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CASE REPORT

Familial Amyloidotic Polyneuropathy with Leptomeningeal and Cardiac Involvement in a Patient with Gly73Glu Transthyretin Gene Mutation — Non-invasive Diagnostic Approach with Multimodality Imaging Findings: a Case Report

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CASE REPORT

In April 2020, a 47-year-old woman presented with peripheral upper and lower limb numbness and recurrent headaches, and a history of transient expressive dysphasia with spontaneous recovery 6 years previously. She also developed gradual cognitive impairment and bilateral sensorineural hearing loss after that. Extensive blood tests and imaging including echocardiogram were all unremarkable. Nerve conduction testing revealed demyelinating sensorimotor polyneuropathy of the lower limbs. Three months previously the patient was admitted with rapid deterioration in her physical and mental condition, as well as lower limb oedema. Chest radiograph showed new bilateral pleural effusions. Magnetic resonance imaging (MRI) brain studies revealed diffuse leptomeningeal enhancement mainly in the central skull base cisterns and bilateral posterior cranial fossa (Figure 1a and b) and diffuse superficial haemosiderosis on susceptibility-weighted imaging (Figure 1c). Subsequent development of a left frontal lobe intracerebral haemorrhage was noted on follow-up images (Figure 1d). Echocardiogram revealed a moderately impaired left ventricular ejection function of 35% and left ventricular hypertrophy with infiltrative features (Figure 2). Blood test for serum free light chain level, as well as urine for proteins were not elevated. Subsequent cardiac MRI (Figures 3 and 4) and technetium-99m pyrophosphate scan (Figure 5) confirmed transthyretin (TTR) amyloidosis. Genetic study indicated a pathological TTR gene (p.Gly73Glu in exon 3). Retrospective review of her family history revealed that her father had died from a cerebral vascular accident in his thirties, and her mother from an unknown neurological condition at an early age.

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Ethics Approval: The patients were treated in accordance with the tenets of the Declaration of Helsinki. Verbal informed consent for all treatments and procedures was obtained from the patient and her husband.

