Incidental finding of transthyretin myocardial amyloidosis in a patient with neurological symptoms and unexplained skeletal pain on bone scintigraphy using ^{99m}Tc-DPD: A case report

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Abstract

Hereditary transthyretin amyloidosis (hATTR) is considered a rare disease. This is precisely why there are cases of undiagnosed transthyretin amyloidosis, in patients present with restrictive cardiomyopathy, with or without neurological or other symptoms. There are cases of incidental detection of hATTR in patients with cardiac or neurological symptoms using whole-body scintigraphy with diphosphonates. In this paper, we present the accidental detection of hATTR in a 65-year-old patient with neurological and cardiac symptoms, who was referred for skeletal scintigraphy with skeletally avid radiopharmaceuticals due to skeletal pain of unknown origin. Significantly increased uptake of radiopharmaceuticals in the myocardium was observed, corresponding to a Perugini score of 3, with semi-quantification of the heart/contralateral lung fixation ratio (H/CL) of 2.6 in the second hour after radiopharmaceutical application. Ultrasound of the heart was in favor of concentric cardiomyopathy. Due to the high suspicion of hATTR, a genetic test was performed, which showed a pathological mutation of the gene for transthyretin. Hereditary hTTR is probably a more common disease than reported in the literature. Using hATTR detection algorithms and raising awareness of the possible existence of this disease, timely diagnosis using scintigraphy with bone avid radiopharmaceuticals and appropriate therapy can help patients and their close relatives.

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Introduction

Hereditary transthyretin myocardial amyloidosis (hATTR) is considered a rare disease. In recent times, the modern diagnostic approach has detected a greater number of cases than was the case in the earlier period [1]. There are cases of accidental detection of this disease, which indicates the need to raise the awareness of doctors about the possible existence of hATTR.

Case presentation

A 65-year-old male patient was referred for skeletal scintigraphy with technetium-99m-diphosphonates (^{99m}Tc-DPD). The patient has peripheral sensory neuropathy and unexplained pain in the axial skeleton and distal extremities, which was the main reason for referral to skeletal scintigraphy with ^{99m}Tc-DPD. Scintigraphy with ^{99m}Tc-DPD was performed according to a standard protocol that included the whole body modality (Figure 1), targeted static scintigrams of the thorax in anterior and posterior projection (Figure 2), and then single photon emission computed tomography (SPECT) of the myocardial region with reconstruction along the sagittal, coronal and transverse axes, through the myocardium (Figure 3).

Due to the significantly increased fixation of the osteotropic radiopharmaceutical in the myocardium two hours after the application of the radiopharmaceutical, which corresponded to grade 3 according to the Perugini score, quantification was also performed, which included the determination of the H/CL ratio. Heart/contralateral lung fixation ratio two hours after the application took a value of 2.6. With high suspicion of the presence hTTR, the patient was referred for an ultrasound examination of the heart and after that for genetic testing.

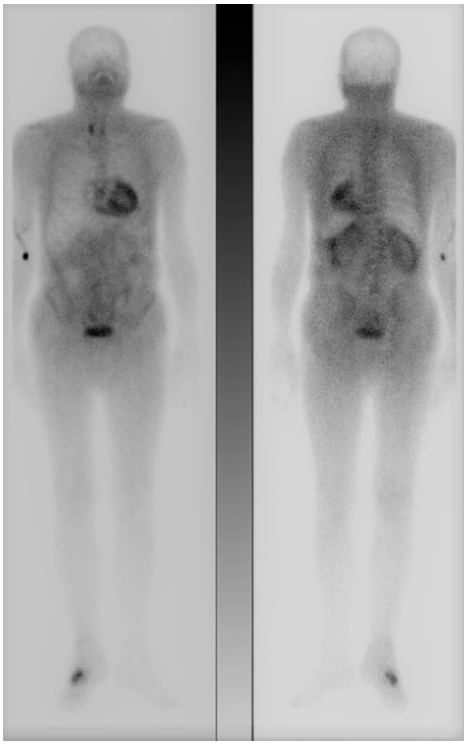

Figure 1. Whole body scintigraphy with ^{99m}Tc-DPD in the anterior and posterior projection. Qualitative assessment corresponding to Perugini score of 3.

