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【 CASE REPORT 】

Deterioration after Liver Transplantation and Transthyretin Stabilizer Administration in a Patient with ATTRv Amyloidosis with a Leu58Arg (p.Leu78Arg) *TTR* Variant

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Abstract:

We herein report a 44-year-old Japanese man with hereditary transthyretin amyloidosis (ATTRv amyloidosis) harboring the variant Leu58Arg (p.Leu78Arg) in *TTR* in whom we conducted an observational study with liver transplantation (LT) and transthyretin (TTR) stabilizers (tafamidis and diflunisal) for 9 years. This patient showed gradual deterioration of sensory, motor, and autonomic neuropathy symptoms after LT. Furthermore, cardiac amyloidosis gradually developed. Although the present case showed deterioration of the symptoms after disease-modifying treatments, LT might be suitable in patients with the same variant if they are young and in good condition due to a long survival after LT.

Key words: transthyretin, ATTRv amyloidosis, liver transplantation, Leu58Arg (p.Leu78Arg), neuropathy, stabilizer

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Introduction

Transthyretin (TTR), a homotetrameric plasma protein produced mainly by the liver, causes systemic amyloidosis (ATTR amyloidosis). Variants of *TTR* have been demonstrated in patients with hereditary ATTR amyloidosis (ATTRv amyloidosis). Several treatments have been administered to patients with ATTRv amyloidosis, including liver transplantation (LT), oral TTR stabilizer administration, and gene silencing. Although most patients with ATTRv amyloidosis carrying the Val30Met (p.Val50Met) variant showed favorable outcomes by applying the above-mentioned treatments, the benefits of these treatments for patients with ATTRv amyloidosis with other variants have been inconsistent (1-3).

Previously, we identified a unique family with ATTRv amyloidosis harboring the variant Leu58Arg (p.Leu78Arg) in *TTR* (4-6). Regarding one affected member of this family [VI-1 in the family tree, as shown in a previous report (5)], we were able to conduct an observational study with disease-modifying treatments, including LT and TTR stabilizers (tafamidis and diflunisal), for nearly nine years. This patient showed gradual deterioration of the sensory, motor, and autonomic neuropathy symptoms after the LT. In addition, cardiac amyloidosis gradually developed. Our findings in this patient provide novel insight into therapies for patients with ATTRv amyloidosis and non-Val30Met *TTR* variants.

Case Report

A 44-year-old man developed erectile dysfunction at 24 years old. The patient showed bilateral visual disturbance due to vitreous opacities and underwent vitreous surgeries at 30 and 33 years old. Slowly progressive orthostatic hypoten-

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sion and hypohidrosis were found to have developed, and the patient showed occasional syncope. Paresthesia at the planta pedis was observed, and the patient was admitted to our hospital at 34 years old. He demonstrated hyposmia and atrophy of the masseter muscles. Distal dominant muscle weakness and atrophy were observed in the upper and lower extremities. The lower extremities were hyporeflexic. Autonomic dysfunction, such as impotence, orthostatic hypotension, diarrhea, hypohidrosis, and dysorexia, were apparent.

A biopsy of the stomach, duodenum, colon, and skin demonstrated TTR-positive amyloid deposition. Congo red staining showed neither strong nor glittering granular birefringence in polarized light (Figure A, B) (7-9). A genetic analysis performed at 34 years old revealed the presence of the *TTR* variant of Leu58Arg (p.Leu78Arg). Diflunisal administration was started four months after the initial admission. Ten months after the first admission, ABO-incompatible segmental living-donor LT from his healthy mother was performed. The details concerning LT have been reported in another case report (10). TTR-positive amyloid deposition was evident in the blood vessel walls of the resected liver. Improvement of diarrhea and sensory disturbance in the lower extremities was observed; however, orthostatic hypotension did not improve. The administration of diflunisal was ceased after the LT.