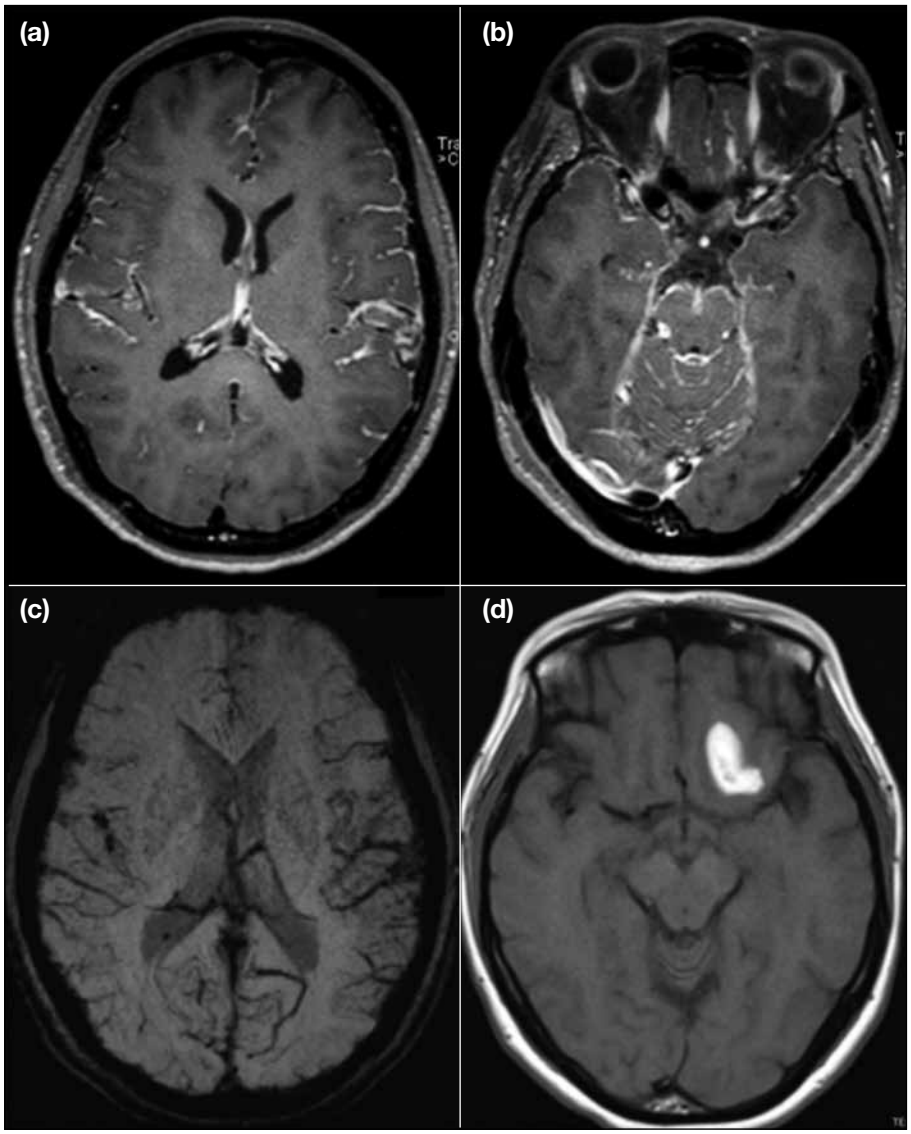

Figure 1. Magnetic resonance imaging (MRI) images of the brain. T1-weighted post-gadolinium axial images of the brain at the level of (a) lateral ventricles and (b) the pons demonstrating diffuse leptomeningeal enhancement involving bilateral cerebral sulci and perimesencephalic region. (c) Susceptibility-weighted image showing diffuse superficial haemosiderosis. (d) T1-weighted axial images of follow-up MRI of the brain 1 month later, showing T1-weighted hyperintense intracerebral haematoma in the left inferior frontal lobe.

The diagnosis of hereditary TTR amyloidosis with cardiac and neurological involvement was made. The patient was referred for detailed evaluation and potential pharmacological treatment of familial amyloidotic polyneuropathy.

DISCUSSION

Hereditary TTR amyloidosis is an exceptionally rare disease. Few cases of hereditary TTR amyloidosis with cardiac involvement or peripheral neuropathy from Val142Ala[1] or Ala117Ser[2] mutations have been reported in Hong Kong. There have been some cases reported from France[3] and Sweden[4], but this is the first in Asia with leptomeningeal involvement of amyloidosis from a Gly73Glu TTR gene mutation.

Familial amyloidotic polyneuropathy is a familial disease characterised by accumulation of amyloid fibrillar proteins in organs and peripheral nerves. Onset is usually between the ages of 30 and 40 years. Systemic involvement includes sensorimotor polyneuropathy, autonomic dysfunction, and cardiac, renal, and hepatic involvement.

TTR amyloidosis is the most common familial amyloidosis. The genetic mutation at the TTR amyloidosis gene causes destabilisation and dissociation of the TTR protein, leading to misfolded monomers that ultimately self-assemble to form amyloid fibrils. There are more than 100 reported mutations of the TTR gene, with Val30Met being the most common. Some

