Splenic regression of amyloid on multi-modality imaging in response to treatment with patisiran and diflunisal in hereditary transthyretin amyloidosis

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Hereditary transthyretin amyloidosis (ATTRv) gives rise to varying patterns of multi-organ amyloid infiltration, characteristically with cardiomyopathic and/or neuropathic phenotypes. Splenic amyloid infiltration is rare but can be visualised by ^{123}I-labelled serum-amyloid-P component (SAP) scintigraphy and cardiac magnetic resonance imaging (CMR). Novel treatments which target hepatic transthyretin (TTR) production have been shown to improve clinical outcomes but there are no studies showing their direct effect on amyloid burden. We report the first case of unequivocal splenic amyloid regression using multi-modality imaging in a patient with ATTRv amyloidosis after treatment with the small interfering RNA drug patisiran and the transthyretin-stabilising drug diflunisal.

A 32-year-old female presented with paresthesiae and bilateral floaters secondary to vitreous aggregates. Fundoscopic and retinal imaging were consistent with ocular amyloidosis. N-terminal pro B-type natriuretic peptide (NT-proBNP) was 419ng/L. Early cardiac amyloidosis was demonstrated on CMR and ^{99m}Technetium 3,3-diphosphon-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy was Perugini grade 3 which, accompanied by normal monoclonal protein studies, was diagnostic of ATTR amyloidosis (1). ^{123}I-SAP scintigraphy demonstrated splenic amyloid. Neurological investigations demonstrated axonal peripheral neuropathy and early autonomic neuropathy. She was confirmed to be heterozygous for a *TTR* mutation encoding the F33V (p.Phe53Val) variant, previously identified in her father who had died from ATTRv amyloidosis. She commenced disease-modifying therapy in September 2017 with both patisiran and diflunisal, reporting gradual improvement in her neuropathic symptoms and functional capacity with no drug-related adverse effects. Figure 1 shows annual SAP and CMR scans performed to assess her disease burden in response to treatment. The colour maps on CMR represent extra-cellular volume (ECV), a surrogate of amyloid deposition within tissues. Progressive reduction in tracer uptake within the spleen on scintigraphy, and ECV within both the spleen and myocardium on CMR, can be appreciated

over a 24-month follow-up period. NT-proBNP concurrently fell to 102 ng/L. This is the first report of unequivocal regression of visceral ATTR amyloid deposits in the absence of liver transplantation, following combination therapy with patisiran and diflunisal.

^{123}I-labelled SAP scintigraphy is used to *quantify* amyloid burden in visceral organs including the spleen but does not quantify amyloid in the heart or nerves. In this regard, CMR imaging allows cardiac amyloid deposition to be accurately *quantified* through measurement of myocardial ECV (2). Measurement of extra-cardiac amyloid burden by ECV on CMR and by SAP scintigraphy have been shown to be strongly correlated in AL amyloidosis (3). In ATTRv, treatment with liver transplantation has been superseded by drugs such as patisiran, which reduces circulating TTR concentration by up to 90% (4). One study has demonstrated cardiac regression through a reduction in CMR-derived ECV in patients with ATTRv following 12 months of patisiran (5). Since splenic amyloid is unusual in ATTR amyloidosis, SAP scintigraphy is of limited value to monitor amyloid turnover. However, this rare ATTRv amyloidosis-causing F33V (p.Phe53Val) TTR variant with splenic amyloid deposits, trackable by serial SAP scintigraphy and corroborated by measurement of ECV using CMR, provides the first unequivocal evidence of splenic amyloid regression accompanying cardiac regression and clinical benefit following medical therapy.

