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Transthyretin cardiac amyloidosis beyond advanced age: two cases in unusually young patient

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a chronic disease characterized by extracellular deposition of misfolded amyloid fibrils in the myocardium [1]. Recent studies indicate that ATTR-CM is underdiagnosed and may be associated with different cardiac diseases including heart failure with preserved ejection fraction, aortic stenosis, and left ventricular (LV) hypertrophy [1,2]. ATTR-CM is typically diagnosed among advanced-age patients, what was confirmed by the first Polish multicenter study on patients with ATTR-CM, where the median age at diagnosis was 76 years (interquartile range: 69–82) [3]. We present two cases involving younger individuals, highlighting that ATTR-CM should also be considered outside the typical age range.

A 51-year-old male with the suspicion of hypertrophic cardiomyopathy, a history of heart failure with reduced ejection fraction, hyperlipidemia, arterial hypertension, hip arthroplasty 15 years prior to hospitalization, and a history of nicotine abuse presented to the Department of Cardiology due to acute decompensated heart failure. The electrocardiogram (ECG) revealed lowered voltage in all limb leads and pseudoinfarct pattern in leads III and aVF (Figure 1A). Transthoracic echocardiography (TTE) has shown a mildly reduced LV ejection fraction of 42% accompanied by a concentric LV hypertrophy, right ventricular hypertrophy, and ground-glass myocardial appearance (Figure 1B). LV global longitudinal strain was reduced (-5.9%) with an apical sparing pattern (Figure 1C). Cardiac magnetic resonance demonstrated abnormal gadolinium kinetics, suggesting myocardial amyloid infiltration.

Second patient, a 56-year-old male with suspected hypertrophic cardiomyopathy and a history of arterial hypertension, singular premature ventricular contractions, benign prostatic hyperplasia and post-Lyme syndrome was referred for advanced cardiovascular evaluation. Moreover, the patient underwent surgery for bilateral carpal tunnel syndrome at the age of 45 and a surgical treatment of a traumatic tear of the left biceps brachii tendon, associated with a rotator cuff injury. The ECG revealed low QRS voltages in the limb leads (Figure 1D). TTE revealed preserved LV systolic function with concomitant LV hypertrophy and grade 3 diastolic dysfunction (Figure 1E). Additionally, right ventricular hypertrophy was present. Furthermore, LV global longitudinal strain was reduced (-13.7%) showing apical sparing pattern (Figure 1F). Cardiac magnetic resonance has shown subendocardial late gadolinium enhancement (Figure 1G).

Both patients had chronically elevated levels of troponin T and N-terminal pro-B-type natriuretic peptide. Additionally, for both cases ^{99m}Tc hydroxymethylene diphosphonate planar scintigraphy complemented by single-photon emission computed tomography imaging was performed according to current recommendations of the Section of Nuclear Medicine of the

Polish Cardiac Society and the Polish Nuclear Medicine Society [4] revealed Perugini grade 3 myocardial uptake, which confirmed the diagnosis of amyloid cardiomyopathy (Figure 1H). In both patients, light-chain cardiac amyloidosis was excluded, as serum free light chain assay, serum and urine protein electrophoresis with immunofixation were negative. For both presented cases, next-generation sequencing of the coding sequences and flanking intronic regions of the TTR gene revealed no pathogenic or likely pathogenic variants and no variants of uncertain significance, confirming the diagnosis of wild-type ATTR-CM

In both patients, guideline-directed therapy for heart failure in the course of cardiac amyloidosis was introduced, and both patients received tafamidis as a targeted treatment of ATTR-CM.

Presented cases emphasize the importance of screening for ATTR-CM if the red flags are present – the younger age should not delay the diagnosis, as delayed initiation of targeted treatment is associated with unfavorable outcomes [1]. Diagnosis of ATTR-CM should include general evaluation, ECG, TTE, laboratory tests with the focus on red flags presented in the European Society of Cardiology guidelines [5], as well as bone scintigraphy, hematological tests and, if needed, CMR and/or endomyocardial biopsy. Proper identification of the red flags may alter the diagnostic pathway and prompt the diagnosis of a specific cause of cardiomyopathy, which remains crucial to improve outcomes.

