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Early View

Research letter

The Utility of Gallium-68 DOTATOC PET/CT in Lymphangioleiomyomatosis

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Abstract

Lymphangioleiomyomatosis (LAM) is a progressive diffuse cystic lung disease. FEV1 is the current outcome measure, however this may underestimate disease burden; better activity biomarkers are needed. Previous reports suggested the presence of somatostatin or analogous receptors in LAM. We hypothesised that Ga^{68}-DOTA PET/CT, utilising a radiolabelled somatostatin analogue could be a molecular imaging technique to demonstrate disease burden. There were no differences in tracer uptake in LAM patients compared to controls and no correlations between PET/CT values and pulmonary-function. This report indicates that somatostatin molecular imaging in LAM is not useful, however other functional imaging approaches may be of benefit.

Introduction

Lymphangioleiomyomatosis (LAM) is a progressive, low-grade, metastasizing neoplasm of women that is characterised by infiltration of the lung parenchyma with abnormal smooth muscle-like cells, resulting in cystic lung destruction.[1] While forced expiratory volume in one-second (FEV1) is the current standard outcome measure used in LAM, there are limitations to its use as a true surrogate of disease severity and may underestimate disease burden. Additionally, pulmonary function testing depends on patient co-operation and there can be significant inter-test variation. Despite vascular endothelial growth factor-D (VEGF-D) being an excellent diagnostic test and biomarker of prognosis,[2] it is not elevated in all patients, hence other biomarkers of disease activity and prognosis are required. Due to the neoplastic nature and the activation of mTOR signalling in LAM, it has previously been investigated whether LAM lesions would demonstrate increased metabolic uptake of [18F]2-fluoro-2-deoxyglucose (FDG) on PET scanning. However, no significant uptake of FDG was demonstrated in LAM lesions or AMLs and this radiotracer was not deemed suitable at determining disease burden or activity in sporadic or tuberous sclerosis associated LAM (TSC-LAM) patients.[3] Patients with LAM may develop chylous complications, including chyloptysis, chylous ascites and chylothorax.[4, 5] Additionally, TSC-LAM can be associated with neuroendocrine tumours which overexpress somatostatin receptors, and octreotide, a somatostatin analogue, is an effective therapy for chylothorax in a variety of conditions, including in LAM.[6, 7] While it is not known if somatostatin receptors are expressed in LAM lesions it is known that somatostatin and urotensin-II are closely related neuropeptides and directly activate both urotensin receptors and somatostatin receptors.[8] Urotensin-II and urotensin receptors are present and expressed to a greater extent in the lungs of LAM patients compared to normal lungs.[9] In prior reports, octreotide scintigraphy demonstrated increased uptake of radiolabelled octreotide diffusely throughout the lungs and kidneys; suggesting the presence of somatostatin receptors or

analogous receptors in LAM.[10] Gallium-68 linked somatostatin receptor PET radiotracers such as Ga-^{68}-DOTATOC (Ga^{68}-DOTA PET/CT) utilise a radiolabelled somatostatin analogue peptide which binds with high-affinity to the somatostatin receptors. Ga^{68}-DOTA PET/CT offers many advantages over octreotide scintigraphy, with significantly higher target-to-background ratio, superior spatial resolution, better sensitivity and potential for simpler quantification.[11] We hypothesised that Ga^{68}-DOTA PET/CT could be a useful molecular imaging technique in LAM that could demonstrate disease burden.

Methods

Following local IRB approval (Ref. No.: RS20-014) patients were recruited from the LAM clinic at St. Vincent's University Hospital and provided informed written consent. Sporadic LAM patients were selected that were not on mTOR inhibitor therapy. Age and sex matched control patients were included from the national neuroendocrine service who had Ga^{68}-DOTA PET/CT with normal lung parenchyma.

All Ga^{68}-DOTA chelated somatostatin analogue peptide PET/CT examinations were performed on a Siemens Biograph mCT PET-CT system (Siemens Healthineers, Forchheim, Germany). A standard PET acquisition from skull base to upper thighs was acquired post-injection of 122.6+/-12.6 MBq of Ga^{68}-DOTA-TyI^3-octreotide (Ga^{68}-DOTATOC) with an average tracer uptake time of 61+/-5 minutes. Non-attenuation corrected and attenuation corrected datasets were reconstructed. The low-dose unenhanced CT component was performed with patients maintaining normal shallow respiration, using a standardised protocol with 140kV, pitch 1.375 and auto mA(15-100mA,noise index 40). CT images were reconstructed with a slice thickness of 2.5mm. A standard clinical PET time of flight ordered subset expected maximisation (OSEM) reconstruction using 2 iterations, 24 subsets and a Gaussian filter was performed. PET images were reconstructed with a slice thickness of 2.5 mm and pixel size of 4 mm.