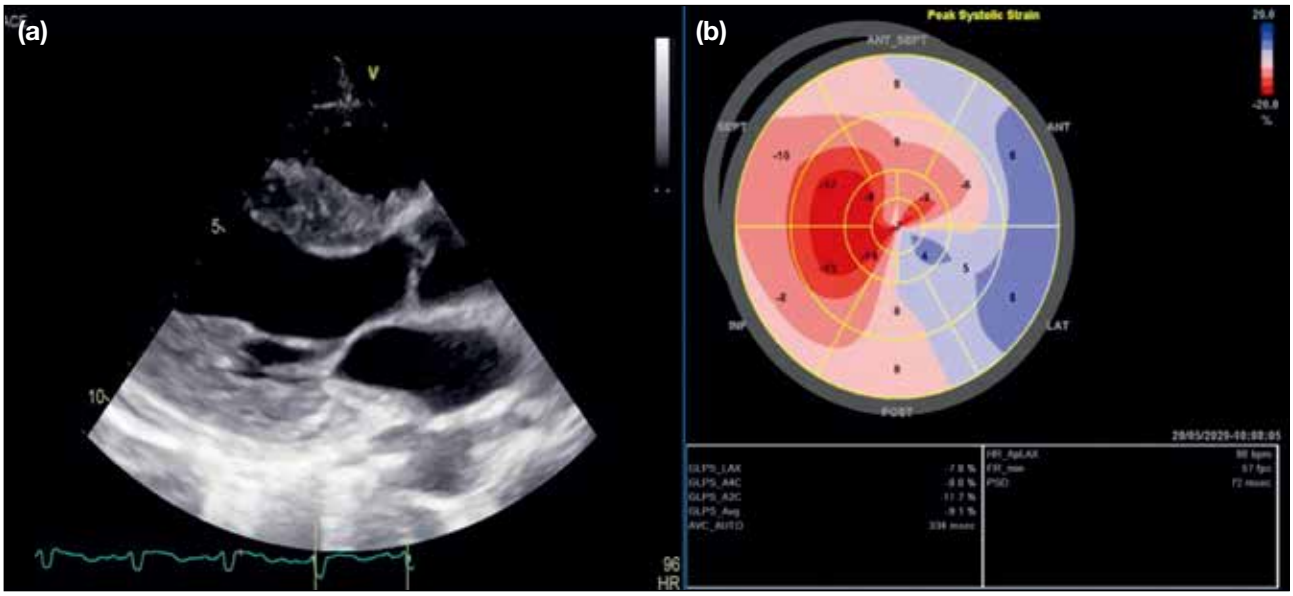

Figure 2. (a) Echocardiogram in parasternal long axis view showing marked increase in left ventricular wall thickness. (b) Strain image showing decreased global longitudinal strain with apical sparing.

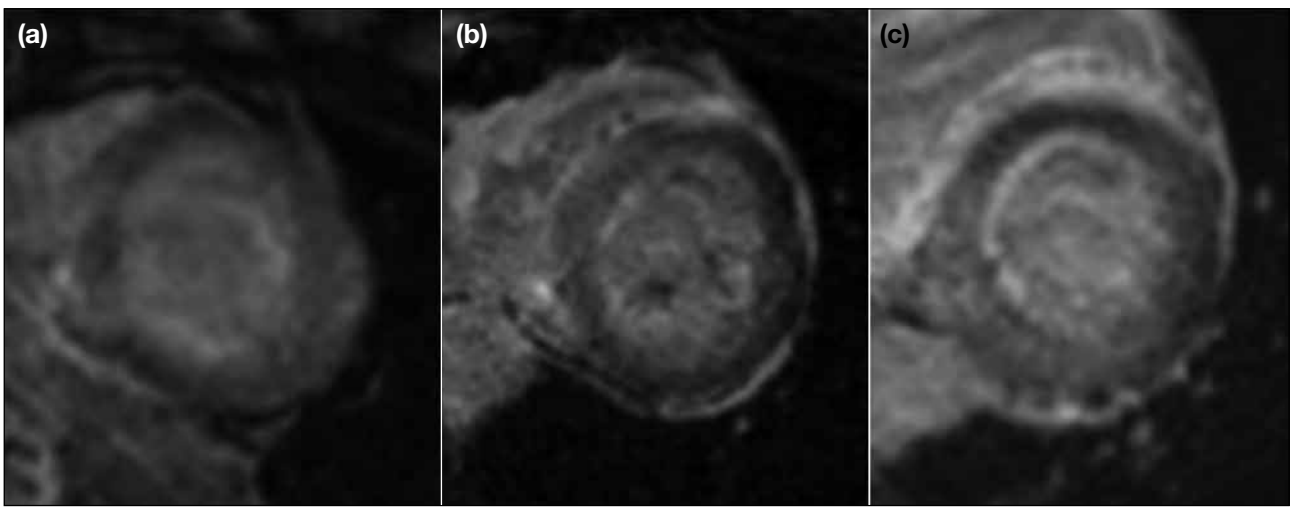

Figure 3. Cardiac magnetic resonance imaging late gadolinium-enhanced short axis images of the left ventricle at the (a) basal, (b) mid and (c) apical levels demonstrating global subendocardial delayed enhancement not following coronary territories.

