CJC Open 5 (2023) 650–653

Case Report

Diffuse 18F-FDG PET Uptake in a Patient With Biopsy-Proven ATTR Cardiac Amyloidosis: A Potential Pitfall in Interpretation

Ahmed Aldajani, MD,[a,b] and Michael Chetrit, MD[a]

[a] Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada

[b] Department of Internal Medicine, Division of Cardiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Eastern Province, Saudi Arabia

Cardiac amyloidosis (CA) is characterized by the aggregation of misfolded proteins forming amyloid fibrils that deposit in the myocardium and other cardiac structures, leading to an infiltrative cardiomyopathy. CA has 2 major subtypes, which have different management and prognosis: transthyretin amyloidosis (ATTR) and amyloid light-chain (AL) amyloidosis.[1] A high clinical index of suspicion is the foundation for diagnosing CA; however, cardiac imaging is critical for its diagnosis in suspected patients.[1] Cardiac positron emission tomography (PET) is a modality that is not reliable for assessing CA.[2] We present a rare case of biopsy-proven CA with positive uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET tracer.

The patient is a 69-year-old woman with a known history of type 2 diabetes mellitus, hypertension, dyslipidemia, bilateral carpal tunnel syndrome, and suspected sarcoidosis with previous anterior uveitis. Her diagnosis of sarcoidosis was suspected based on prior chest computed tomography (CT) scans, demonstrating mediastinal lymphadenopathy suggestive of sarcoidosis, with no evidence of interstitial lung disease and normal pulmonary function tests. She had a family history of dilated cardiomyopathy in her mother and pulmonary sarcoidosis in her 2 sisters. Her medications included aspirin, losartan, amlodipine, rosuvastatin, and metformin.

She was in her usual state of health, with no cardiac complaints, until August 2020, when she developed atypical chest discomfort and shoulder pains. She denied any exertional chest pain, shortness of breath, or other cardiac symptoms. Her electrocardiogram showed normal sinus rhythm, right bundle branch block, and left anterior fascicular block (Fig.1A). A transthoracic echocardiogram was requested, demonstrating concentric left ventricular (LV) remodeling with a left ventricular ejection fraction of 60%-65%, moderate diastolic dysfunction, and severely reduced global longitudinal strain (GLS) of -11.6%, with preservation of the apex suggestive of CA (Fig. 1, B and C). Given these echocardiographic findings, she was referred to cardiology for further workup.

The clinical suspicion for amyloid arose; thus, serum protein electrophoresis, serum free light chain testing, and a technetium-99m pyrophosphate scintigraphy (^{99m}Tc-PYP) scan were requested. Her serum protein electrophoresis and serum free light chain tests were negative, with no evidence of hematologic dyscrasias. Her high-sensitivity troponin-I level was mildly elevated at 26.6 ng/L (normal: $<$ 17.5 ng/L). Her subsequent ^{99m}Tc-PYP scan and associated single-photon emission computerized tomography (SPECT) of the thorax demonstrated increased activity throughout the left heart, greater than that in the rib cage, localizing to the myocardium, indicating a Perugini score of 3 (Fig. 1, D and E). She also underwent cardiac magnetic imaging (CMR), which demonstrated normal biventricular volume and systolic function and concentric remodeling/thickening of the LV up to a thickness of 14 mm. Also present was an almost circumferential subendocardial late gadolinium enhancement (LGE) pattern involving the anterior, lateral, and inferior wall with septal mid-myocardial LGE. This pattern of circumferential subendocardial LGE is in keeping with CA (Fig. 1, F-I). However, given the patient's history of suspected sarcoidosis and confounding by 2 possible infiltrative etiologies (sarcoid and amyloid), an ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET)/CT scan was arranged to see if both myocardial uptake and/or uptake in the lymph nodes occurred. The ^{18}FDG-PET/CT scan showed low-grade heterogeneous diffuse radiotracer accumulation in the LV wall radiotracer uptake, possibly related to sarcoidosis or ATTR-CA, which can be associated with inflammatory changes of lymphohistiocytic infiltration around the amyloid protein deposition in the myocardium (Fig. 1J-L).