Qualitative and semi-quantitative analysis was performed in a random order, blinded to the clinical information. Qualitative global assessment of pulmonary Ga^{68}-DOTATOC uptake was performed using a three-point visual scale: 1=less than mediastinal blood pool (MBP); 2=greater than MBP but less than liver; 3=greater than liver. Semi-quantitative maximum standardised uptake value (SUV_{max}) measures of pulmonary Ga^{68}-DOTATOC uptake were performed in each lobe by drawing a region of interest (ROI) of ~1cm in each lobe. For patients with LAM, the ROI was drawn in cyst-adjacent parenchyma. A freehand ROI was outlined in the arch of the aorta, avoiding the aortic walls, to define SUV_{max} MBP. A target to background ratio (TBR) was calculated for each lobe by dividing the lobar SUV_{max} by MBP SUV_{max}.

Results

Four female patients aged 49, 53, 55 and 82, with LAM underwent whole body Ga^{68}-DOTA PET/CT. Three of the female patients were post-menopausal and one perimenopausal. The median DLCO was 59.75%, median FEV1:58.5% and median VEGF-D=641pg/mL. There was no qualitative difference in tracer uptake in any region of the lung or extrathoracically in LAM patients compared to controls, with all studies having a score of 1 (i.e. less than MBP) (Figure 1A-D) Moreover, there was no significant difference in the overall mean lobar SUV_{max} of LAM lungs except in the left upper lobe (0.33) compared to control (0.2075) ($p= 0.0275$), however this is unlikely of any significant importance. (Figure 1E) Crucially, there were no differences in the target to background ratio (TBR) in any lobe of LAM compared to controls (Figure 1F) indicating that there was no significant uptake of Ga^{68}-DOTATOC in the lungs of patients compared to controls. There were no significant correlations between mean SUV_{max} or TBR values and pulmonary function measures in patients with LAM. Of note, there were incidental findings noted of moderate hydronephrosis in one patient requiring intervention, and a pulmonary nodule which required surveillance.

Discussion

The results of this pilot study indicate that there is no demonstrably increased uptake of Ga^{68}-DOTATOC in LAM and that somatostatin receptor analogue functional imaging is unlikely to be of utility as an imaging biomarker in this disease. Despite the small number of studies, the severity of LAM varied in this group. The DLCO ranged from 25% predicted to 110% predicted. Three LAM patients had angiomyolipomas with two having undergone surgical removal. No patient was on rapamycin at the time of imaging although one patient had been previously but stopped due to side effects and two patients have since been commenced on rapamycin. Two patients required supplemental oxygen. There were no significant differences in radiotracer uptake, indicating a lack of signal for this modality. This current study using Ga^{68}-DOTATOC PET/CT suggests that earlier proposal that there is somatostatin receptor-bearing tissue in LAM is likely incorrect and that treatment with octreotide is unlikely to be of benefit through any direct mechanism.[10] This is important to report as it excludes this imaging approach or other somatostatin molecular imaging modalities in LAM in the future. Other functional imaging approaches may be of benefit in the future such as Ga^{68}-NEB PET/CT[12] or C^{11}-Glutamine PET/CT designed to assess whether increased glutamine uptake in LAM lesions, previously demonstrated in mechanistic preclinical studies of LAM, has utility as a clinically meaningful biomarker.[13] Further studies are required to identity improved diagnostic and prognostic approaches in LAM.