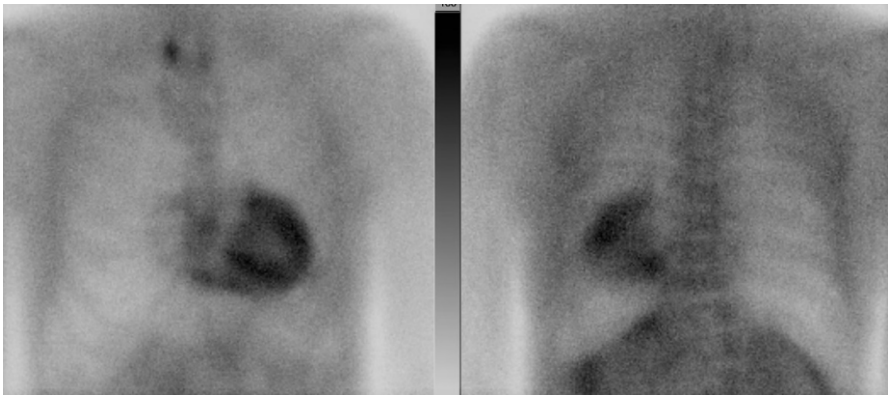

Figure 2. Targeted static scintigrams of the thorax in anterior and posterior projection, with evaluation corresponding to Perugini score 3 and heart/contralateral lung fixation ratio (H/CL ratio) 2.6 two hours after radiopharmaceutical application.

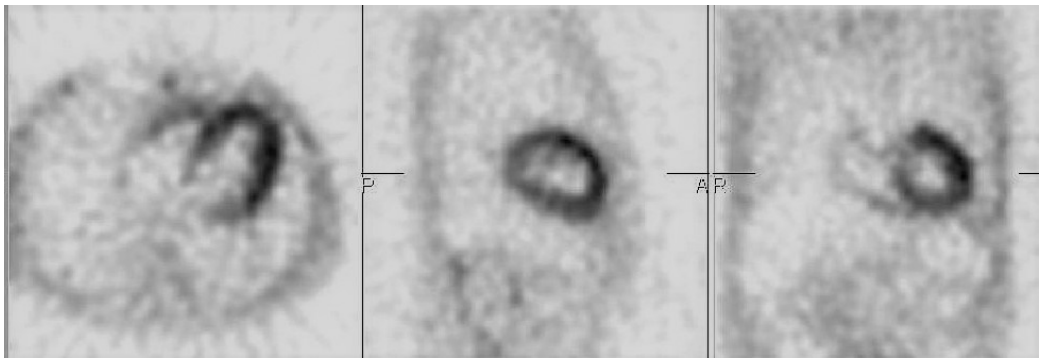

Figure 3. Single photon emission computed tomography reconstruction along the transverse, sagittal, and coronal axes with evident increased fixation of radiopharmaceuticals in the myocardium.

Ultrasound examination of the heart showed pronounced concentric hypertrophy of the left ventricle. Septum thickness of 19mm. A "flashing" of the myocardium was registered (sparkling). The internal diameters of the left ventricle were within normal limits, the mass of the left ventricle was increased, and the left mass index chamber 249gr/m^2 was significantly increased. The global longitudinal strain rate (GLS) of the left ventricle was reduced -10.9%. A picture of reduced mobility of the myocardium was registered with basal and medial levels, and the mobility of the apical part of the left ventricle was preserved. The global contractile function of the left ventricle was at the lower limit of normal. A diastolic filling was impaired and the stroke volume of the left ventricle was reduced. There was mitral insufficiency. The left atrium was dilated. The diastolic function of the left ventricle was impaired according to the type of filling restriction, with a markedly reduced amplitude of the A wave E/A 2.25. The tissue Doppler velocity of the lateral annulus E` 6cm/sec, medial annulus 5cm/sec, the E/E`avg ratio increased to 15.8 and indicated increased left ventricular filling pressure in diastole. The isovolumetric relaxation time of the left ventricle isovolumic relaxation time (IVRT) was shortened by 55msec. The size of the right chamber was increased. There was tricuspid regurgitation with a systolic flow velocity of 2.92m/sec. The pressure in the pulmonary artery was increased: 50mmHg. The inferior vena cava was dilated and inspiratory collapse was weakened. There was a small circular pericardial effusion 1mm behind the posterior wall (Figure 4).

After that, the patient was referred for a genetic examination. The presence of a hATTR gene mutation on chromosome 18 was detected. The inheritance model was autosomal dominant, with the variant NM_000371.3 c.148G>A p.(Val 50Met) Exon: 2/4. Variant classifications, according to American College of Medical Genetics (ACMG) recommendations for classification [2] were used to interpret the obtained results: Pathogenic - class 1; Probably pathogenic - class 2; Variant of undetermined significance - class 3; Probably benign - class 4; Benign - class 5). The obtained result of the genetic test corresponded to the missense pathogenic variant.