Article information

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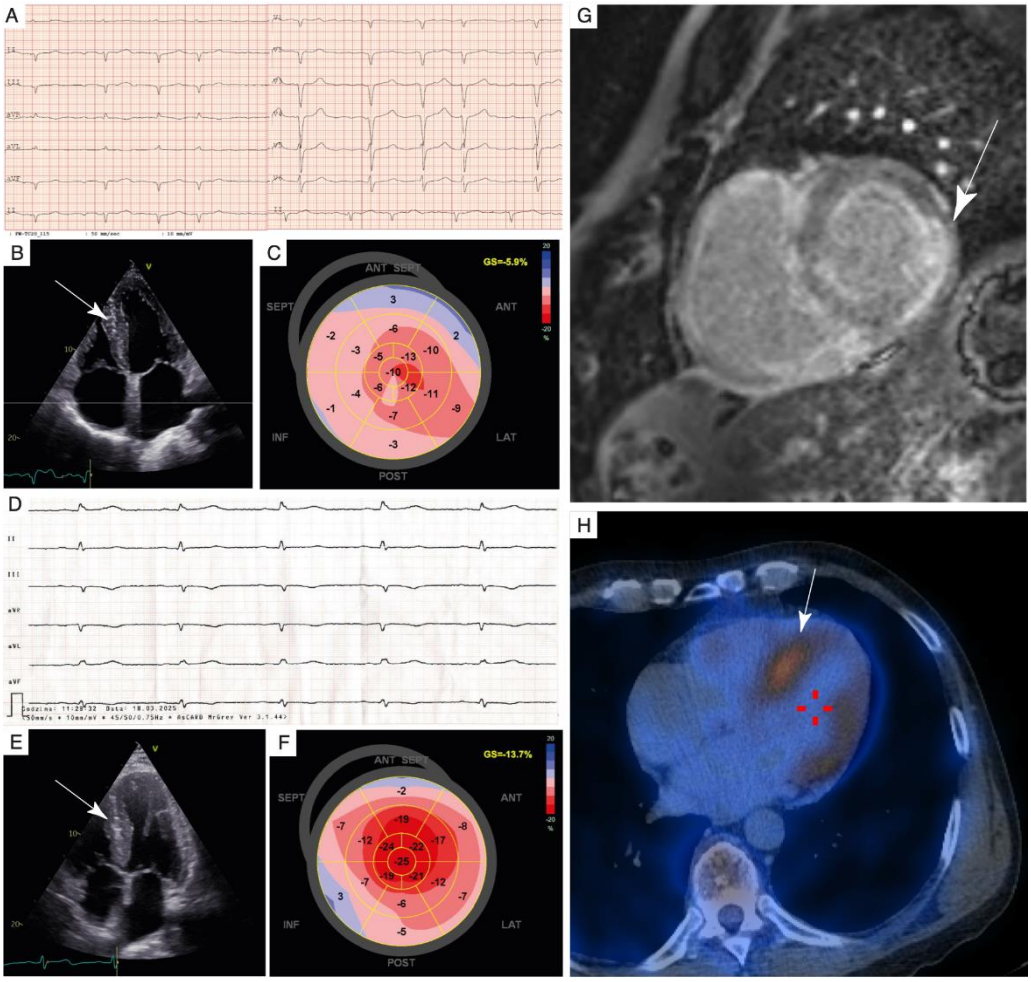

Figure 1 A-C – non-invasive cardiological assessment of the 51-year-old patient; **A** – baseline resting electrocardiogram showing low QRS voltage in all limb leads and pseudoinfarct pattern in leads III and aVF; **B** – transthoracic echocardiography (TTE) revealing thickened interatrial septum (arrow), thickened valves, granular sparkling; **C** – TTE revealing reduced global longitudinal strain (–5.9%) with the apical sparing strain pattern; **D-F** – non-invasive cardiological assessment of the 56-year-old patient; D - baseline resting electrocardiogram showing lowered voltage of QRS complexes in leads I. II, III, aVR, aVL, and aVF; **E** - TTE

revealing thickened interatrial septum (arrow), thickened valves, granular sparkling; **F** – TTE revealing reduced global longitudinal strain (–13.7%) with the apical sparing pattern; **G** – cardiac magnetic resonance of the 56-year-old patient showing subendocardial and intramural (arrow) late gadolinum enhancement; **H** – fusion image of ^{99m}Tc hydroxymethylene diphosphonate scintigraphy and computed tomography of the 51-year old patient revealing elevated heart muscle uptake (arrow)

Short title: Transthyretin cardiac amyloidosis in two unusually young patients