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RESEARCH LETTER

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[18F]-florbetaben PET/CT is sensitive for cardiac AL amyloidosis

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1 | INTRODUCTION

Immunoglobulin light chain amyloidosis (AL) is a haematological disease characterized by a clonal population of plasma cells that produces monoclonal light chains, either kappa or lambda, and extracellular deposition of amyloid insoluble fibrils, deriving from misfolded proteins, assembled in beta-pleated sheets. The insoluble protein deposits may interfere with the functions of several target organs, the most frequently affected being heart, kidney, liver and peripheral nervous system. Organ involvement could be unknown for several years before diagnosis, due to the asymptomatic deposition until organ dysfunction or, in poor prognosis cases, organ failure and that causes the short median survival after diagnosis (median 3 years).[1,2]

In the last years, different techniques have been introduced to detect earlier amyloid deposition, both directly on the tissue, like Congo Red staining,[3] immunochemistry, electronic microscopy, mass spectrometry on periumbilical fat biopsy or on tissues involved, and, indirectly, by cardiac imaging, namely echocardiography, MRI or PET/TC.[4]

Cardiac involvement in amyloidosis is a major determinant of clinical presentation and may be present in primary immunoglobulin light chain-derived amyloidosis (AL) and transthyretin-related amyloidosis (ATTR) and may cause heart failure with frequently delayed diagnosis, since specific early signs or symptoms are missing and often differential diagnosis between ATTR and AL amyloidosis is difficult. Concerning ATTR, sensitive diagnostic tool, as diphosphonate bone tracer.

Scintigraphy,[5] has been recently introduced, instead of no imaging approach is as accurate in evaluate AL amyloidosis. Scintigraphy with diphosphonates, in fact, is currently recommended as a cornerstone examination in patients with suspected CA (cardiac amyloidosis): intense cardiac uptake without biohumoral evidence of monoclonal component is diagnostic for ATTR, whereas other tests including cardiac magnetic resonance and histological amyloid confirmation

are required in patients with no or mild uptake, as well as in patients with monoclonal component.

Referring to AL, cardiac ultrasound and circulating biomarkers are currently with the testing of NT-proBNP,[6] troponins, free light chains,[7] 24hs proteinuria and creatinine, may raise the clinical suspicion of AL amyloidosis.[8] Actually, the most relevant biochemical value, correlated to AL suspect, seems to be represented by free light chains, but often endomyocardial biopsy remains the only option to obtain a correct diagnosis of AL amyloidosis.

2 | MATERIALS AND METHODS

In this retrospective study, we aimed to explore the sensitivity of a new imaging technique, [18F]-Florbetaben PET/CT respect to common blood tests or periumbilical fat biopsy, cardiac biopsy or other tissues biopsy in a cohort of 33 patients, referred to the Division of Cardiovascular Medicine of the Fondazione Monasterio and Haematology Unit in University of Pisa from July 2016 to January 2023 (Table 1). All patients had an established diagnosis of cardiac AL amyloidosis, demonstrated by cardiac biopsy or peripheral organ biopsy associated to supportive findings at Cardiac Ultrasound or MRI. Among the whole population, 42% of patients presented also renal impairment and 30% other organ involvement (e.g. thyroid, liver, lung, skin, bowel).

[18F]-Florbetaben is a 18F-labelled polyethylene glycol stilbene derivative with high affinity and specificity for beta-amyloid plaques, approved in March 2014, to estimate β amyloid brain neuritic plaque density in adult patients affected by cognitive impairment who are being evaluated for Alzheimer's disease or other causes of cognitive decline.

A pilot study, in 2016, explore the utility of this tracer in amyloidosis. Law et al. enrolled 14 patients (5 AL, 5 TTR vs 4 patients in the control group) and demonstrated higher retention index in AL patients compared with the ATTR.[9]

Based on our previous demonstration,[10] published in 2021, a delayed static scan could differentiate AL to ATTR amyloidosis, due to the higher florbetaben uptake in the first one.

[18F]-Florbetaben PET/CT in our cohort was performed by dynamic reconstruction from list-mode scan (60 minutes) during the intravenous infusion of 300 MBq/mL of [18F]-Florbetaben followed by a saline flush of 10 mL (1 mL/s); the patients mean whole body exposure due to the radiopharmaceutical was 5.8 mSv. The patients then underwent a delayed static cardiac scan 110 min after [18F]-florbetaben injection.[10]

TABLE 1 Clinical, histological and biohumoral characteristics of patients with AL Amyloidosis underwent to [18F]-Florbetaben PET/CT.

