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[18F]Florbetaben PET-CT confirms AL amyloidosis in a patient with Waldenström's Macroglobulinaemia.

Running title: [18F]Florbetaben PET-CT confirms AL amyloidosis

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Systemic amyloid light chain (AL) amyloidosis is rare complication of Waldenström's Macroglobulinaemia (WM) and 6% of patients with AL amyloidosis have WM or an IgM monoclonal protein at presentation.[1] Symptoms of peripheral neuropathy (PN) are present in about 20% of patients with WM at diagnosis, and up to 50% are affected at some time in the course of their disease.[1] The neuropathy is most frequently a distal chronic symmetrical, predominantly sensory polyneuropathy related to the presence of pathogenic monoclonal anti-myelin associated glycoprotein (MAG) antibodies.[2] Where atypical features exist, such as predominant motor involvement, patchy localisation, rapid progression or autonomic dysfunction, alternative causes including amyloidosis, cryoglobulinaemic vasculitis and direct nerve infiltration must be considered.[3] Diagnosis of isolated neuropathic amyloidosis is challenging particularly as tissue biopsy other than the affected nerves may be negative for amyloid deposits. Patchy amyloid deposits in nerves or nerve plexii are well described but rare and even more challenging to diagnose. [4]

Here, we report the case of a 51-year-old male with WM, who presented eight years following the initial diagnosis with progressive sensory disturbance in his distal upper limbs and bilateral wasting and weakness of the small muscles of the left hand. At presentation, he had weight loss, night sweats, monoclonal IgM of 55g/L and bone marrow consistent with lymphoplasmacytic lymphoma. He obtained a very good partial response to six cycles of R-CHOP, followed by autologous stem cell transplant conditioned by BCNU, Etoposide, Cytarabine and Melphalan (BEAM). He had remained well until shortly before his neurological presentation, but was under closer review due to a rising paraprotein. Clinical examination was consistent with a patchy, multifocal bi-brachial plexopathy. Nerve conduction studies confirmed this with a patchy sensorimotor neuropathy with non-uniform conduction slowing, likely to be predominantly in the distal plexus and below.

CT scan showed mild further size increase of long-standing, slowly progressing lymphadenopathy above and below the diaphragm. MRI scans of the brain, spinal cord and brachial plexi did not reveal a cause of the patient's symptoms. FDG PET-CT showed isolated high uptake in the mediastinal nodes (SUVmax of up to 12.1) but non-specific modest uptake in the more assessable peripheral nodes (nodal uptake similar to, or less than, liver background activity of SUVmax 3.4, but higher than mediastinal blood pool of SUVmax 1.8) (Figure 1&2). There was no specific hypermetabolism at the brachial plexus or peripheral nerves, nor any extranodal abnormality. His CSF showed normal protein of 0.42 g/L, no cells but a raised CSF IgM commensurate with the serum. The M-protein was rising (24.6 g/L) but blood tests for anti-MAG antibodies and cryoglobulin were negative. Overall the patchy bibrachial neuropathy in the context of the known WM progressing despite treatment gave a strong clinical suspicion of amyloidosis. There was no evidence of systemic amyloidosis on investigations with normal cardiac biomarkers, no proteinuria, normal echocardiogram, no evidence of amyloid deposition on a bone marrow biopsy, and a normal ^{123}I labelled serum amyloid P component and ^{99m}Tc DPD scintigraphy.

Owing to a gradual but steady deterioration in his neuropathy, he received a trial of high dose methylprednisolone, which had no effect. Three months later, repeat MRI showed some thickening of the ulnar nerve suggestive of an infiltrative process, yet a site amenable to biopsy without morbidity remained elusive.

An [^{18}F]florbetaben PET-CT scan was performed in an attempt to identify neural amyloid deposition. This was performed within two months of the FDG PET-CT. 300MBq of [^{18}F]florbetaben was injected into a peripheral vein, with scan acquisition starting 90 minutes post injection. No discrete peripheral neural uptake was observed. However, this unexpectedly showed clearly abnormal, marked increased focal uptake throughout the known lymphadenopathy above and below the diaphragm, despite there being no measurable further increase in nodal disease burden by CT criteria since the FDG PET-CT (range of nodal [^{18}F]florbetaben uptake SUVmax 7.4-18.6; by comparison, mediastinal blood pool SUVmax was 1.5 & liver parenchymal SUVmax was 8.5).(Figure 1&2) This provided justification for relatively less-invasive, targeted, percutaneous biopsy of a modestly enlarged axillary node. Histology showed that the lymph node was effaced by lymphoplasmacytic infiltrate and there was pathological thickening of the blood vessels walls. Amyloid deposition was confirmed by demonstration of typical Congo red staining with characteristic birefringence under cross-polarised light (see figure 3). Confirmation of the presence of amyloid in this WM patient contributed to the justification for the subsequent recommencement of specific treatment and the need to aim for a deeper response than might otherwise be regarded as adequate.

[^{18}F]florbetaben is a novel PET tracer, which has been shown to accurately detect beta-amyloid plaques in the brains of patients to aid diagnosis of Alzheimer's Disease. [5] There have been a few reports and *in vitro* results suggesting that similar thioflavin like, ^{18}F-labelled PET tracers may have utility in identifying amyloid deposition in tissues other than the brain. *In vitro* binding of [^{18}F]florbetapir has been demonstrated in autopsy myocardial specimens. Interestingly, although [^{18}F]florbetapir binds to both AL amyloid and transthyretin (ATTR) amyloid, binding was significantly higher to AL amyloid.[6] One previous case report demonstrated the potential ability of [^{18}F]florbetapir to detect peripheral nerves involvement, with a small case series suggesting utility in assessing amyloid deposition in the heart. [7,8] Another isolated report with [^{18}F]florbetaben had shown its potential utility in systemic amyloidosis staging. This latter report contrasted the abnormal increased uptake in a patient with cardiac and renal amyloidsis, with the normal [^{18}F]florbetaben distribution in a healthy control subject. [9] Additionally [^{18}F]florbetapir shows uptake in a number of tissues outside of the heart – in a recent of series of 17 patients studied at the UK National amyloidosis centre, all 17 showed extra-cardiac uptake at more than one site (Wagner and Wechalekar – personal communication – manuscript under review).