Figure Legends

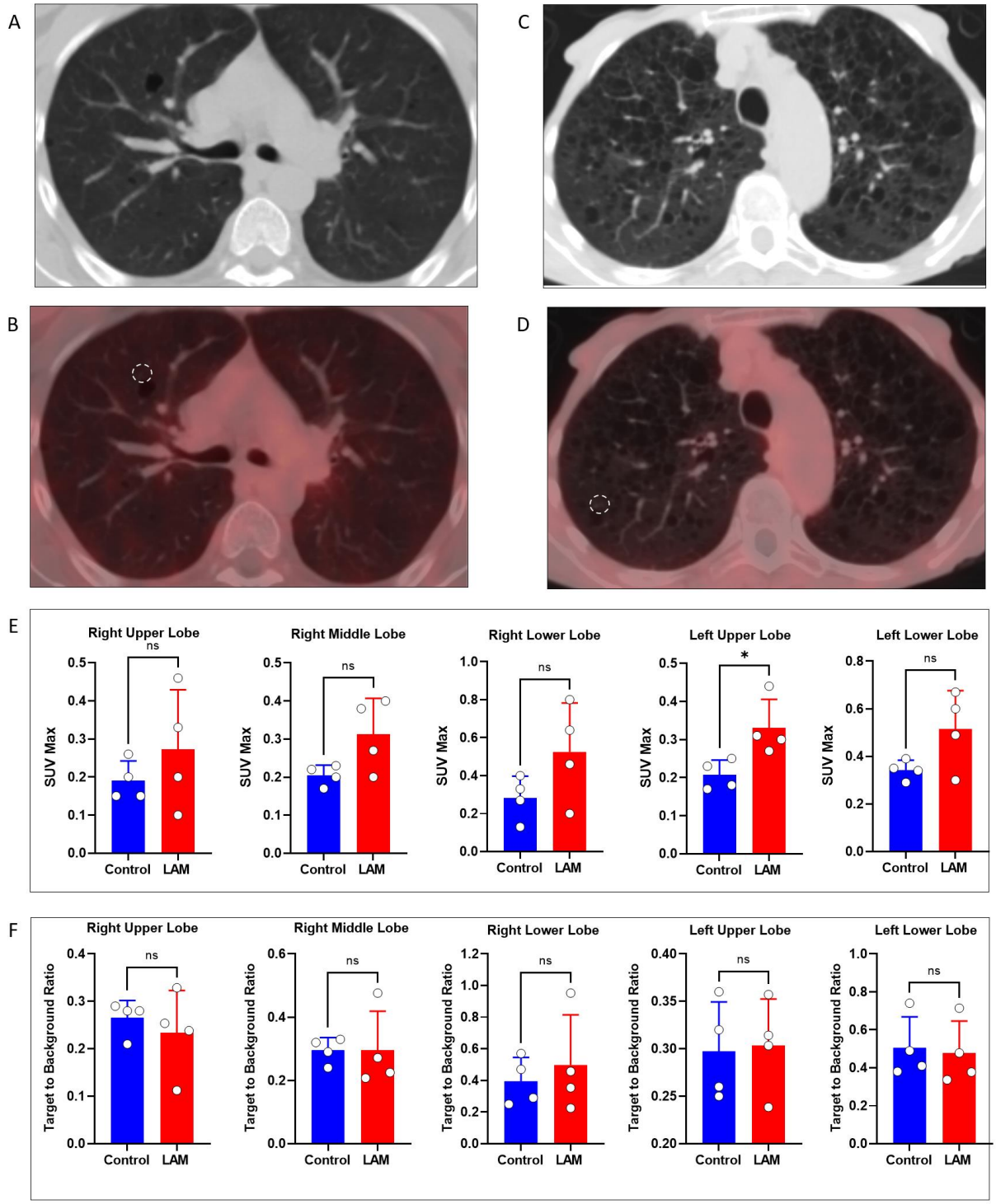

Figure 1: Qualitative and quantitative assessment of Ga^{68}-DOTATOC PET-CT in LAM

(A) Axial CT thorax image at the level of the carina in a patient with mild LAM (FEV1:99%, DLCO 88%) demonstrates occasional scattered thin walled cysts. (B) No increased tracer uptake evident on the axial fused Ga^{68}-DOTATOC PET-CT image (SUV_{max} window range 0-5). (C) A separate patient with severe LAM (FEV1:36%, DLCO:25%) has innumerable cysts demonstrated on this axial CT thorax image at the level of the aortic arch. (D) No increased pulmonary tracer uptake evident on Ga^{68}-DOTATOC PET-CT. Sample region of interest (ROI) demonstrated on PET images panels B and D, dashed line. (E) Semi-quantitative maximum standardised uptake value (SUV_{max}) measures of pulmonary Ga^{68}-DOTATOC uptake in lungs of patients with LAM (red bars) and controls (blue bars). (F) Target to background ratio (TBR) for each lobe calculated by dividing the lobar SUV_{max} by mediastinal blood pool (MBP) SUV_{max} in lungs of patients with LAM (red bars) and controls (blue bars). Each dot represents an individual patient. (n=4 LAM and n=4 control, unpaired Student's t test, *=$p<0.05$).

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