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CASE REPORT

Florbetaben PET for early and non-invasive diagnosis of light chain amyloidosis: a case report and brief review of the literature

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Abstract
Light chain amyloidosis is a hematological disease requiring rapid diagnosis and urgent therapeutic intervention. The confirmation of the clinical suspicion demands invasive methods, in order to demonstrate histological involvement of organs. Substantial efforts are required especially for cardiac localization, because of mimicking conditions and non-specific symptoms. Florbetaben PET is an emerging powerful tool for early and non-invasive diagnosis and for detection of atypical sites of deposits. The present paper reports the case of a 72-year-old man diagnosed with light chain amyloidosis with cardiac and thyroid involvement early identified through this promising imaging technique.

Keywords Light chain amyloidosis · Florbetaben PET · Systemic amyloidosis · TTR amyloidosis · Early diagnosis

Introduction

Amyloidosis is a rare protein misfolding disorder due to extracellular deposition of amyloid inducing progressive organ failure. Commonly target organs are the heart, kidneys, nervous system, liver and gastrointestinal tract; however, all organs can be involved [1].

The most frequent disorders which lead to cardiac amyloidosis (CA) are immunoglobulin- derived light chains amyloidosis (AL-amyloidosis) and transthyretin amyloidosis (TTR- amyloidosis); both can cause systemic disease [2].

CA caused by both these entities may lead to progressive heart failure with preserved ejection fraction due to restrictive cardiomyopathy. Since early clinical symptoms are nonspecific, CA is frequently missed or misdiagnosed. However, early diagnosis of AL- amyloidosis is imperative to improve the outcome: without intervention, median survival from the clinical onset is about 6 months [1].

Identify and differentiate CA is crucial because therapeutic options and prognosis between AL and ATTR are different and in view of emerging treatment opportunities [3].

While the diagnostic gold standard for CA remains endomyocardial biopsy, this invasive manoeuvre is not required if amyloid is confirmed in another organ or if cardiac amyloid involvement can be determined using an imaging method [4].

In this regard, Gillmore at al. stated that bone scintigraphy enables the diagnosis of cardiac ATTR-amyloidosis to be made reliably without the need for histology in patients who do not have a monoclonal gammopathy [5].

About the non-invasive identification of cardiac AL-amyloidosis, instead, nuclear techniques like 18 F-Florbetaben PET are emerging as powerful tools. Fluorine 18 [18 F]-Florbetaben is a 18 F-labeled stilbene derivative which has a high binding affinity to brain beta amyloid and shows promise to identify and differentiate among cardiac amyloid disease entities [6].

We report a case of a patient with an initial diagnosis of MGUS who subsequently developed AL-amyloidosis with cardiac and extra cardiac localizations and his diagnostic pathway, which includes an innovative imaging methodic like [18 F]-florbetaben PET/CT.

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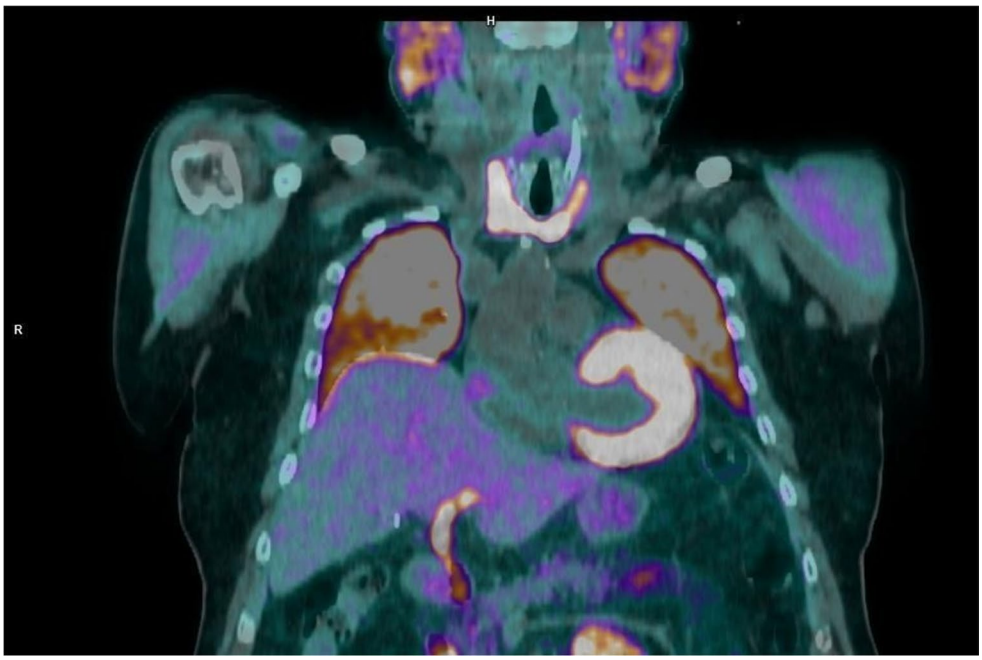


