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CASE REPORT
Heart failure

Wild-type transthyretin amyloid cardiomyopathy: expect the unexpected—a case report

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Background General interest and incidence are increasing in wild-type transthyretin amyloidosis (ATTRwt) in recent time. As patient population increases, further knowledge of the management of the frequently encountered interacting cardiac comorbidities is requested to improve treatment of ATTRwt patients.

Case summary A 73-year-old male ATTRwt patient presented to the outpatient clinic (Day 0) with dyspnoea, leg swelling, and palpitations. At diagnosis, 3 years prior to presentation, he exhibited only minor signs of ATTRwt. At Day 0, clinical examination revealed atrial fibrillation and mild peripheral oedema. Anticoagulant and symptomatic treatment with beta-blocker and diuretics was initiated, and the patient was planned for sub-acute direct cardioversion, and the patient was discharged with a Holter monitor to outpatient care. At Day 7, analysis of the monitoring demonstrated spontaneous conversion to sinus rhythm and, unexpectedly, episodes of high-rate self-remittent sustained monomorphic ventricular tachycardia (VT) and frequent ventricular ectopic beats. At Day 8, a sub-acute coronary angiography was performed which revealed a significant proximal left anterior descending artery stenosis which was treated with percutaneous coronary intervention (PCI) and subsequently an internal defibrillator was implanted. Following visits at 1- and 3-month post-PCI at the outpatient clinic revealed no VT and suppression of ventricular ectopic beats.

Discussion The case illustrates some of the frequently encountered cardiac comorbidities (e.g. atrial fibrillation, ventricular arrhythmia, and ischaemic heart disease) associated with ATTRwt. A high level of suspicion is warranted to identify treatable cardiac conditions [atrial fibrillation, atrioventricular (AV) block, and ischaemic heart disease] and to uncover potentially fatal cardiac conditions in patients with ATTRwt.

Keywords Case report • ATTRwt • Ventricular tachycardia • Ischaemic heart disease • Atrial fibrillation • ICD

ESC curriculum 5.3 Atrial fibrillation • 5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators • 6.1 Symptoms and signs of heart failure • 6.5 Cardiomyopathy

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Learning points

- Co-existing cardiac comorbidities (e.g. atrial fibrillation, ventricular arrhythmia, and ischaemic heart disease) are frequent in wild-type transthyretin amyloidosis (ATTRwt) disease.
- Ischaemic heart disease might be exacerbated by ATTRwt and can result in ventricular tachyarrhythmia.
- A high level of clinical suspicion is recommended to identify important cardiac comorbidity and manifestations of ATTRwt (conduction disease, ischaemic heart disease, and atrial fibrillation).

Introduction

Wild-type transthyretin amyloidosis (ATTRwt) is characterized by progressive amyloid myocardial infiltration leading to the development of restrictive cardiomyopathy.[1] The prevalence of ATTRwt increases with age, affects predominantly males, and presents most often with heart failure symptoms, and the disease is associated with increased morbidity and mortality.[2] Non-invasive diagnostics (bone scintigraphy) and greater awareness of ATTRwt have led to an increase in incidence in recent years,[3] in which new pharmacological disease-modifying treatments, i.e. tafamidis, also have become available.[4] Consequently, attention has increased on the clinical management of co-existing cardiac comorbidities among ATTRwt patients whose life expectancy is expected to improve.[5]

In this case report, we present an early disease stage ATTRwt patient and illustrate the emerging issue of managing comorbidities in ATTRwt.