A follow-up examination 16 months after LT showed mild deterioration of sensory disturbance with stable autonomic dysfunction (Figure C). We used the modified familial amyloid polyneuropathy (FAP) clinical scoring system reported by Tashima et al. in 1999 (1) to assess the clinical manifestations of the present patient. Approximately three years after LT, the patient showed gradual deterioration of muscle weakness in the upper and lower extremities (Figure D). Furthermore, worsening of his sensory disturbances was obvious. Four years after LT, ophthalmological surgery was performed again on the left eye due to vitreous opacities and glaucoma. Six months later, the right eye underwent surgery due to vitreous opacities and glaucoma. Fifty-seven months after LT, prescription of tafamidis was started. The patient showed continuous worsening of the manifestations of motor and sensory neuropathy and stabilization of autonomic dysfunction (Figure C). Transthoracic echocardiography after LT demonstrated cardiac involvement with a gradual increase in thickening of the interventricular septal thickness at end-diastole (IVSTd) and posterior wall thickness at end-diastole (PWTd) and a decrease in the percent fractional shortening (%FS) (Figure E). ^{99m}Technetium-pyrophosphate scintigraphy results, which are useful methods for the diagnosis of cardiomyopathy due to ATTR amyloidosis (11), were positive for TTR amyloid deposition.

Seventy-six months after LT, a skin biopsy showed an amount of amyloid deposition similar to that obtained at the initial admission. At the nine-year follow-up after LT, the patient demonstrated apparent deterioration of sensory and motor dysfunction, albeit without obvious autonomic disturbance progression or visceral organ damage (Figure C). Regarding daily living activities, assistance with canes and lower extremity orthoses were necessary to allow him to walk; however, the patient was able to live with minimum assistance.

Discussion

We herein report a patient with ATTRv amyloidosis harboring the Leu58Arg (p.Leu78Arg) *TTR* variant who underwent LT and showed three years of stabilization followed by deterioration of sensory and motor symptoms and cardiac involvement. The patient developed autonomic dysfunction with slow progression and vitreous opacities, followed by progressive manifestations of sensory and motor neuropathy and cardiac involvement. The total clinical course was 21 years, including a 9-year post-LT follow-up period.

Phenotypic heterogeneity in patients with ATTRv amyloidosis with the same variant is common (12). To date, there has only been one family with ATTRv amyloidosis harboring the Leu58Arg (p.Leu78Arg) *TTR* variant (13). The father of the present patient showed progressive sensory, motor, and autonomic polyneuropathy phenotypes with cardiac and leptomeningeal involvement with a nine-year clinical course in total. Furthermore, the paternal grandmother of the present patient showed a later onset and slower progressive carpal tunnel syndrome and vitreous opacities than the patient himself (5, 6). The present patient had clinical manifestations of both affected members with a longer clinical course.

ATTRv amyloidosis with the Val30Met (p.Val50Met) *TTR* variant has a more favorable outcome after LT than that with non-Val30Met *TTR* variants in terms of the overall survival (1, 3, 14); indeed, the overall survival of patients with ATTRv amyloidosis with the non-Val30Met variant was less than 20% at 15 years after LT (3). Regarding LT in patients with ATTRv amyloidosis with the Val30Met (p.Val50Met) variant, a case series of 6 patients demonstrated stabilization or minor improvement of the manifestations at 30 months (mean) (range 12-48 months) of follow-up after LT (1). In another case series, 8.6 years (median) (range 0.3-15.9 years) of follow-up showed that LT reduced the worsening of clinical manifestations in patients with ATTRv amyloidosis with the Val30Met (p.Val50Met) variant (14). The median total score according to the modified FAP clinical scoring system of patients who underwent LT was 11.5 (range 5-55) out of 96 at 8.6 years (median) after LT (14). The total score of the modified FAP clinical scoring system in the present patient was 38 of 96, at 107 months after LT (Figure C). The effectiveness of LT in the present patient was less than that in patients with the Val30Met variant.