As it was a case of hereditary amyloidosis, the patient's children were subjected to genetic testing for the existence of a transthyretin gene mutation. The existence of a genetic mutation of the mentioned gene was detected in both daughters of the patient, which is why both of them were included in the protocol for cardiological and neurological monitoring, so that in the event of the appearance of clinical symptoms and signs, therapy for transthyretin amyloidosis would be included in time.

The patient signed an informed consent for the publication of the obtained results.

All diagnostic studies were performed according to valid protocols and according to the principles of the Declaration of Helsinki.

Discussion

Cardiomyopathy caused by hereditary transthyretin amyloidosis is considered a rare disease. However, recent studies show the presence of gene mutation in a more significant part of the population than was thought until recently [3]. Transthyretin is a protein transporter for thyroxine and is mostly synthesized in the liver [4]. It consists of tetramers whose misfolding and precipitation practically create the condition for causing transthyretin cardiomyopathy [5]. The gene for transthyretin is located on chromosome 18, and the most common mutation is called Val30Met, which is a replacement of valine at position 30 with methionine. Misfolding and aggregation of transthyretin in the myocardium result in a rigid, less mobile myocardium, with the subsequent onset of restrictive cardiomyopathy.

Several reasons make the correct diagnosis of hATTR difficult. Heart weakness, which is one of the main signs of hATTR, is mostly associated with other diseases, such as hypertensive cardiac cardiomyopathy. At the same time, most doctors are not familiar with the algorithm for diagnosing transthyretin

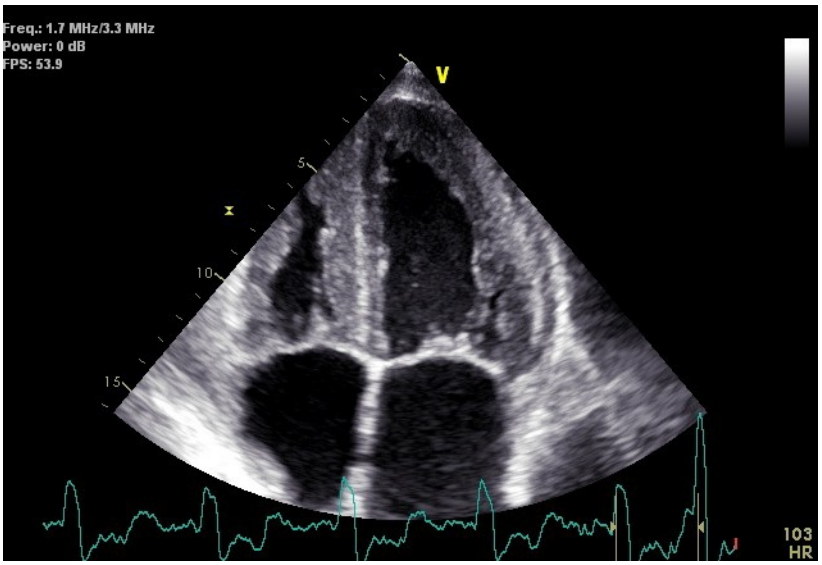

Figure 4. An ultrasound examination of the heart.

amyloidosis. Increased left ventricular myocardial thickness associated with low voltage is one of the signs for the existence of hATTR, but there are data that this sign is positive in only 25%-40% of patients with hATTR [6]. Deformation of the heart detected by ultrasound examination shows significant accuracy in the diagnosis of hATTR, especially in the presence of reduced longitudinal strain. The occurrence of the so-called sparing of the apex was recorded [7], where there is a reduction of strain in the middle and basal parts of the myocardium of the left heart chamber, while the apical parts show preservation of strain [8]. Cardiac magnetic resonance imaging shows progress in differentiating hATTR cardiomyopathy (hATTR - CM) from other cardiac diseases using T1-enhanced mapping relative to cardiomyopathy of other etiologies [9].

Myocardial biopsy and congo red staining of histological preparations remain the gold standard for the diagnosis of hATTR heart disease. However, myocardial biopsy is an invasive method and as such is actually the last line of diagnosis for hATTR CM [10]. Sparing biopsies for detecting hTTR such as adipose tissue biopsies did not show high accuracy in detecting amyloid deposition in hATTR and the accuracy of such biopsies in for example wild-type hATTR - CM showed values of only 15% [11].

