Transthyretin cardiac amyloidosis: A case report

Abstract:

Introduction : Cardiacamyloidosisis due to theextracellular accumulation of insoluble fibrillarproteinswhichprogressively alter the function of the myocardium. The prognosisdepends on the severity of the cardiacinvolvement. Transthyretincardiacamyloidosis (TTR) is the mostcommon. Itcanbewild-type (ATTRwt), hereditary (ATTRv) or senile (wild TTR). The diagnosis of cardiacamyloidosis has greatlyimprovedin the last decade and isbased on multimodalimaging, mainlyechocardiography and bonescintigraphy**. Case report:** We report the case of a male patient hospitalized for heartfailure due to transthyretincardiacamyloidosis. **Conclusion:** Recognition of thispathologyis essential becausecardiological management isspecific and conventionaltreatments for heartfailurecanbeharmful. Onlyspecifictreatmentscan slow down or stop the infiltration process.

Keywords: Cardiacamyloidosis, diagnostic imaging, bonescintigraphy, TTR-stabilizingtherapy.

Introduction:

Amyloidosis is a systemic disease characterized by the extracellular accumulation of insoluble fibrillar proteins that accumulate and invade tissues, interfering with their normal function. This process is dynamic and active as the fibrils proliferate and divide. Amyloidosis is classified according to the biochemical nature of the amyloid protein involved in the deposition. About twenty proteins can form amyloid fibrils (transthyretin, immunoglobulin light chain, fibrinogen, apo A1, etc...) (1).While more than 30 proteins are known to be responsible for amyloidosis, only 9 can accumulate in the myocardium to cause significant heart disease.

The most common cardiac amyloidosis is transthyretin amyloidosis (2). Transthyretin (TTR) is a protein that is synthesized by the liver in monomeric form. These monomers assemble into tetramers, which carry proteins (e.g. thyroid hormone, vitamin D) into the bloodstream. There are two types of transthyretin amyloidosis (TRTA):

- Wild-type ATTR, formerly known as senile systemic amyloidosis: where the precursor is unmutated TTR (ATTRwt), which occurs almost exclusively as hypertrophic cardiomyopathy (HCM) in men over 50. The cause of this amyloidosis is unknown, but it is associated with ageing. This disease has long been underestimated among cardiac syndromes. It accounts for 13% of heart failure with preserved left ventricular ejection fraction (LVEF) and 16% of aortic stenosis in men undergoing transcatheter aortic valve implantation (TAVI) (2).
- Hereditary ATTR: the familial form in which TTR is mutated (ATTRv, v for variant) (2). Transmission is autosomal dominant. More than 120 pathogenic mutations in the gene encoding TTR have been identified and their prevalence varies according to country and improvements in cardiological diagnosis (3). Tissue damage varies according to the mutation, resulting in different phenotypes: cardiac, neurological or mixed. In a multicentre study, 6% of hypertrophic cardiomyopathies were associated with a TTR gene mutation (4). The Val122Ile mutation is the most common

worldwide, occurring in 3.6% of Afro-Caribbean individuals. The first mutation identified was Val30Met, which is mainly observed in patients of Portuguese origin and leads to the onset of neuropathy at the age of 25-30 years, with a slow but fatal course. The penetrance of these ATTR mutations varies according to geographical origin. Cardiac amyloid infiltration is complicated by thickening of the myocardium, valves and pericardium and conduction disturbances. Initially, cardiac involvement suggests hypertrophic cardiomyopathy (HCM), followed by restrictive cardiomyopathy.

Case report:

A 78 year old manwith a knownmedical history of: diabetes mellitus,ischemic heart disease and hypertrophic cardiomyopathy, under appropriate therapy, was admitted withNYHA class IV dyspnea with orthopnea and increased lower limb volume.

Clinical examination revealed global signs of heart failure :the patient was tachycardic, polypneicwith 90% oxygen saturation, orthopnea, lower limb edema reaching the knee, jugular venous distention and crepitus rales in 1/3 of the 2 lung fields.No friction rubs or heart murmurs were noted.

Hiselecrtrocardiogramshowedsinus rhythmwith a ventricular rate of 75bpm, a low voltage in peripheral leadsandantero-septo-apical R wave abrasionwithout conduction disturbances.Chest x-ray showed bilateral pleural effusion of low abundance without parenchymal abnormalities and a normal cardiac silhouette.