In view of the prior pyrophosphate scan findings, amyloidosis with an inflammatory component was suspected

Received for publication February 18, 2023. Accepted May 11, 2023.

Corresponding author: Dr Ahmed Aldajani, Division of Cardiology, McGill University Health Centre, 845 Rue Sherbrook O, Montreal, Quebec, H3H 0G4, Canada. Tel.: +1-514-934-1934.

E-mail: Ahmed.aldajani@mail.mcgill.ca

See page 653 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.05.004

Novel Teaching Points

- Despite advancements in multimodality imaging, it still has limitations; therefore, complementary cardiac imaging modalities must be used. A tissue biopsy may be required despite best efforts.
- FDG-PET positivity in cases of CA is more likely to be associated with the AL type than with the ATTR type, and it is likely to be related to the associated inflammatory process and less likely to indicate the coexistence of 2 different infiltrative diseases.
- PET scan for the detection of CA is likely to be more useful using amyloid-directed molecule tracers, rather than FDG tracers, for which more studies are needed.

more. The patient eventually underwent an endomyocardial biopsy with proteomic analysis by mass spectrometry of Congo red-positive areas, indicating amyloid deposition of ATTR-type amyloidosis. She remained asymptomatic, with New York Heart Association I symptoms, and did not require diuretics. She was started on diflunisal, with the plan to start tafamidis for mortality benefit.

Discussion

The initial workup for CA should include a 12-lead electrocardiogram, troponin, brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac imaging, namely transthoracic echocardiogram. Screening for plasma cell dyscrasia is important to ensure early referral to hematology-oncology, for initiation of appropriate chemotherapy.[1] Despite using serum biomarkers for risk assessment of CA, the biomarkers themselves are nonspecific. For this reason, imaging remains a requisite component of the diagnostic algorithm for CA.[2] Using different cardiac imaging modalities as complementary to each other plays a crucial role in the diagnostic evaluation of patients with suspected CA.[1]

Echocardiography remains an excellent initial screening modality for cardiomyopathies, given its safety and accessibility. The most common finding is increased LV wall thickness (> 12 mm).[3] Suspicion grows when this finding is