Summary figure

Year	Event
Mar 2016	Surgical intervention: unilateral carpal tunnel syndrome.
Nov 2019	Diagnosis of wild-type transthyretin amyloidosis (ATTRwt) (screening study) (scintigraphy and endomyocardial biopsy positive for ATTRwt).
Day 0 Aug 2022	Current presentation: shortness of breath, palpitation (atrial fibrillation), and mild swelling of lower legs. Treatment with diuretics, beta-blocker, anti-coagulation, and planned sub-acute direct cardioversion. Discharged for outpatient care.
Day 7	Result of 48-h Holter monitoring: paroxysmal atrial fibrillation (2 h). Three episodes of ventricular tachycardia (VT), ~20% ventricular ectopic beats.
Day 8	Coronary angiography: proximal left anterior descending artery stenosis—percutaneous coronary intervention performed simultaneously. Anti-thrombotic and anti-cholesterol treatment added.
Day 13	Implantation of a dual chamber implantable cardioverter defibrillator (DDD-ICD).
Day 42 Sep 2022	At 1 month follow-up: New York Heart Association (NYHA) 1, no VT, and reduction of ventricular ectopy.
Day 104 Nov 2022	Three-month DDD-ICD monitoring: no evidence of VT.

Case presentation

At Day 0 (2022), a 73-year-old male with known ATTRwt presented to the outpatient clinic with shortness of breath, mild swelling of the lower legs, and palpitations with onset within the recent 2 weeks.

Three years prior, he was diagnosed with ATTRwt following participation in a screening trial for transthyretin amyloidosis (ATTR) in patients with previous carpal tunnel surgery.[6] At diagnosis, he was asymptomatic without any history of cardiovascular disease. His electrocardiogram (ECG) showed sinus rhythm with borderline

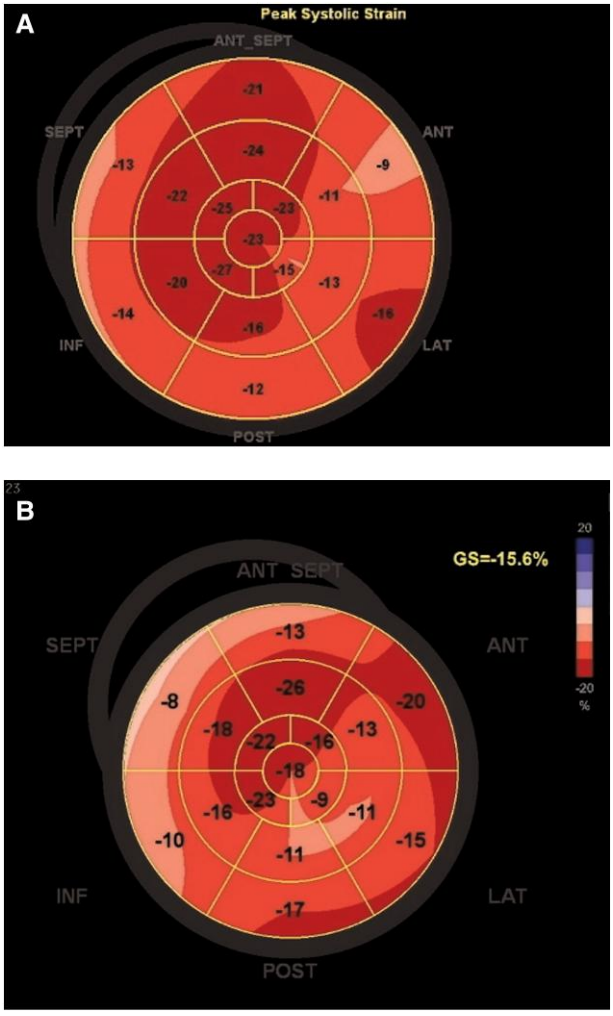

Figure 1 Global longitudinel strain plot at diagnosis (A) and at 3-month follow-up (B) after contact to outpatient clinic.

