNAi therapy (25) may become mainstream alternatives to DLT in the future.

The NCS findings of this case suggested relatively demyelinating changes, which did not meet the criteria of CIDP, unlike axonal or small fiber neuropathy observed in typical ATTRm. The neurological symptoms of this case were not similar to those of the donor patient; indeed, autonomic dysfunction was inconspicuous in this case. Dissociative sensory disturbance was not obvious, and symptoms might not have been remarkable because the neuropathy was in an early stage. There were some cases in non-endemic area of Japan that had disturbances with myelinated fibers from an early stage of ATTRm (26). The present case exhibited different clinical findings from typical cases in the endemic area of Japan, but the finding of PYP scintigraphy was coincident with the findings from previous ATTRm cases (27).

**Table 2. Previous Cases of Hereditary ATTR Amyloidosis after Domino Liver Transplantation.**

Reference	Gender	Age at DLT	Age at neuropathy onset	Cause of DLT	Histology	TTR variant	Symptom			
							motor	sensory	Autonomic	
8	M	47	55	HCV cirrhosis, HCC	Nerve, GI wall	Val30Met	-	+	-	
9	F	50	57	PBC	GI wall	Val30Met	-	+	-	
10	F	65	72	HCC, HCV cirrhosis	GI wall	Gly47Glu	-	+	-	
11	M	54	63	Hemangioendothelioma HCV cirrhosis	Nerve	Val30Met	+	+	+	
12	M	54	59	HCC, HBV, HCV cirrhosis	Nerve, LSG	Val30Met	-	+	-	
	M	72	75	HCC, HBV cirrhosis	Nerve, LSG	Val30Met	-	+	+	
	M	60	65	HBV cirrhosis	Nerve	Val30Met	-	+	+	
	M	45	53	HCV, alcoholic cirrhosis	Nerve, LSG	Val30Met	-	+	-	
13	M	59	68	HBV & HCV cirrhosis	AFT	Val30Met	+	+	+	
14	M	35	46	PSC	AFT	Val30Met	-	+	-	
15	F	43	52	HBV, HCC	GI wall, AFT	Glu54Gly	-	+	+	
16	M	66	ND	HCC, HCV cirrhosis	Nerve, GI wall	Unclear*	+	+	+	
	M	62	ND	alcoholic cirrhosis	Nerve, GI wall	Unclear*	-	+	+	
	M	60	ND	HBV cirrhosis	Nerve	Unclear*	-	+	+	
	M	60	ND	HCV cirrhosis	Nerve	Unclear*	-	-	-	
	M	64	ND	HCC, HCV cirrhosis	ND	Unclear*	-	-	-	
	F	62	ND	HCV cirrhosis	ND	Unclear*	-	-	-	
	M	64	ND	HCC, HCV cirrhosis	Nerve	Unclear*	-	+	+	
	F	61	ND	alcoholic cirrhosis	ND	Unclear*	-	-	-	
	M	58	ND	HCC, HCV cirrhosis	ND	Unclear*	-	-	+	
	M	61	ND	HCC, HBV cirrhosis	GI wall	Unclear*	-	-	-	
	M	66	ND	alcoholic cirrhosis	ND	Unclear*	-	-	-	
	M	59	ND	HCC, HCV cirrhosis	Nerve, GI wall	Unclear*	-	-	-	
	F	61	ND	HCV cirrhosis	GI wall	Unclear*	-	-	-	
	M	66	ND	HCV cirrhosis	ND	Unclear*	-	-	+	
	M	62	ND	HCV cirrhosis	ND	Unclear*	-	-	-	
	M	64	ND	HCC, HCV cirrhosis	GI wall	Unclear*	-	-	+	
	F	62	ND	HCC, HCV cirrhosis	ND	Unclear*	-	-	-	
	17	M	62	67	Cirrhosis, HCC	AFT	Val71Ala	ND	ND	ND
	18	F	50	ND	PBC	+	Val30Met	-	+	-
		M	35	ND	cirrhosis	+	Val30Met	-	+	+
M		41	ND	PSC	-	Val30Met	-	-	-	
M		30	ND	cirrhosis	+	Tyr114Cys	-	-	-	
M		60	ND	HBV cirrhosis	+	Ser50Ile	-	+	-	
F		52	ND	PBC	-	Val30Met	-	-	-	
F		53	ND	HBV cirrhosis	+	Val30Met	-	-	-	
F		35	ND	BA	+	Val30Met	-	+	-	
M		40	ND	HCV cirrhosis, HCC	-	Val30Met	-	-	-	
F		23	ND	BA	-	Val30Met	-	-	-	
M		57	ND	HCV cirrhosis, HCC	-	Val30Met	-	-	-	
M		18	ND	BA	+	Val30Met	-	-	-	
M		58	ND	cirrhosis	+	Val30Met	-	+	+	
M		43	ND	HCV cirrhosis	-	Val30Met	-	-	-	
M		56	ND	cirrhosis, HCC	-	Val30Met	-	-	-	
M		58	ND	HCV cirrhosis, HCC	-	Val30Met	-	-	-	
M		54	ND	HBV cirrhosis	-	Val30Met	-	-	-	
M		35	ND	PBC	-	Val30Met	-	-	-	
F		45	ND	cirrhosis	-	Val30Met	-	-	-	
M		53	ND	HCV cirrhosis, HCC	-	Leu55Pro	-	-	-	
M	62	ND	HCV cirrhosis	-	Val30Met	-	-	-		
M	59	ND	HBC cirrhosis, HCC	-	Val30Met	-	-	-		
This case	M	54	64	Polycystic liver	Myocardium	Ser50Arg	-	+	-	

M: male, F: female, DLT: domino liver transplantation, HCV: hepatitis C virus, PBC: primary biliary cirrhosis, HCC: hepatocellular carcinoma, HBV: hepatitis B virus, PSC: primary sclerosing cholangitis, BA: biliary atresia, GI: gastrointestinal tract, LSG: labial salivary gland, AFT: abdominal fat tissue, TTR: transthyretin, ND: not described

\* Unclear means that except for one case of Val71Ala mutation, all other patients were Val30Met mutation, but it was unspecified which is Val 71 Ala mutation.

Autonomic dysfunction is a significant prognostic element of ATTRm; the prognosis improves if the onset and development of autonomic dysfunction are inhibited, as in the present case. In addition, this case confirmed that regular follow-up after DLT from ATTRm is very important for the early detection of neurological symptoms. We will follow this case closely, particularly with respect to the inhibitory effects of tafamidis on not only peripheral neuropathy but also systemic organs, such as myocardial dysfunction.

### Conclusions

We herein reported the first case of amyloid polyneuropathy and myocardial amyloidosis at 10 years after DLT from a donor with ATTRm and a *TTR* Ser50Arg mutation and reviewed similar cases of other *TTR* mutations. Regular follow-up after DLT from an ATTRm donor and the early detection of neurological symptoms were very important.

**The authors state that they have no Conflict of Interest (COI).**

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