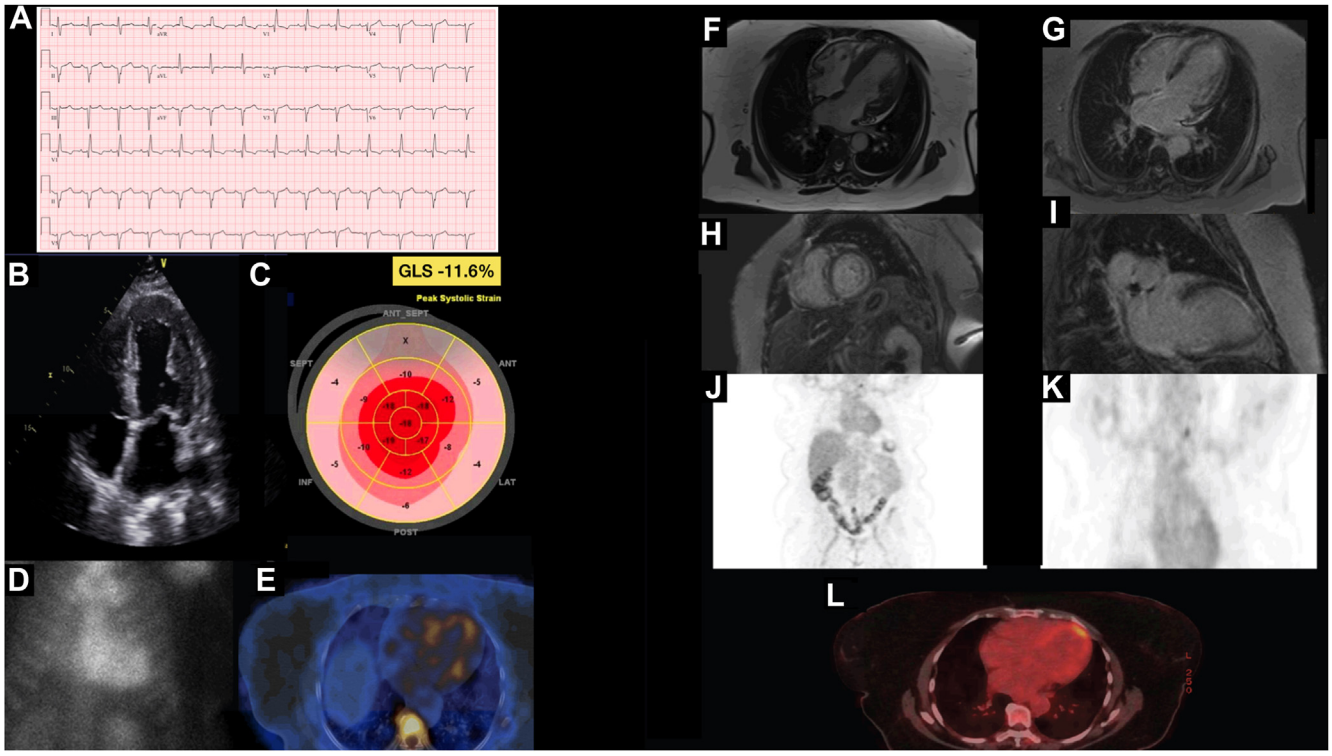

Figure 1. Electrocardiography (ECG) and multimodality imaging. (**A**) ECG; (**B, C**) echocardiography; (**D, E**) pyrophosphate scintigraphy (PYP) scan; (**F-I**) cardiac magnetic resonance (CMR); (**J-L**) ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). (**A**) ECG demonstrating normal sinus rhythm, left-axis deviation, right bundle branch block, and left anterior fascicular block. (**B**) Apical 4-chamber view on echocardiogram demonstrating concentric left ventricular remodeling, moderate left atrial enlargement, and mild thickening of aortic and mitral valve leaflets. (**C**) Strain imaging demonstrating severely reduced global longitudinal strain (GLS) of -11.6%, with preservation of the apex suggestive of cardiac amyloidosis. (**D**) PYP scan demonstrating diffusely increased activity throughout the left heart, of greater intensity than that in the rib cage, localizing to the myocardium, indicating a Perugini score of 3. (**E**) Single-photon emission computerized tomography images demonstrating increased uptake localizing to the myocardium. (**F, G**) 4-chamber long-axis CMR balanced steady state free precession (bSSFP) image (**F**) and late gadiolinoum enhancement (LGE) sequences (**G**); (**H**) apical short-axis LGE view; (**I**) 2-chamber vertical long-axis view demonstrating almost circumferential subendocardial LGE. (**J-L**) FDG PET/computed tomography demonstrating low-grade heterogeneous diffuse radiotracer accumulation in the left ventricular wall greater than that in the anterolateral wall.

Table 1. PET characteristics of patients with CA

Case	Year	Age, y/sex	Type of CA	Other organs involved	Positive FDG-PET	FDG uptake location	Uptake pattern
Our case	2022	69/F	ATTR	N	Y	Heart	D
Tanaka et al.[3]	2021	73/M	ATTR	N	Y	Heart (suboptimal dietary preparation)	D
Gazzili et al.[7]	2020	64/M	AL	———	Y	Heart	D
Lee et al.[6]	2015	55/M	AL	Stomach/colon	Y	Heart	D
		65/M	AL	Pancreas	Y	Heart	D
		55/M	AL	Kidney	Y	Heart	D
		43/M	AL	Kidney	Y	Heart, kidney	D
		68/F	AL	Colon	Y	Heart, colon	D
		56/M	AL	———	Y	Heart	D
		57/M	AL	———	Y	Heart	D
		68/M	AL	———	Y	Heart	D
		60/F	AL	———	Y	Heart	D
		74/M	AL	———	Y	Heart	D
Mekinian et al.[4]	2012	67/M	AL	N	N	——	——
		70/M	AL	Pulmonary	Y	Lung	——
		56/M	AL	Kidney/liver/muscular/joint	Y	Muscular/joint	——