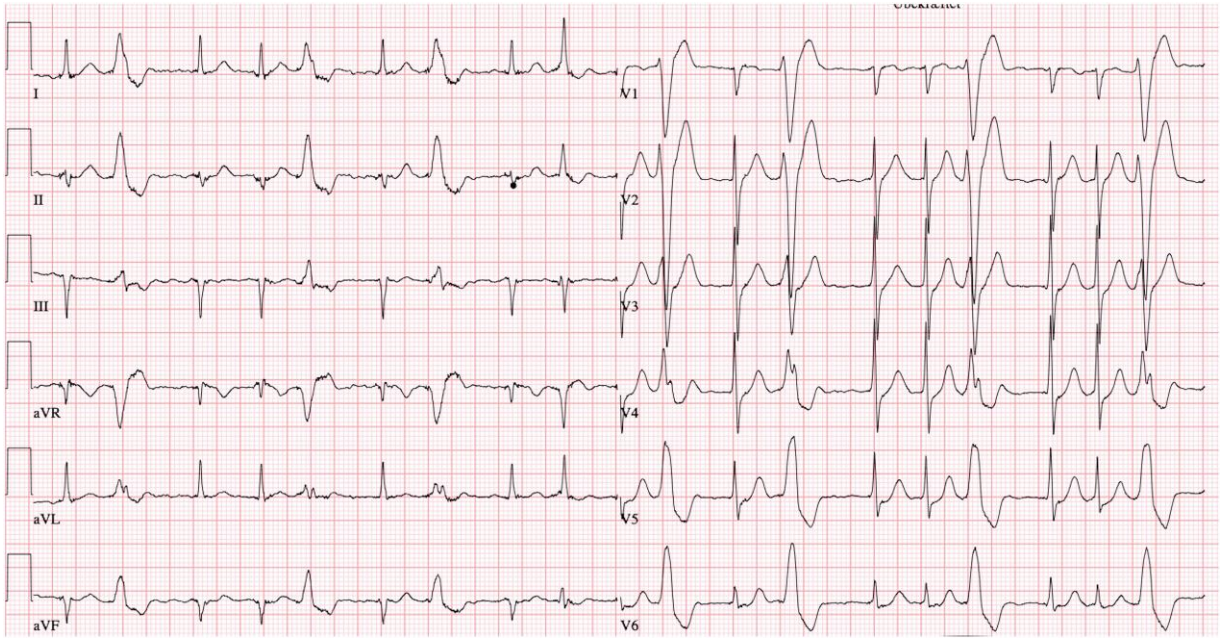

Figure 2 ECG showing atrial fibrillation and frequent monomorphic ventricular ectopy.

low voltage in the limb leads, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was slightly elevated at 390 ng/L (normal < 300 ng/L). Echocardiography demonstrated mild increased left ventricular (LV) wall thickness of 12 mm, LV ejection fraction (LVEF) 70%, and normal LV global longitudinal strain (LVGLS) −18.8% with borderline apical sparring pattern (*Figure 1A* and *Supplementary Material S1A*). The diagnosis of ATTRwt was established by a positive bone scintigraphy—Perugini grade 2 (see *Supplementary Material S2*)—and by endomyocardial biopsy. Genetic testing was negative for variant ATTR. He was subsequently followed untreated for 3 years with stable parameters.

At Day 0, cardiac examination of the patient showed mild leg oedema, no heart murmurs, irregular heart rate of 110 b.p.m., elevated blood pressure (150/80 mmHg), ECG with atrial fibrillation, and frequent ventricular ectopy (*Figure 2*). Echocardiography revealed LVEF 57%, increased wall thickness of 14 mm, and tricuspid regurgitant gradient of 18 mmHg. Serum NT-proBNP was 436 ng/L. No further imaging was ordered. Furosemide (40 mg daily), low dosage of metoprolol (50 mg daily), and dabigatran (150 mg × 2 daily) were initiated immediately. Following discharge, a 48-h Holter monitoring was performed and a direct current cardioversion (DCC) preceded by transoesophageal echocardiography was planned within 3–4 weeks. However, at Day 7, the Holter monitoring analysis revealed that the atrial fibrillation ceased after 2 h and sinus rhythm remained subsequently. Unexpectedly, three episodes of symptomatic (palpitations) monomorphic ventricular tachycardia (VT) was observed with a frequency of 255 b.p.m. and a duration of 40–60 s (*Figure 3*). In addition, ∼20% of total beats were ectopic unifocal ventricular beats. At Day 8, the coronary angiography demonstrated a highly significant stenosis of the proximal left anterior descending artery (LAD) which was treated by direct percutaneous coronary intervention (PCI) (see *Supplementary Material S3A* and *B*). Clopidogrel 75 mg × 1 was added with a treatment duration of 12 months. The unifocal ventricular ectopy vanished immediately after the PCI as observed by in-hospital cardiac telemetry, and the patient was asymptomatic at same-day discharge. At Days 12–14, as a consequence of the characteristics of the monomorphic VT, the ATTRwt diagnosis, and the presence of paroxysmal atrial fibrillation, it was decided by consensus to implant a dual chamber implantable cardioverter defibrillator (DDD-ICD). Tafamidis was not considered as it is not currently approved by Danish Health Authorities.