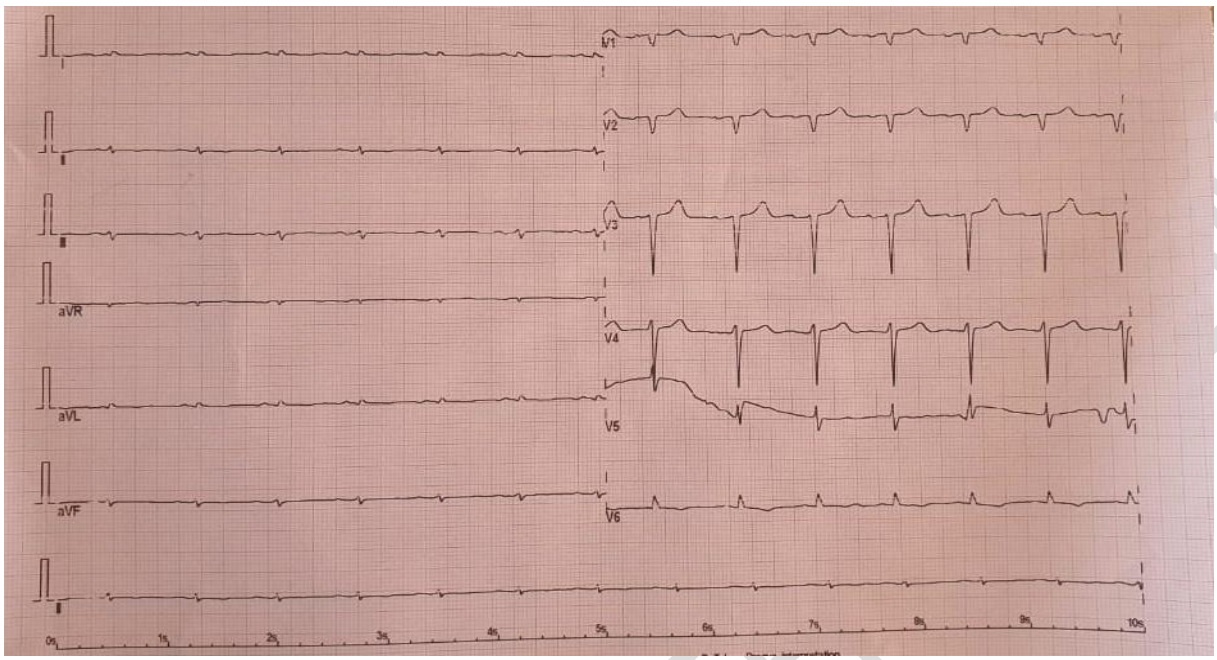
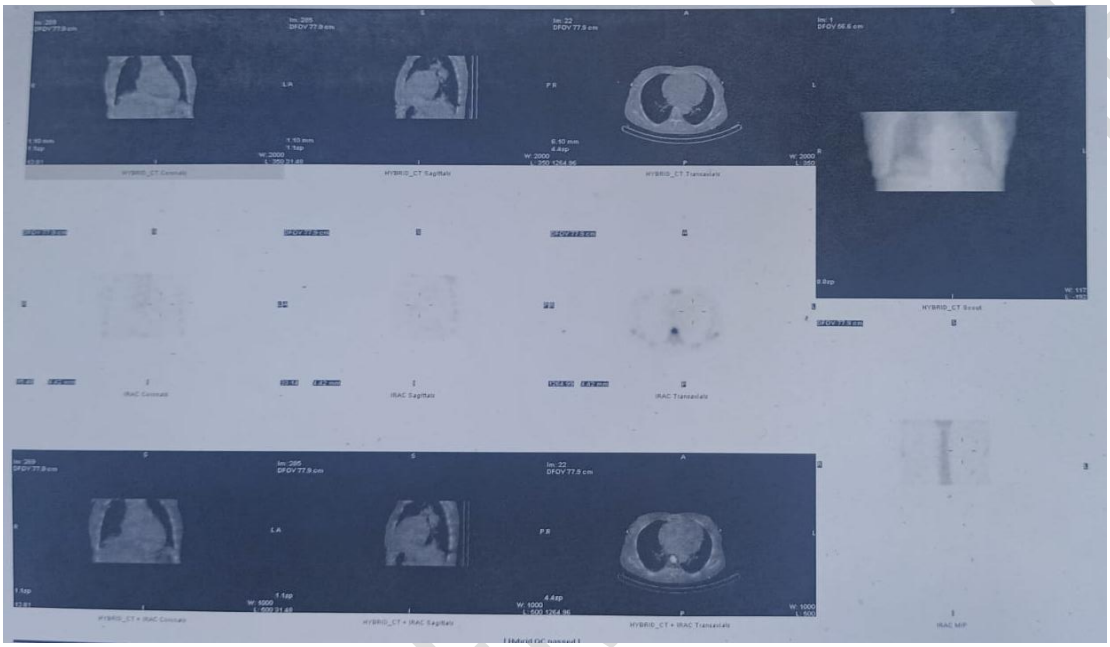