	AL patients ($n = 33$)
Male, *n*	22 (33)
Age, years	65.2 (41–85)
Multiple myeloma associated to AL amyloidosis, *n*	20 (33)
Creatinine, mg/dL	1.49 (0.54–7.13)
NT-proBNP, ng/L	7944 (537–70,000)
hs-Troponin T, ng/L	111,76 (25–203)
FLC ratio	443.89 (1.18–11,700)
24 h proteinuria, mg/dL	2595 (119–9696)
AL positive cardiac biopsy, *n*	17 (33)
AL positive in periumbilical fat, *n*	18 (33)
AL positive bone marrow biopsy, *n*	10 (33)
AL positive other tissues biopsy, *n*	8 (33)
[18F]-Florbetaben PET at diagnosis, *n*	19 (33)
Previous therapies lines before PET, *n*	0.6 (0–5)
Therapy after PET:	
DaraCyBorDex, *n*	6 (33)
CyBorDex, *n*	13 (33)
AlkPdn, *n*	4 (33)
LenDex, *n*	2 (33)
Others, *n*	6 (33)
None therapy, *n*	2 (33)

3 | RESULTS

[18F]-florbetaben PET/CT was performed at time of diagnosis in 19 patients, while it was performed during the follow up in 11 patients. Amyloid insoluble fibrils were detected in 18/24 (75%) patients evaluated for Periumbilical fat, and in only 10/24 patients (42%), by bone marrow biopsy.

In our study cohort, endomyocardial biopsy demonstrated amyloid deposits in 17/17 patients.

Blood tests were available for all patients at the time of [18F]-florbetaben PET/CT.

29 patients (87.8%) of study cohort presented elevated NT-pro BNP levels, as a cardiac damage sign, that anyway could be not only related to AL cardiac involvement, but could also depends on other cardiological conditions and other cardiac damage's causes (hypertension, diabetes, dyslipidaemia, etc.) and may also not be suggestive in older population, due to abnormal level of the NT-proBNP in the older age patients.[6]

Moreover, concerning to troponin HS levels, all population enrolled, evaluated for troponin levels, showed abnormal values. In our study cohort, 24hs Proteinuria could not be considered as a significative parameters due to low

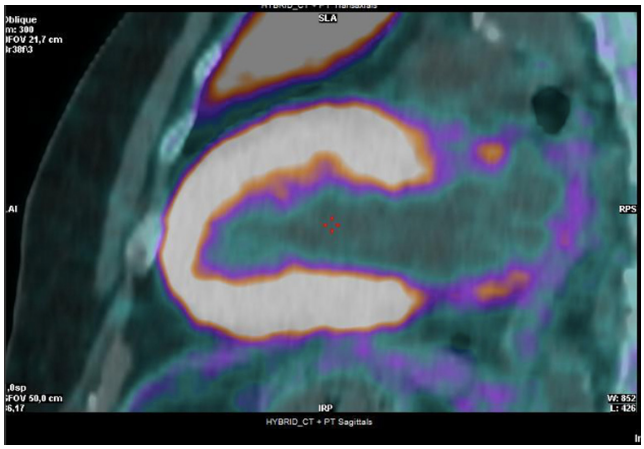

FIGURE 1 [18F]-florbetaben cardiac positron emission tomography scan in patient with AL.

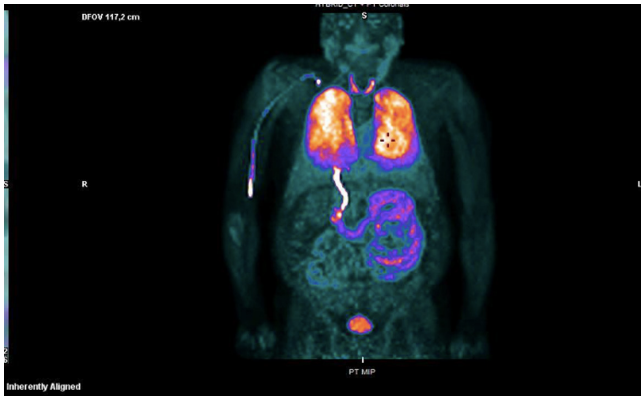

FIGURE 2 Other localizations of amyloidotic fibrils in the same patient. The [18F]-florbetaben positron emission tomography scan shows pathological positivity in lung and thyroid, histological site of AL detection, and normal hepatic, urinary and intestinal uptake.

number of patients who collected urine in 24 h (24.2%) at the time of PET/TC scan, even though the high percentage of patients enrolled with renal impairment, and, furthermore, creatinine levels in 60.6% of patients with renal involvement were normal.[8] Concerning the most relevant parameter of higher production of immunoglobulin light chains, FLC ratio,[7,10] analysed by *Freelite® assays*,[11] was normal in 3 patients with established diagnosis suggesting a lower sensitivity of dosing FLC compared to [18F]-florbetaben PET/CT (Figure 1). Notably, [18F]-florbetaben PET/CT uptake was also consistent in extra cardiac tissues of amyloid histological deposition, as shown in 8 patients who presented a demonstrated histological diagnosis of AL amyloid insoluble fibrils in other organs, such us liver, lung or thyroid (Figure 2).