At 1- and 3-month follow-up (Day 42/110), the patient was well-being and asymptomatic. The ECG (*Figure 4*), a 48-h Holter monitor examination and ICD interrogation revealed persistence of sinus rhythm, no recurrent VT, and a marked reduction of ventricular ectopic beats to <1% of total beats. Echocardiography demonstrated minor subclinical changes with a reduction of LVEF to 60% and LVGLS to −15.6% with local mildly reduced LV strain values in the anterolateral segments (*Figure 1B*) (see *Supplementary Material S1B*). N-terminal prohormone of brain natriuretic peptide was 537 ng/L.

Discussion

The present case demonstrates the plethora of clinical considerations encountered when managing patients with ATTRwt. Firstly, atrial fibrillation is common in ATTRwt with a prevalence of 40–70%.[7] Wild-type transthyretin amyloidosis patients with symptomatic atrial fibrillation are likely to benefit clinically, haemodynamically, and prognostically from maintenance of sinus rhythm.[8] However, high rates of recurrence,[8] safety concerns with DCC (atrial thrombi),[9] and occasional intolerance to amiodarone complicate treatment. In this patient, an initial rhythm control strategy was planned due to symptoms, mild disease stage (National Amyloidosis Centre stage 1), and first-time occurrence of atrial fibrillation. Until DCC, a low dosage of metoprolol was initiated to regulate the atrial fibrillation and to reduce the ventricular ectopy. Nonetheless, beta-blockade should, if possible, be avoided in ATTRwt as the ATTRwt haemodynamics is characterized by a low stroke volume and chronotropic dependency to maintain normal cardiac output.[10]

Disease-modifying treatment, i.e. tafamidis, was not initiated as Danish Health Authorities have not financially approved tafamidis for