AL, amyloid light-chain; ATTR, transthyretin amyloidosis; CA, cardiac amyloidosis; D, diffuse; F, female; FDG, ^{18}F-fluorodeoxyglucose; M, male; N, no; PET, positron emission tomography; Y, yes.

combined with increased LV wall mass, mitral annular tissue Doppler imaging < 5 cm/s, biatrial enlargement, small pericardial or pleural effusions, and severe aortic stenosis, especially the paradoxical, low-flow, low-gradient severe aortic stenosis variant.[2] Deformation imaging using GLS calculations has enhanced the utility of echocardiography. CA has a classic diffusely decreased GLS with relative apical sparing and is the best predictive parameter for CA by echocardiography.

A comprehensive CMR evaluation for CA includes morphologic and functional assessment of the cardiac chambers using cine imaging, evaluation of native T1 signal, assessment of LGE, and extracellular volume measurement. It helps diagnose CA, especially when echocardiography is indeterminate.[2] The primary purpose of CMR in CA is to exclude or confirm the presence of cardiac amyloid by its ability to characterize myocardial tissue, especially in undifferentiated increased ventricular thickness. The amyloid protein deposition in the myocardium significantly prolongs the T1 relaxation time, increasing native myocardial T1 values, resulting in a sensitivity of 90% and a specificity of 87% for the detection of CA.[2] Deposited amyloid fibrils have an affinity for gadolinium-based agents, usually resulting in diffuse subendocardial gadolinium uptake. A CMR-based LGE pattern has been shown to have a diagnostic sensitivity of 85%, and specificity of 92%.[2,3] In LGE imaging, when nulling of the myocardium is attempted (making the myocardium dark and the blood pool bright), the blood pool and amyloid-infiltrated myocardium undergo nulling together, giving an appearance of a dark blood pool suggestive of CA.[2] Comparing T1 values pre- and post-contrast allows for estimation of the extracellular volume, which is elevated in CA ($\geq$ 40%) and has been shown to most closely mirror the amyloid burden and treatment response.[2]

The use of nuclear imaging for the diagnosis of CA also plays a crucial and unique role. Of the bone-seeking radiotracers, ^{99m}Tc-PYP is the most studied for use in CA imaging. It is the first radiotracer demonstrating high sensitivity and specificity for differentiating ATTR-CA from AL-CA. Radiotracer uptake is graded visually by comparing the cardiac uptake to bone on planar images. In the absence of monoclonal proteins in the blood and urine, a grade 2 or 3 positive Perugini score is highly specific for diagnosing ATTR-CA without the need for a biopsy, with a specificity and positive predictive value $> 98\%$.[2] The utility of PET scans for diagnosing CA has been studied, with conflicting evidence depending on the tracer, which may suggest their unsuitability.[2] FDG uptake is usually significant in conditions with inflammation and the presence of mononuclear cells, making FDG-PET a reliable imaging modality to detect hematologic malignancy, but evidence supporting its use in amyloidosis is lacking.[4] Although in cardiac sarcoidosis, FDG-PET provides high diagnostic performance, with a sensitivity of 89% and specificity of 78%,[5] its utility in cardiac amyloidosis still needs to be clarified.[4] In cardiac sarcoidosis, ^{18}F-FDG accumulates in active cardiac sarcoidosis lesions, typically producing patchy uptake, and correlates with overall prognosis. ^{18}F-FDG uptake helps monitor disease activity and response to therapy. Performing whole-body ^{18}F-FDG-PET/CT helps evaluate extracardiac involvement, an essential step in assessing sarcoidosis.[5]