forms, including the Gly73Glu mutation, will lead to a preferential involvement of the leptomeninges and meningovascular walls, as well as amyloid-derived vitreous opacity, thus they are termed leptomeningeal or oculoleptomeningeal amyloidosis.

Clinically these patients present with manifestations including headache, dementia, ataxia, spastic paralysis or convulsion.[5] MRI is the most sensitive modality to identify the leptomeningeal abnormalities, demonstrating intermediate T1-weighted signal intensity and contrast enhancement of the leptomeninges along the Sylvian fissures, cerebral sulci, cisterns and surface of the brainstem, as in our case, and also along the surface of the cerebellum and spinal cord. Due to the abnormal cerebral and leptomeningeal vessels, these patients are prone to intracerebral, subarachnoid, or subdural haemorrhages.

There are multiple differentials for diffuse

leptomeningeal enhancement. Nodular leptomeningeal thickening is usually seen in leptomeningeal carcinomatosis. Tuberculous meningitis and neurosarcoidosis can both demonstrate smooth or nodular leptomeningeal enhancement although they are predominantly located in the vicinity of basal cisterns. It can sometimes be difficult to differentiate various causes of leptomeningeal disease. Compatible clinical features should raise prompt consideration of a diagnosis of familial cerebral amyloid angiopathies.

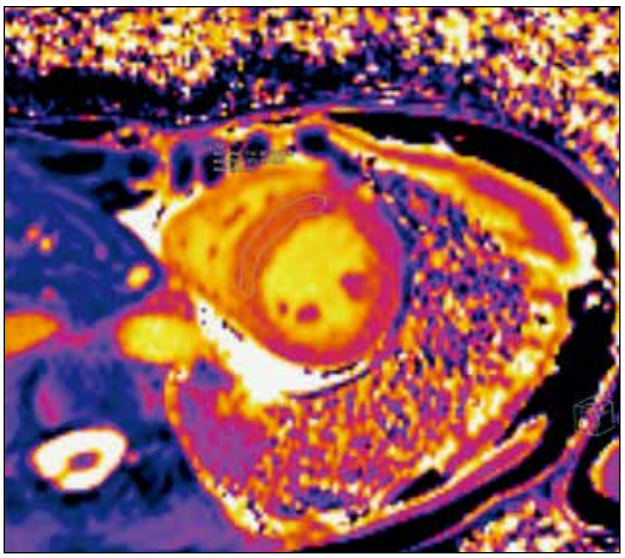

Figure 4. Cardiac magnetic resonance imaging native T1 mapping showing marked elevation of T1 value of the myocardium, measuring 1273 ms (normal myocardial T1 mapping value in our centre: 1019 ± 41 ms).

The pathogenesis of sporadic-type cerebral amyloid angiopathy is vastly different to that of the familial type. The sporadic type more commonly affects the elderly people. Unlike familial cerebral amyloid angiopathy, the sporadic form is characterised by progressive amyloid-β protein deposition on the walls of small- to medium-sized arteries, arterioles and capillaries in the cerebral and cerebellar cortices, with vessel wall thickening, endothelial dysfunction and a loss of compliance leading to fragile vessels. This causes intracranial macro- and micro-haemorrhages. On MRI, gradient echo sequences or susceptibility-weighted imaging are helpful to depict these macro- and micro-bleeds that are usually distributed in a lobar predilection. Other non-specific findings include cerebral atrophy and cerebral white matter signal changes. There is seldom extensive leptomeningeal deposition or enhancement in the sporadic type.