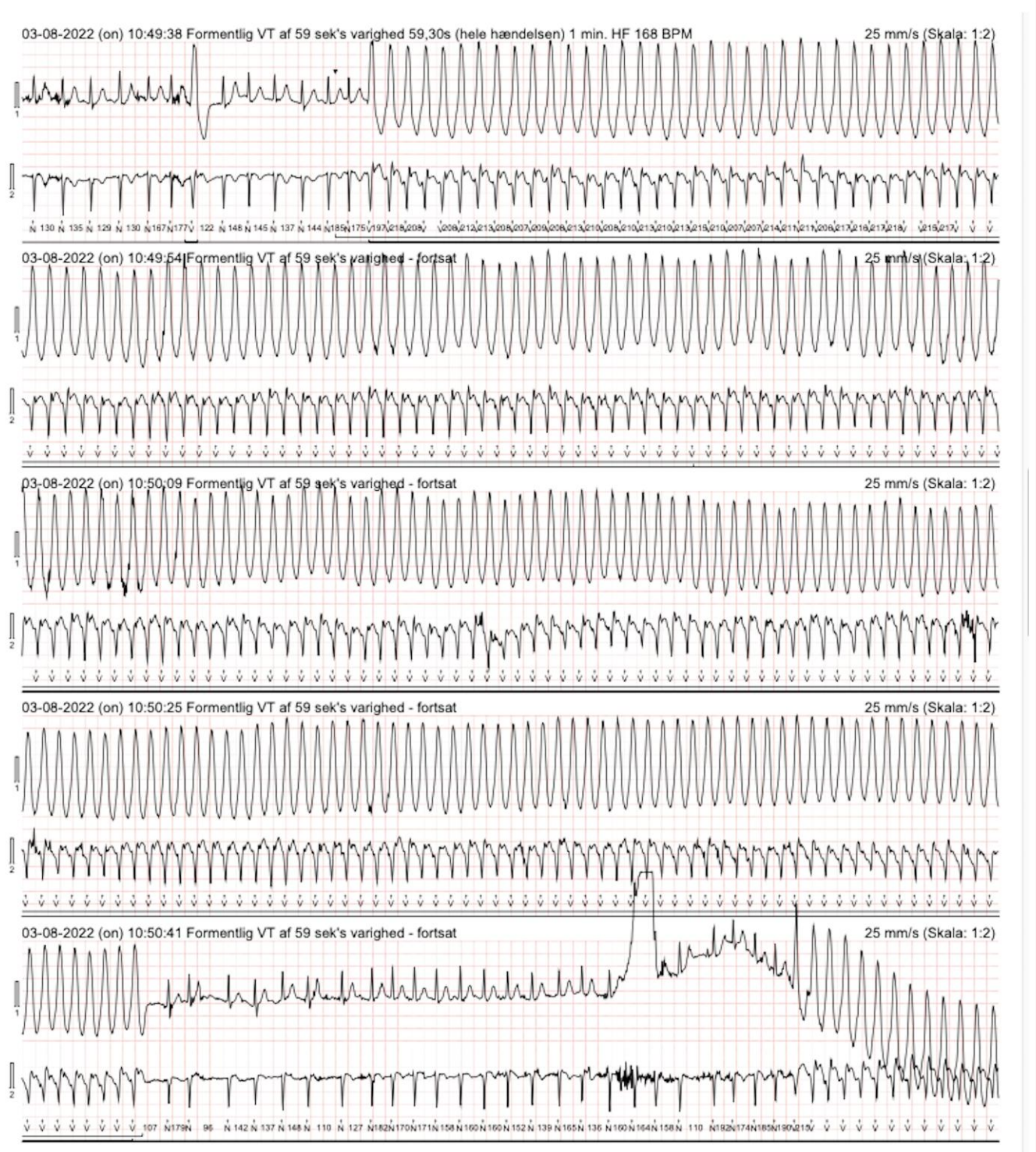

Figure 3 Holter monitoring showing atrial fibrillation interrupted by episodes of ventricular tachycardia.

the treatment of ATTRwt. Irrespectively, this patient would have been an ideal candidate for tafamidis treatment with initiation at a very early disease stage.[4]

Monomorphic VT, which was present in this patient, can be observed in most cardiomyopathies, in patients with scar tissue after myocardial infarction,[11] and can occasionally be observed during acute myocardial ischaemia.[12] The monomorphic VT in this case was likely worsening in chronic myocardial ischaemia caused by the LAD stenosis and a component of intramyocardial ischaemia often seen in patients with ATTRwt cardiomyopathy.[13,14] The interstitial