Those sites of AL depositions performed [18F]-florbetaben positron emission tomography scan pathological positivity, affirming the technique's utility also in detecting other unexpected AL deposition sites.

4 | DISCUSSION

Earlier diagnosis is a challenge in AL amyloidosis and has a relevant impact on patients life expectancy. [18F]-florbetaben PET/computed tomography may represent a promising non-invasive tool for the diagnosis of AL amyloidosis.

We demonstrate that late static [18F]-florbetaben PET acquisitions can discriminate cardiac involvement due to AL amyloidosis from ATTR amyloidosis and from other non-CA (cardiac amyloidosis) conditions mimicking infiltrative disorders.

According to our study, despite an increase in serum levels of free light chains anticipates the development of AL amyloidosis by many years, we also demonstrate, monitoring cardiac involvement with [18F]-florbetaben PET/CT, that AL amyloidosis patients with cardiac deposition fibrils could present normal levels of FLC ratio. That evidence supports more relevance in heart failure patients to perform PET/TC if AL amyloidosis is suspected, instead of only blood examinations or B-Mode Ultrasound or MRI monitoring.

Moreover, NT-pro BNP and troponin elevation, although very sensitive for cardiac involvement, are not specific for amyloid infiltration, because the higher levels of those parameters could be related to other substantial cardiological conditions concealing the cardiac AL damage, that is hypertrophic cardiomyopathy or other cardiac deposition disease.

Notably, [18F]-florbetaben PET/CT uptake was also consistent with extra cardiac tissues amyloid histological demonstration, proving it could be able to explore all sites of amyloid deposits and suggesting to perform it any times AL deposition is suspected. As detected in Figure 2, in other localizations of amyloid deposition, such as thyroid, demonstrated by target biopsy, the [18F]-florbetaben positron emission tomography scan shows pathological positivity. That could represent, an attractive diagnostic tool to retrieve other unexpected localization of amyloid fibrils.

Our study limitations are represented by the low number of patients enrolled and its retrospectivity. Even thought, still, our cohort of AL amyloidosis patients is the largest studied so far with [18F]-florbetaben PET, a prospective and multicentre study can expand and confirm the data, providing thorough clinical, biohumoral, and instrumental characterization of all subjects, including amyloid histological demonstration and comparing it to [18F]-florbetaben PET/CT uptake, also in unexpected sites of AL demonstration.

As future perspective, moreover, as soon as this technique become validated, we hypothesize that [18F]-florbetaben PET/CT could be also useful in order to demonstrate the reduction of AL deposits, during the follow up of patients who underwent to anti-amyloid monoclonal antibodies

treatment, suggesting it as a safe and specific monitoring method to evaluate the treatment efficacy.

5 | CONCLUSIONS

[18F]-florbetaben PET/CT may represent a promising non-invasive first-step tool for the diagnosis of AL amyloidosis, which is still often challenging and delayed.

Our results, when confirmed on a larger basis, may support a central role of [18F]-florbetaben PET imaging in the diagnostic process of patients presenting with suspected CA.[12]

According to demonstrated efficacy of the [18F]-florbetaben PET/CT, we suggest to perform it to each patients who present heart failure suspicious of AL amyloidosis to detect early amyloid deposits, due to high sensitivity, more than FLC, and almost safety profile. Therefore, [18F]-florbetaben PET/CT can be able to explore all sites of amyloid deposits, suggesting it as valid technique to retrieve also unexpected or asymptomatic tissue of AL deposition.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. The first draft of the manuscript was written by RCC and GB and all authors commented on previous version of the manuscript. AG and DG analysed the reported [18F]-florbetaben PET/CT scan samples. GV and AA, belonging to Cardiology Division, suspected amyloidosis in patients referred to their Unit. RCC, GB and MLDG, in Haematology Division, visited each AL patients during follow up and performed the research. SG, GB and ME supervised the project. All authors reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no competing interest exists.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are openly available in https://pubmed.ncbi.nlm.nih.gov. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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