Fig. 1 [18 F]-florbetaben PET/CT scan (November 2022) shows intense myocardial and thyroid uptake

Case presentation

This is a case of a 72-year-old male of Caucasian heritage who was followed at Hematology Division, Pisa University Hospital since 2012.

He was initially diagnosed with monoclonal gammopathy of undetermined significance (MGUS) IgG lambda in 2012, when he underwent bone marrow biopsy that showed 8% plasma cell infiltration. Laboratory findings at diagnosis showed monoclonal IgG lambda paraprotein level of 0,8 g/dl, normal levels of hemoglobin, creatinine, calcium, NT-proBNP and lactate dehydrogenase. Serum free light assay was not available at presentation.

Afterwards, periodic follow up with clinical evaluation on an annual basis and biannual laboratory tests were conducted, with substantial stability of the hematologic condition for about 10 years.

In September 2022, during a routine cardiology evaluation, an echocardiography was performed, which documented preserved systolic biventricular function and left ventricular hypertrophy, more evident within the interventricular septum and the inferior wall.

In November 2022, under suspicion of systemic infiltrative disease, he underwent a further cardiologic evaluation, which confirmed left ventricular hypertrophy, with IVS 16 mm at echocardiography evaluation. After that, he was referred to the Nuclear Medicine Unit to undergo a [18 F]-florbetaben PET/CT (Fig. 1), which documented intense myocardial accumulation of the radio-pharmaceutical in the left ventricle (SUV medium 8,3) with involvement of the free wall of the right ventricle and atrial walls bilaterally, diffuse thyroid and extraocular muscles uptake, findings suggestive for systemic AL amyloidosis with cardiac involvement. Moreover, bone scintigraphy was performed, with negative results for ATTR. In view of the medical history and the thyroid uptake at PET Florbetaben, a complete thyroid evaluation with FNAB/FNAC was accomplished, with positive Congo Red stain indicative of thyroid amyloidosis.

In March 2023 periumbilical fat biopsy was performed to confirm the diagnosis of AL amyloidosis, however Congo Red stain resulted negative. Therefore, to confirm heart involvement, patient underwent cardiac magnetic resonance, confirming septal hypertrophy (max 15 mm) and nuanced subendocardial enhancement of the basal segments of the left ventricle, associated with increased values of native T1 and ECV, and subsequent confirmatory endomyocardial biopsy. It revealed amyloid deposits stained with Congo Red with apple-green birefringence under polarized light. Laboratory findings showed NT- proBNP 2446 pg/ml, HS troponin-T 40,94 ng/l, dFLC 214,61 mg/dl.

In June 2023 bone marrow aspiration revealed 6% plasma cells with abnormal flow cytometry and light chain restrictions lambda.

Based on these investigations, the diagnosis of AL-amyloidosis with cardiac involvement stage 4 Revised Mayo 2012, 3 A Mayo 2004, NYHA class II was made.

In August 2023 the patient was enrolled in a research protocol and started therapy with monoclonal antibody anti-amyloid fibrils, in addition to the standard of care DaraCyBorDex regimen, which consists of a combination of daratumumab plus bortezomib plus cyclophosphamide, and dexamethasone, which was still ongoing at the time of this report.

Discussion

There is increasing interest to develop PET tracers able to identify amyloid deposits, to differentiate between subtypes of cardiac amyloidosis and to quantify the disease burden and the response to treatment [4].

18 F-florbetaben is a stilbene derivative with high binding affinity to brain amyloid beta pleated sheets that was studied first in patients with Alzheimer disease; however, there are evidence in literature on its application for extracerebral amyloid involvement [7].