Although an acceptable benefit with LT has been reported in patients with ATTRv amyloidosis with the Leu55Pro (p.Leu75Pro) variant (15), patients harboring the Ala36Pro (p.Ala56Pro) variant demonstrated a poor outcome (16). However, ATTRv amyloidosis with the Leu58His (p.Leu78His) variant, which corresponds to the same site as the variant

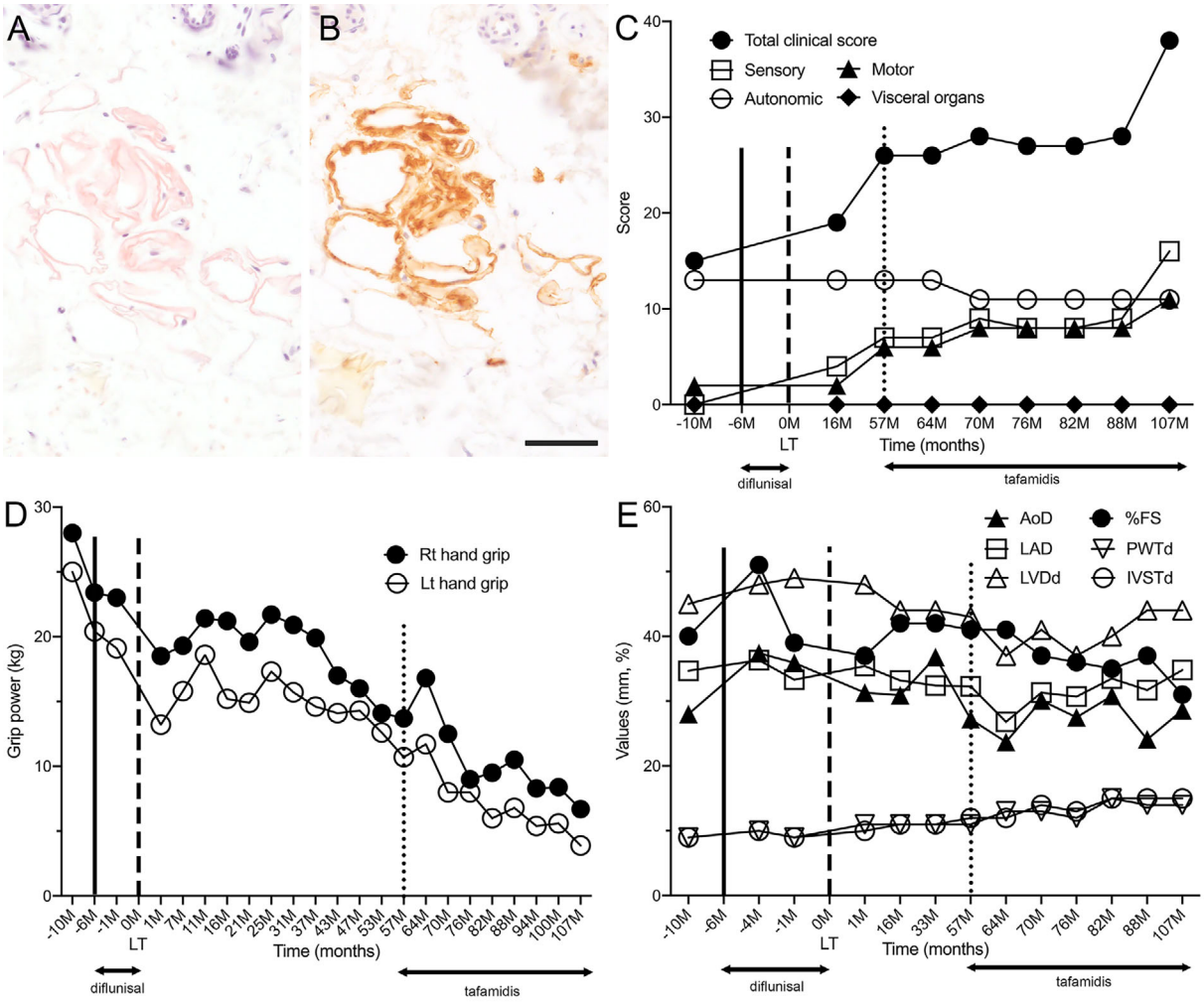

Figure. **A histopathological analysis and changes in scores of the modified familial amyloid polyneuropathy (FAP) scoring system, hand grip power, and results of the transthoracic echocardiography of the present patient are shown here. Transthyretin-positive amyloid deposits are shown by Congo red (A) and immunolabeling for transthyretin (rabbit monoclonal, EPR3219; Abcam, Tokyo, Japan; 1: 1,500) (B) around the adipose tissue obtained by a skin biopsy. Scale bar, 50 μm (A, B). The modified FAP scoring system reported by Tashima et al. in 1999 (1) was used to assess the clinical manifestations of the present patient. The scoring system has four domains: sensory impairment, autonomic dysfunction, motor function, and visceral organ impairment. Twenty-four points were assigned to each domain, and the total clinical score was calculated as the sum of the scores of all domains (96 points in total). The total clinical score and scores of the sensory impairment and motor function show a gradual increase after liver transplantation (LT), whereas autonomic dysfunction and visceral organ impairment are stable (C). Hand grip power is stable until 37 months after LT and then shows continuous deterioration (D). Transthoracic echocardiography demonstrates a gradual increase in cardiac wall thickening [posterior wall thickness at end-diastole (PWTd) and interventricular septal thickness at end-diastole (IVSTd)] with a decrease in percent fractional shortening (%FS), albeit without apparent changes in the aortic root diameter (AoD), left atrial diameter (LAD), and left ventricular end-diastolic diameter (LVDd) (E). The solid line, dashed line, and dotted line indicate the time of initiation of oral diflunisal administration, time of LT, and time of initiation of oral tafamidis administration (C-E), respectively. AoD: aortic root diameter, FAP: familial amyloid polyneuropathy, IVSTd: interventricular septal thickness at end-diastole, LAD: left atrial diameter, LT: liver transplantation, LVDd: left ventricular end-diastolic diameter, %FS: percent fractional shortening, PWTd: posterior wall thickness at end-diastole**

found in the present patient but differed in the substituted amino acid, showed a 76% survival rate at 10 years after LT (17). Furthermore, a patient with ATTRv amyloidosis with the Leu58His (p.Leu78His) variant who developed neuropathy at 56 years old showed stabilization at 1 year after LT followed by deterioration of polyneuropathy (18). The