Positive ^{18}F-FDG uptake in CA is rare and has been reported only in case reports, described in Table 1. The pattern of ^{18}F-FDG uptake in reported cases was diffuse rather than patchy. In a case series describing 10 patients with amyloid light-chain (AL) amyloidosis and FDG-PET uptake patterns, 3 had known cardiac involvement, with FDG uptake in other organs involved but no uptake in the heart.[4] In another study of 15 patients with histologically confirmed AL amyloidosis, 10 patients had cardiac involvement with diffuse myocardial uptake of FDG.[6] Only one case was reported of ATTR-CA in a 73-year-old man undergoing FDG-PET for lung cancer staging, demonstrating tracer uptake in the left ventricle, although the test was limited by suboptimal diet preparation.[3] Recently, new amyloid-directed molecule tracers (^{18}F-florbetapir, ^{18}F-florbetaben, and ^{11}C-Pittsburgh Compound B [PIB]) showed success in imaging B-amyloid plaques in Alzheimer's patients, thus holding promise for use in CA detection.[2,5] Pilot studies of these agents have shown that they detect both AL-CA and ATTR-CA but have a higher affinity for the AL type than for the ATTR type.[5]

Our case is the first confirmed ATTR-CA case with positive FDG uptake by PET scan, with proper preparation with a

14-hour fast, a low-carbohydrate diet 24 hours before the study, and blood glucose levels < 11.1 mmol/L at the time of the study. The complexity in our case is the fact that the patient has a history of suspected sarcoidosis, with an echocardiogram and CMR suggestive for CA, with a very positive ^{99m}Tc-PYP test in the absence of hematologic markers, but also a weakly positive ^{18}F-FDG-PET scan, which could be representative of either cardiac amyloidosis and/or sarcoidosis or could be a false-positive result from inadequate glucose suppression. In the literature, the PET-positive amyloid cases usually have been associated with the AL type of CA, with only one other case of ATTR, which could have been a false-positive result, similar to our case. The endomyocardial biopsy confirmed the diagnosis of CA. The inflammation process, suggested by the FDG uptake, may play a role in the detection of CA, but more data and studies are required to determine if this is the case.

Conclusion

CA that has a positive uptake on FDG-PET is very infrequent, and this finding is potentially misleading. It is more commonly seen in AL-CA. To our knowledge, this is the first confirmed case described in the literature of ATTR-CA with a weakly positive PET uptake with proper preparation. The uptake could be due to the ATTR-protein itself or the inflammatory process as in AL-CA, or it could be a false-positive result in ATTR, similar to a previously reported case in the literature. This case highlights the importance and limitations of multimodality imaging in its current state in diagnosing cardiomyopathies, with further development required. This case is an important contribution to the literature on the role of multimodality imaging in CA and an essential reminder not to exclude CA as a possibility in patients with a positive FDG-uptake pattern on PET.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective case report using de-identified data; therefore the IRB did not require consent from the patient.

Funding Sources

The authors have no relevant funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Fine NM, Davis MK, Anderson K, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement on the evaluation and management of patients with cardiac amyloidosis. Can J Cardiol 2020;36:322-34.
2. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2-evidence base and standardized methods of imaging. Circ Cardiovasc Imaging 2021;14:e000029.
3. Tanaka H, Hosono M, Kanagaki M, et al. A case of cardiac amyloidosis incidentally detected by bone scintigraphy. Asia Ocean J Nucl Med Biol 2021;9:71-5.
4. Mekinian A, Jaccard A, Soussan M, et al. 18F-FDG PET/CT in patients with amyloid light-chain amyloidosis: case-series and literature review. Amyloid 2012;19:94-8.
5. Hotta M, Minamimoto R, Awaya T, et al. Radionuclide Imaging of cardiac amyloidosis and sarcoidosis: roles and characteristics of various tracers. Radiographics 2020;40:2029-41.
6. Lee JH, Lee GY, Kim SJ, et al. Imaging findings and literature review of (18)F-FDG PET/CT in primary systemic AL amyloidosis. Nucl Med Mol Imaging 2015;49:182-90.
7. Gazzilli M, Bertoli M, Albano D, et al. Cardiac amyloidosis incidentally detected by 18F-FDG PET/CT. J Nucl Cardiol 2020;27:2429-31.