In CA, it was first studied by Law et al. in 14 patients with both ATTR and AL CA and control subjects with hypertensive heart disease. The authors found diffusely increased myocardial radiotracer uptake in all AL and ATTR patients and no radiotracer uptake in the control subjects when using a cutoff of 40% of retention, suggesting a potential role of this tracer in differentiating between CA and other conditions leading to left ventricular hypertrophy. 18F- Florbetaben did not readily differentiate between AL and ATTR-amyloidosis, however a higher myocardial SUV variability was noted for AL cases compared to ATTR [4, 8].

In another study, which involved 9 patients with suspected CA AL, Baratto et al. investigated the potential role of 18 F-Florbetaben PET/MRI imaging in the diagnosis of CA and detection of other sites of involvement. In this case series, abnormal PET-Florbetaben accumulation was noted on delayed whole-body imaging in extracardiac sites of amyloid involvement, like bone marrow, stomach, brain, salivary glands, tongue, spleen, skeletal muscles, ocular muscles, thyroid, pleura, kidneys and lungs. These findings suggest that this imaging technique is a promising tool for detecting systemic amyloid deposition and may provide information about organs involved by disease, for both histological examination and treatment [9].

Furthermore, in a study by Kircher et al., 18 F-Florbetaben PET/CT imaging was evaluated in comparison to more established imaging modalities such as echocardiography, CMR and DPD scintigraphy in detecting CA. Cardiac involvement was identified both visually and by quantitative analysis, including calculation of myocardial tracer retention (MTR). This study found that different subtypes of amyloid (AL, ATTR, AA) had different retention patterns, with AL being the highest, in line with previous results obtained by Law et al. MTR correlated with both morphologic and functional parameters measured by CMR and echocardiography, but not with cardiac biomarkers. In 4/22 patients a follow up PET/CT was performed after treatment, which showed changes in tracer retention correlating with treatment response.

18 F-Florbetaben PET/CT may be also able to detect CA at early stage and earlier than other techniques, as showed by the follow up of the only patient (#17, AL-amyloidosis) with discordant imaging results at baseline: while both CMR and echo were negative, 18 F- Florbetaben PET was suggestive of myocardial involvement. Over the next 15 months, the patients developed heart failure and follow up PET showed higher MTR compared to baseline [10].

Recently, Genovesi et al. conducted a study that involved 40 patients with biopsy-proven diagnoses of CA (20 AL, 20 ATTR) and 20 patients with initial suspicion of CA, but later diagnosed with non-CA pathology. They underwent a cardiac PET/CT scan with a 60-minute dynamic 18 F-Florbetaben acquisition in conjunction with 4 additional static scans at 5,30,50 and 110 min after radiotracer injection. Qualitative visual analysis showed intense early cardiac uptake in all subsets; patients with AL displayed high ad persistent uptake in all static scans, whereas both ATTR and NCA revealed a continuous decrease after the early 5 min scan. These observations were in accordance with the results of semiquantitative analysis, which demonstrated higher mean standardized uptake value (SUV mean) in patients with AL over the whole acquisition period compared to a progressive and significant decrease in TTR and in patients with NCA, respectively. These data show that 18 F- Florbetaben seems to have a type-specific amyloid binding-affinity to AL that leads to a more persistent uptake and less wash-out in comparison with ATTR and NCA [3, 6].

The presented case shows intense myocardial accumulation of the radio-pharmaceutical and subsequent histological demonstration of cardiac involvement in systemic AL- amyloidosis. Moreover, 18 F-Florbetaben PET reveals other atypical sites of involvement like thyroid and extraocular muscles, which are uncommonly involved organs. Diffuse thyroid uptake was subsequently deepened by FNAB/FNAC procedure, with positive Congo Red stain indicative of thyroid amyloidosis.

Conclusions

18 F-Florbetaben PET/CT is an innovative, non-invasive imaging technique which can distinguish between cardiac amyloidosis and other mimicking conditions and may differentiate CA subtypes (e.g. ATTR and AL-amyloidosis). This technique may also be able to identify CA at very early stage and even earlier than CMR and echocardiography.

In addition, it may be a promising tool for identifying systemic amyloid deposits, even in atypical locations (e.g. thyroid).

In closing, 18 F-Florbetaben PET/CT may acquire a central role in the diagnostic process of patients with suspect AL-amyloidosis and may be useful in early diagnosis, which in AL- amyloidosis is still often delayed.

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Declarations

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Competing interests The authors declare no competing interests.

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