same report described another patient harboring the same variant who developed neuropathy at 47 years old and showed gradual worsening of polyneuropathy in 6 years after LT (18). Since the same variant did not show similar outcomes in patients with ATTRv amyloidosis, it is difficult to conclude whether or not patients with the Leu58Arg (p. Leu78Arg) variant should be treated with LT. The present patient, however, survived for approximately nine years after LT. Therefore, LT might be considered for patients with the same variant. It has been shown that deterioration of the manifestations after LT in patients with ATTRv amyloidosis is associated with the deposition of wild-type TTR (19, 20). TTR gene silencing therapy was able to be applied to the present patient to prevent continuous aggregation of wild-type TTR in the affected tissues (18).

Why patients with non-Val30Met variants, including the present patient, showed less favorable outcomes than those with Val30Met variant after LT is unclear. However, ATTR fibril types may be related to the clinical phenotype and outcome after treatment (7-9, 21). There are two types of ATTR fibrils comprising a mixture of truncated and full-length ATTR (type A) or only full-length ATTR (type B) (7). Patients with type A ATTR have a late onset and may be associated with a less favorable clinical course after LT (22), whereas patients with type B ATTR, such as those with the Val30Met (p.Val50Met) variant, have an early onset of ATTRv amyloidosis (8). Almost all patients with non-Val30 Met ATTRv amyloidosis have type A fibrils (8). The two types demonstrate different results on Congo red staining (7-9). Furthermore, an ultrastructural study revealed that early-onset Val30Met ATTRv amyloidosis had long amyloid fibers, whereas the amyloid fibrils were short in patients with ATTRv amyloidosis of late-onset Val30Met and non-Val30Met cases (9, 21). A biochemical analysis was not performed in the present patient; however, the TTR amyloid deposited in the biopsied tissue in the present patient may have been type A (Figure A), which shows resistance to currently available therapies for ATTRv amyloidosis.

In conclusion, we encountered a patient with ATTRv amyloidosis with the Leu58Arg (p.Leu78Arg) *TTR* variant who received combination therapy with LT and TTR stabilizers. Although the present case showed deterioration of his symptoms after LT and TTR stabilizer administration, LT might be considered in patients with the same variant if they are young and in good condition.

Informed consent was obtained from the patient for this case report. Ethical approval for submitting a case report is waived by the medical ethics committee of Kanazawa University.

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

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