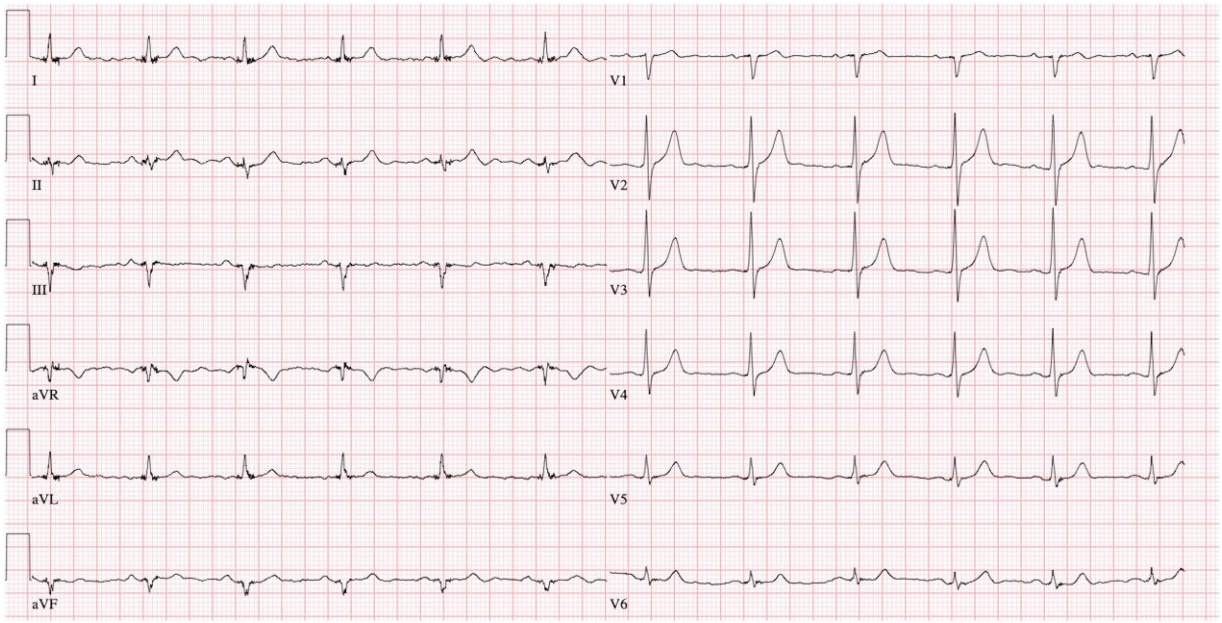

Figure 4 ECG showing sinus rhythm without ventricular ectopy.

amyloid myocardial infiltration is also believed to have potential toxic effects on the myocytes and could theoretically facilitate re-entrant circuits and thus predisposition of ventricular arrhythmias.[1,11] In addition to VT suppression after PCI, the frequent unifocal ventricular ectopy stopped and was not present at follow-up. This indicates that myocardial ischaemia was likely the triggering factor for the unifocal ventricular ectopic activity and sustained VT. In general, ventricular arrhythmias are frequent in ATTRwt, but sustained VT is assumed to be rare.[15] However, the evidence is scarce and inadequate for any definite conclusion.

The effect of ICD therapy as secondary prevention in patients with ATTRwt cardiomyopathy is uncertain as no randomized controlled trials have been performed and are unlikely to be carried out due to the relative rarity of the disease, age characteristics of the patients, and the general prognosis. The indication for ICD therapy in rare diseases is most often evaluated on an individual basis as exemplified with the present case. Even though the LAD lesion was treated by PCI and the VT was subsequently suppressed, it was considered that the cause of the monomorphic VT could be multi-factorial involving the amyloid cardiomyopathy itself. As the present patients was relatively young, in an early disease stage, and without major comorbidities, it was by consensus decided to implant an ICD.

Conclusion

In this case report, we present a patient with ATTRwt with several clinical issues including significant arrhythmias, ischaemic heart disease, and progressive infiltrative cardiomyopathy. The present case illustrates that clinicians need to be aware of the frequently occurring cardiovascular comorbidities and the potential interaction with the ATTRwt cardiomyopathy to ensure appropriate treatment.

Further insights are warranted to address the effect and necessity of various medical treatments and interventions in ATTRwt patients.

Lead author biography

Dr Jens Kæstel Skov has achieved his medical studies at Aarhus University, Denmark, in 2018. He has a particular interest in cardiology and has a 1-year residency at the Cardiology Department of Herning, Denmark, and Cardiology Department at Aarhus University Hospital, Denmark. He is currently working in a PhD programme with a focus on a trial of screening of ATTRwt amyloidosis among patients with atrioventricular (AV) block.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: The patient has consented to the publishing of the case report in line with the COPE best practice guidelines.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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