The only imaging modality that achieves high accuracy in detecting the presence of hATTR-CM is a scintigraphic examination using bone-seeking radiopharmaceuticals. In Europe, there is a choice of three different osteotropic radiopharmaceuticals that are labeled with ^{99m}Tc. Technetium-99m-pyrophospate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxylic acid (DPD) and ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) [12].

The exact mechanism of biodistribution of these radiopharmaceuticals and their elevated deposition in the myocardium in the presence of hATTR - CM is not fully known, but it is assumed to occur due to the presence of microcalcifications in the myocardium, which is affected by amyloid deposition in the heart muscle in the presence hATTR - CM [13]. The use of scintigraphic methods of detection of hATTR - CM must be carried out according to certain algorithms, for several reasons.

The results of the scintigraphic study, regardless of the level of radiopharmaceutical uptake, cannot rule out the existence of light chain amyloidosis. Therefore, it is necessary to always detect monoclonal chains in serum and urine. Light chain amyloidosis cannot be ruled out without a biopsy, not necessarily of the myocardium, but for example of the bone marrow, so in the case of a positive scintigraphic finding, it is necessary to carry out the aforementioned diagnostics to rule out the existence of light chain amyloidosis. Adherence to the performance algorithm also implies the interpretation of scintigraphic findings not only from early scans, but from scintigrams performed two hours after radiopharmaceutical application because the blood pool on early scans can mimic the existence of Perugini grade 1 or even 2. In some cases, it is necessary to perform a SPECT study precisely because of the correct detection of increased uptake of radiopharmaceuticals by the myocardium in relation to the blood pool or soft tissues.

In addition to checking scintigraphic findings, it is possible to perform quantification with diphosphonate radiopharmaceuticals and not only with pyrophosphate, all in order to confirm the existence of increased uptake by the myocardium due to the presence of hATTR - CM [14].

In conclusion, transthyretin amyloidosis of the myocardium is probably much more common than is commonly believed in the population of patients with cardiomyopathies. By following the algorithms for recognizing symptoms and clinical signs, i.e. the correct use of scintigraphy with bone-seeking radiopharmaceuticals, it is possible to timely detect transthyretin cardiomyopathy, whether it is hereditary transthyretin amyloidosis or wild-type amyloidosis. With this approach in the era of accepted therapies for transthyretin amyloidosis, it is possible to provide significant help to the patients and their heirs if it is a question of the hereditary type of transthyretin amyloidosis.

Bibliography

1. Aimo A, Merlo M, Porcari A et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail* 2022; 24(12): 2342-51.
2. Richards S, Aziz N, Bale S et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17(5): 405-24.
3. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med* 2017; 19: 733-42.
4. Kelly JW, Colon W, Lai Z et al. Transthyretin quaternary and tertiary structural changes facilitate misassembly into amyloid. *Adv Protein Chem* 1997; 50: 161-81.
5. Westermark P, Sletten K, Johansson B, Cornwell GG. Fibril In Senile Systemic Amyloidosis Is Derived From Normal Transthyretin. *Proc Natl Acad Sci USA* 1990; 87: 2843-5.
6. Rapezzi C, Merlini G, Quarta CC et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation* 2009; 120: 1203-12.
7. Kiotsekoglou A, Saha SK, Nanda NC, Lindqvist P. Echocardiographic diagnosis of cardiac amyloidosis: Does the masquerader require only a "cherry on top"? *Echocardiography* 2020; 37(11): 1713-5.
8. Pagourelias ED, Mirea O, Duchenne J et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. *Circ Cardiovasc Imaging* 2017; 10: e005588.
9. Martinez-Naharro A, Treibel TA, Abdel-Gadir A et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. *J Am Coll Cardiol* 2017; 70: 466-77.
10. Pellikka PA, Holmes DR Jr., Edwards WD et al. Endomyocardial biopsy in 30 patients with primary amyloidosis and suspected cardiac involvement. *Arch Intern Med* 1988; 148: 662-6.
11. Bowen K, Shah N, Lewin M. AL-Amyloidosis Presenting with Negative Congo Red Staining in the Setting of High Clinical Suspicion: A Case Report. *Case Rep Nephrol* 2012; 2012: 593460.
12. Li W, Uppal D, Wang YC et al. Nuclear Imaging for the Diagnosis of Cardiac Amyloidosis in 2021. *Diagnostics (Basel)* 2021; 11(6): 996.
13. Stats MA, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. *Cardiovasc Pathol* 2016; 25: 413-7.
14. Hutt DF, Fontana M, Burniston M, et al. Prognostic utility of the Perugini grading of ^{99m}Tc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017; 18: 1344-50.