Figure 1: electrocardiogram of our patient revealing sinus rhythm with a ventricular rate of 75bpm, a low voltage in peripheral leads and antero-septo-apical R waveabrasion

Transthoracicechocardiographywas performed and showeda biventricular hypertrophic cardiomyopathy with a symmetric left ventricular wall thickness of 22mm, a scintillating myocardial appearance and a preserved systolic function out of 56%.Thus a spontaneous echo contrast casts doubt on apossible thrombosis.The right ventricle was hypertrophic and slightly dysfunctional , both atria were dilated. Doppler showed a restrictive mitral profileand a grade II tricuspid regurgitationwith a cocardial strain appearance. TTE also showed a pericardial effusion measuring 10mm circumferentially.

The patient underwent medical depletion therapy and a series of investigations. Thehemogram was normal and liver function was preserved. Urine Bence Jones protein was negative. Serum immunoelectrophoresis was normal. Salivary gland biopsy revealed no amyloid deposition.

Cardiac MRI was performed and showed increased T1 mapping with late subendocardial gadolinium enhancement, indicating probable cardiac amyloidosis. A radioisotope was avidly uptaken by the myocardium, corresponding to a grade 3 uptake on Tc-pyrophosphate scintigraphy. **Cardiac amyloidosis was diagnosed, and TTR-stabilizing therapy was initiated.**Unfortunately, our patient died three months after tafamidis treatment.



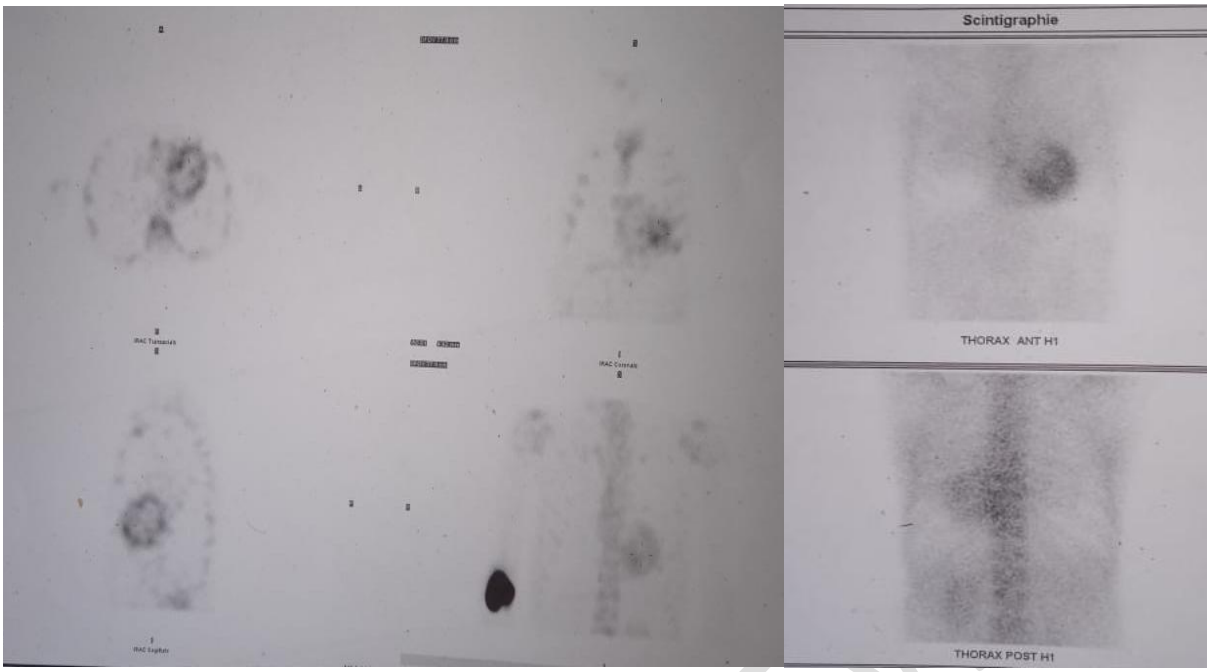


Figure 2: Tc-Pyrophosphate scintigraphy proving a grade 3 uptake

Discussion:

TTR is a liver-synthesized protein normally involved in the transport of the hormone thyroxine and retinol-binding protein.ATTR can be inherited as an autosomal dominant trait caused by pathogenic variants in the TTR gene *(ATTRv) or by the deposition of ATTRwt*(wild-type transthyretin protein), previously called senile cardiac amyloidosis.It can infiltrate other organs, most commonly the autonomic and peripheral nervous systems, but cardiac involvement, when present, determines the prognosis.