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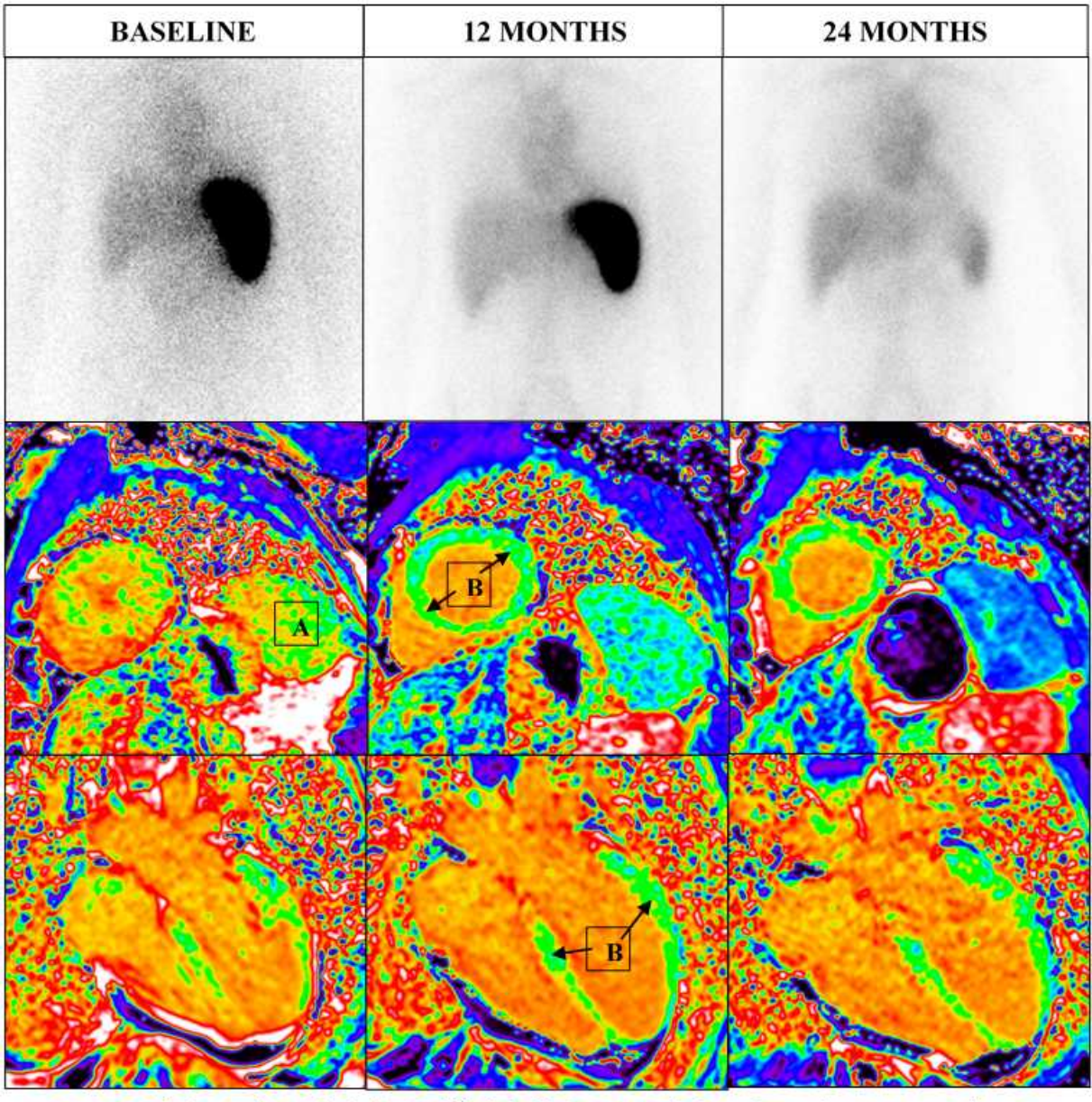

Figure 1. Serial anterior whole body ^{123}I-labelled SAP scintigraphy and MRI scans in a patient receiving patisiran and diflunisal over 2 years. SAP imaging (top-row) shows marked splenic amyloid infiltration at baseline with gradual regression and near-normal splenic signal after 24 months of treatment (top-right). MRI imaging (middle and bottom-row) shows ECV colour maps which represent the degree of amyloid infiltration within the spleen (A) and myocardium (B). At baseline (middle-left), there is marked splenic amyloid infiltration (orange, yellow and green), regressing gradually over time (middle-right; predominantly blue). Cardiac (B) regression can be also be seen.