Cardiac involvement is also common in familial amyloidosis, and patients usually present with heart failure or refractory arrhythmia. Endomyocardial biopsy has historically been the gold standard for a definitive diagnosis of cardiac amyloidosis. Recent study suggests that suspicious cardiac MRI findings with a grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy in a patient with no monoclonal protein in serum or urine has specificity and positive predictive value of 100% in the diagnosis of TTR cardiac amyloidosis.[6] This obviates the need for endomyocardial biopsy in some patients.

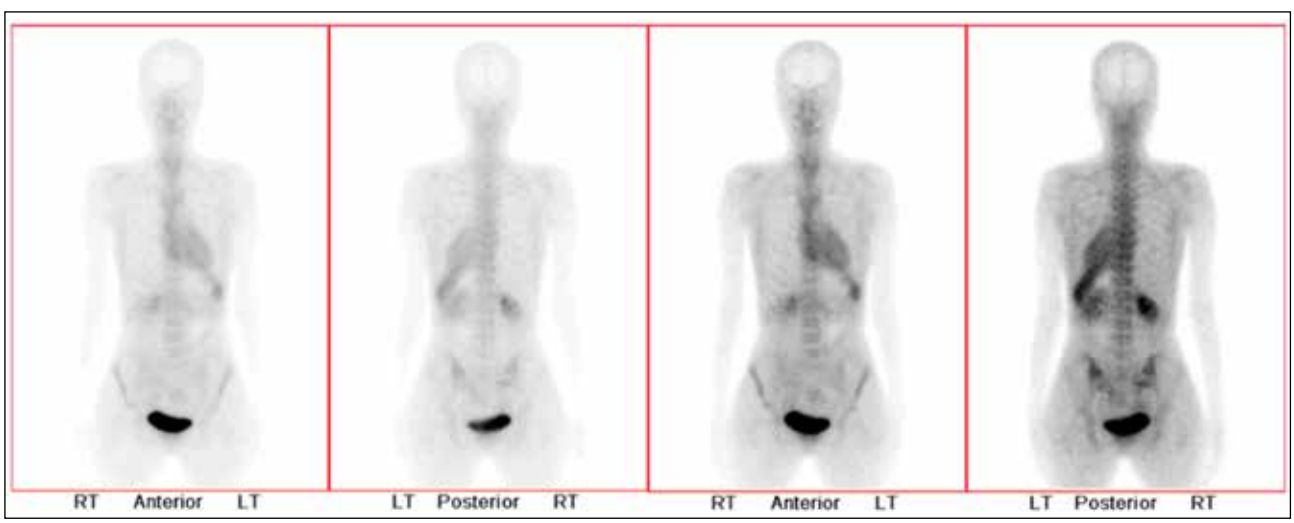

Figure 5. Technetium-99m pyrophosphate radionucleotide scan (post 3-hour image) showing moderate myocardial radiotracer uptake. Myocardial uptake is higher than bone uptake, indicating a grade 3 myocardial radiotracer uptake.

There are several pharmacological interventions that can be applied to prevent the formation of amyloid proteins. They include suppression of TTR synthesis (patisiran, inotersen), stabilisation of TTR to prevent misfolding into amyloid proteins (tafamidis, diflunisal), as well as TTR fibril degradation and absorption (doxycycline-tauroursodeoxycholic acid, monoclonal anti-serum amyloid protein antibody).[7] Patients may also benefit from liver transplantation or a combined heart and liver transplant, with potential long-term histopathologic regression of amyloid deposits. Prognosis is variable, depending on the TTR variants, age, nutritional status and the severity of neuropathy and cardiac amyloid involvement. A multidisciplinary approach is often key to successful management of patients with hereditary amyloidosis.

In conclusion, the finding of a constellation of unique neurological and cardiac findings in this patient utilising various imaging modalities enabled us to diagnose this uncommon multisystem disease whose initial clinical presentation is often non-specific.

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