Both AL-CA and ATTR-CA lead to diffuse amyloid fibril deposition in the heart causing thickening of both ventricles resulting in a non-dilated ventricle that is stiff and poorly compliant leading to a progressive diastolic filling abnormalities. The atria are universally affected with interatrial septal thickening, followed by poor atrial function and increased rates of atrial fibrillation (ATTR++). The valves are usually thickened, usually with mild to moderate regurgitation. Coronary involvementhas been reported with ischemia and angina while the epicardial coronary arteries remain normal,otherwise systolic function is preserved. Pericardial involvement may result in small pericardial effusions.

Cardiac manifestations are nonspecific and include symptoms of heart failure and/or conduction and rhythm disturbances (flutter and atrial fibrillation). Q waves are often observed on the electrocardiogram, and are related to the amount of amyloid infiltrate (5).

ATTR-CM can be an obscure diagnosis because its presentation can mimic other well-established cardiac problems, most commonly aortic stenosis, hypertrophic cardiomyopathy, and AL amyloidosis. Patients typically present with heart failure but preserved EF with left-sided congestive signs: dyspnea on exertion is common; however, it can also present with more right-sided heart failure symptoms. The first manifestation of CA may be rhythmic with an atrial fibrillation or complete heart block and /or cardioemboliccomplications. Angina with

normal coronary arteriesmay occur, rarely leading to cardiogenic shock due to diffuse ischemia. Low cardiac output may also cause fatigue and weakness, especially on elderly patients. Low to normal blood pressure in a previously hypertensive patient leading to discontinuation or reduction of antihypertensive therapy may be the first sign.

The prognosis of cardiac amyloidosis isprimarily cardiac. The median survival rate is of 50% at 3 years (9).

Extracardiac manifestations are diverse, and mostly occur several years before cardiac manifestations (6). They could help to detect ATTRs earlier (6). They vary according to the type of amyloidosis: carpal tunnel syndrome, deafness (7), rupture of the long biceps tendon, narrow lumbar canal and, more rarely in ATTRv as in AL, periorbital ecchymosis and macroglossia. In ATTRv, neurological damage is predominant in the autonomic nervous system and peripheral nerves, with damage to long-dependent fibers. Involvement of the autonomic nervous system may be prominent (ATTRv) and affect all autonomic functions, leading to severe orthostatic hypotension, gastroparesis responsible for incoercive vomiting and dyskalemia, and disturbances of genitourinary functions. Allof these manifestations severely impact the quality of life of patients(8).

Classic cardiac biomarkers have been shown to be persistently elevated in ATTR-CM and have been incorporated into its staging and prognosis. Serum troponin levels have been found to be persistently elevated in the absence of overt cardiomyopathy. Similarly, pro-B-type natriuretic peptide may be elevated disproportionately to the patient's clinical heart failure.

The ECG can be helpful, showing nonspecificsigns: low voltage, a classic finding for CA,pseudoinfarction pattern with Q waves in the early precordial leads mimicking a previousanteroseptal myocardial infarction,and wide QRS complexes are more common in ATTR, whereas lowvoltage is more common in AL-CA.

Imaging remainsthe cornerstone of noninvasive diagnosis of ATTR-CM. The three modalities that have been shown to be useful in the diagnosisof ATTR-CM are transthoracic echocardiography, cardiovascular magnetic resonance (CMR), and cardiac scintigraphy.

"TTE, apical sparing on strain imaging increased the likelihood ofdiagnosing CA, but with modest sensitivity and specificity: a symmetric left ventricular hypertrophy is common, the ventricles are withusually smaller dimensions than normal, while the atria are dilated with a restrictive filling pattern. Due to the thick and dense myocardium, the classic term "speckled appearance" is often used to describe the myocardium.Pleural and pericardial effusions are not uncommon, although they are often dismissed as trivial in terms of hemodynamic significance.Ejection fraction is usually preserved, but cardiac output is low due to decreased ventricular volume. Apical sparing with the easily recognizable **bull's-eye pattern** on thepolar map can help differentiate CA from other forms of LV hypertrophy suchas hypertension or HCM with good sensitivity and specificity" (12).

MRI T1myocardial mapping shows significantly increased native T1 times.The addition of gadolinium enhancement helps todetect infiltrative cardiomyopathies. The inability to

suppress the myocardial signal (inability for the gadolinium to leave the myocardium) or thepresence of diffuse subendocardial or transmural enhancement suggests of amyloidosis with impressive sensitivity and specificity.

Currently, the only imaging modality that allows accurate diagnosis of the exact type of cardiac amyloidosis is nuclear scintigraphy using bone-avid radiotracers.99mTcPYP myocardial radiotracer uptake is graded by the semiquantitative visual score of cardiac retention compared to rib uptake.

Unlike AL amyloidosis,which has circulating biomarkers (light chains), ATTR-CM has not been shown to have specific biomarkers for which to testfor. Tissue biopsy with histopathology and immunohistochemistry has been used to definitively diagnose amyloidosis. Cardiac amyloidosis is confirmed when an endomyocardial biopsy shows amyloid deposits after Congo red staining, regardless of the degree of left ventricular (LV) wall thickness.It can also be confirmed when amyloid deposits within an extracardiac biopsy are accompanied by either characteristic features of cardiac amyloidosis on echocardiography, in the absence of an alternative cause for increased LV wall thickness, or by characteristic features on cardiac magnetic resonance.Identification of amyloid should be followed by classification of the amyloid fibril protein.

Transthyretingenesequencingisused to diagnose hereditarytransthyretinamyloidosis, and only the absence of a mutation canconfirm the diagnosis of ATTRwtamyloidosis in the presence of ATTR. This test shouldbeperformedsystematicallyin all cases of ATTR, regardless of age, ascardiacATTRvismostcommonlydiagnosedafter the age of 70 (10)(14).

Therapeutic management of heart failure in amyloidosis is aimed at limiting fluid retention by adjusting blood volume (13). Beta-blockers are particularly detrimental in severe forms, due to their negative inotropic, dromotropic and chronotropic effects: in cardiac amyloidosis, cardiac output is essentially dependent on heart rate. The causes of this dependence are a reduction in systolic ejection volume due to thickening of the ventricular walls at the expense of the ventricular cavity, and a reduction in contractility (10).

Anticoagulation is often required due to the high risk of thromboembolic events in patients with cardiac amyloidosis. It is imperative to search for intracardiac thrombus before performing electrical cardioversion, even if the patient has been anticoagulated for a long time, as the presence of a thrombus may contraindicate this procedure (15). Atrial arrhythmias are common in cardiac amyloidosis, and rate control may be difficult. Pacemaker implantation may be useful in some symptomatic patients with marked chronotropic incompetence. As the pathological process is dynamic and evolving, the risk of conduction abnormalities (BAV3, BSA) must be constantly reassessedby monitoring the PR and QRS spaces and their prolongation. Resynchronization can be discussed in cases of preserved LVEF, or even more so if there is a risk, or especially if there is a risk.

“Until recently, treatment of ATTR-CA was aimed at managingsymptoms and disease-related complications. However, novel and experimental therapies are emerging for thetreatment of ATTR-CA wild-type (ATTRwt-CA) and hereditary/variant (ATTRv-CA) are emerging” (11).

Liver transplantation remains the established treatment for variant TTR-related amyloid neuropathy and cardiomyopathy, but small molecule drugs may prove to beeffective alternatives to surgery. ATTR-CA treatment strategies target different steps along the ATTR-CA amyloid production process. ATTR fibrillogenesis, can eitherbereduced using spharmacological agents that bind to the thyroxine binding pockets called:stabilizer drugs, such as **Tafamidis**, like diflunisal, interact with theTTR's thyroxine binding pocket andincreasetetrameric stability. Other treatments aim toreduce or halt amyloid deposition by making less TTR available for dissociation and deposition in the heart and nerves by silencing TTR mRNA translation: Two gene silencer therapies : Parisiran, whichimproves LV basal LS, NT proBNP,and ameliorates abnormal LV geometric patterns; and Inotersen, which improves clinical manifestations. Immunotherapy is also being investigated for the treatment of ATTR-CA .Another class of pharmacological agents aims to disrupt and clear the ATTR amyloid fibrils, but has shown modest results.

Conclusion:

ATTR occurs in up to 14% of patients with heart failure with preserved ejection fraction. The systemic involvement of the disease makes both diagnosis and treatment of ATTR- CA challenging. Considerable progress has been made with therapeutic options that improve the prognosis.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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