The results of the [^{18}F]florbetaben PET-CT scan in this case were remarkable and surprising, given the exhaustive investigations that had taken place previous to this. It demonstrates the utility of [^{18}F]florbetaben PET in identifying lymphoid amyloid uptake - an anatomical site that can be silent on conventional workup.

The identification of amyloid in this case justified commencing systemic therapy with an approach that will be tailored to account for the confirmed amyloid diagnosis. Our experience along with other isolated reports suggest potential added value of these novel PET tracers in the diagnostic work up of haematology patients at risk of developing amyloidosis.

Trials are currently on-going to assess the utility of ^{18}F-labelled tracers for assessing cardiac amyloid and peripheral nerve in general cohorts. Nevertheless, systematic evaluation of its impact in guiding management of haematological patients, for which confirmation of the presence of amyloidosis is highly relevant, would be needed.

TF, ML, AW, SW and SD wrote and edited the paper. SW and JB devised the PET protocol and made the figure. SD, ML, AW were coordinating the patients clinical care.

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Figure 1

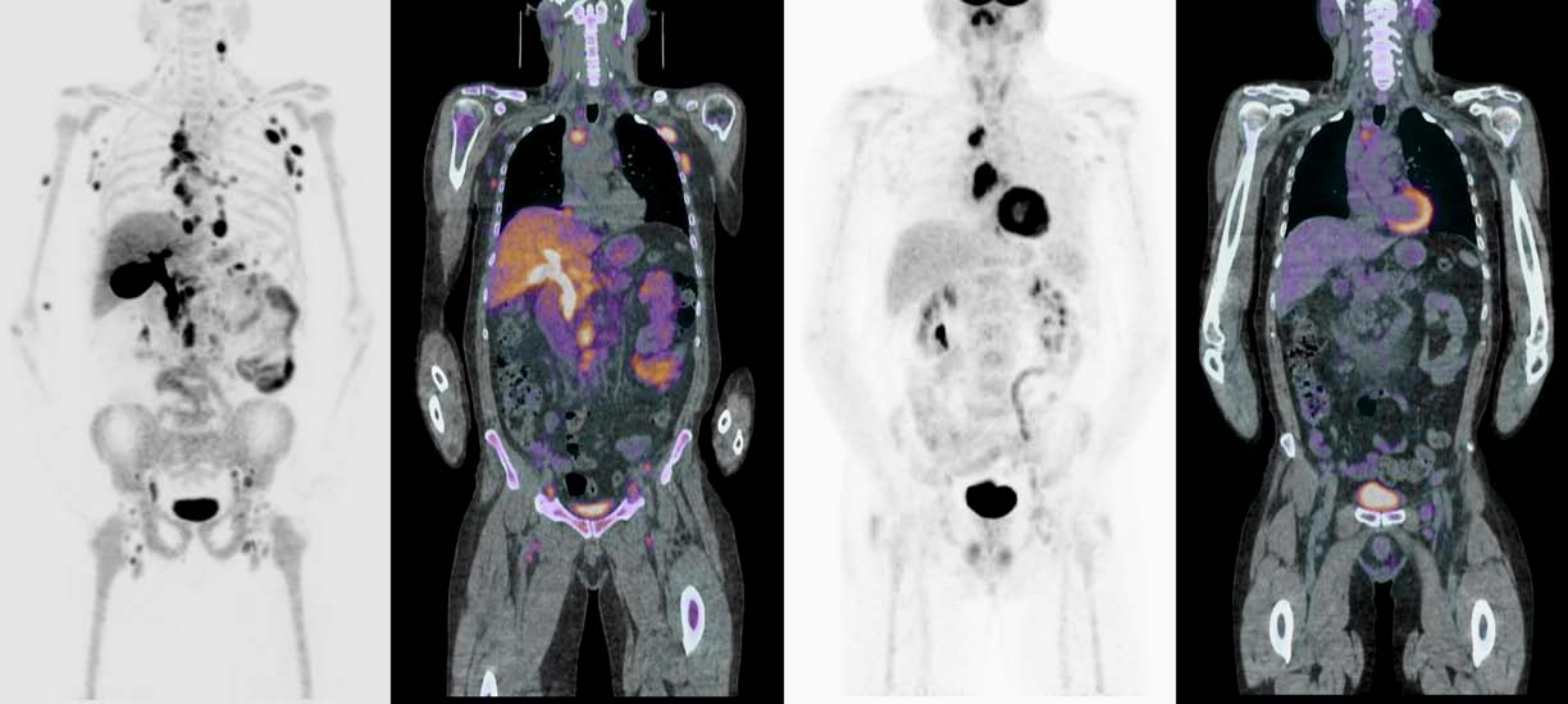
Coronal image Sections. From left to right: a) Maximum intensity projection (MIP) of the whole body [^{18}F]florbetaben PET-CT; b) Coronal fused PET-CT view of [^{18}F]florbetaben PET; c) MIP of the whole body FDG PET-CT; d) Coronal fused PET-CT view of the FDG PET-CT. These overview images show marked focal increased [^{18}F]florbetaben uptake in numerous size prominent lymph nodes above and below the diaphragm. These mostly only show non-specific modest FDG uptake, apart from a cluster in the mediastinum. See text for details on uptake values.

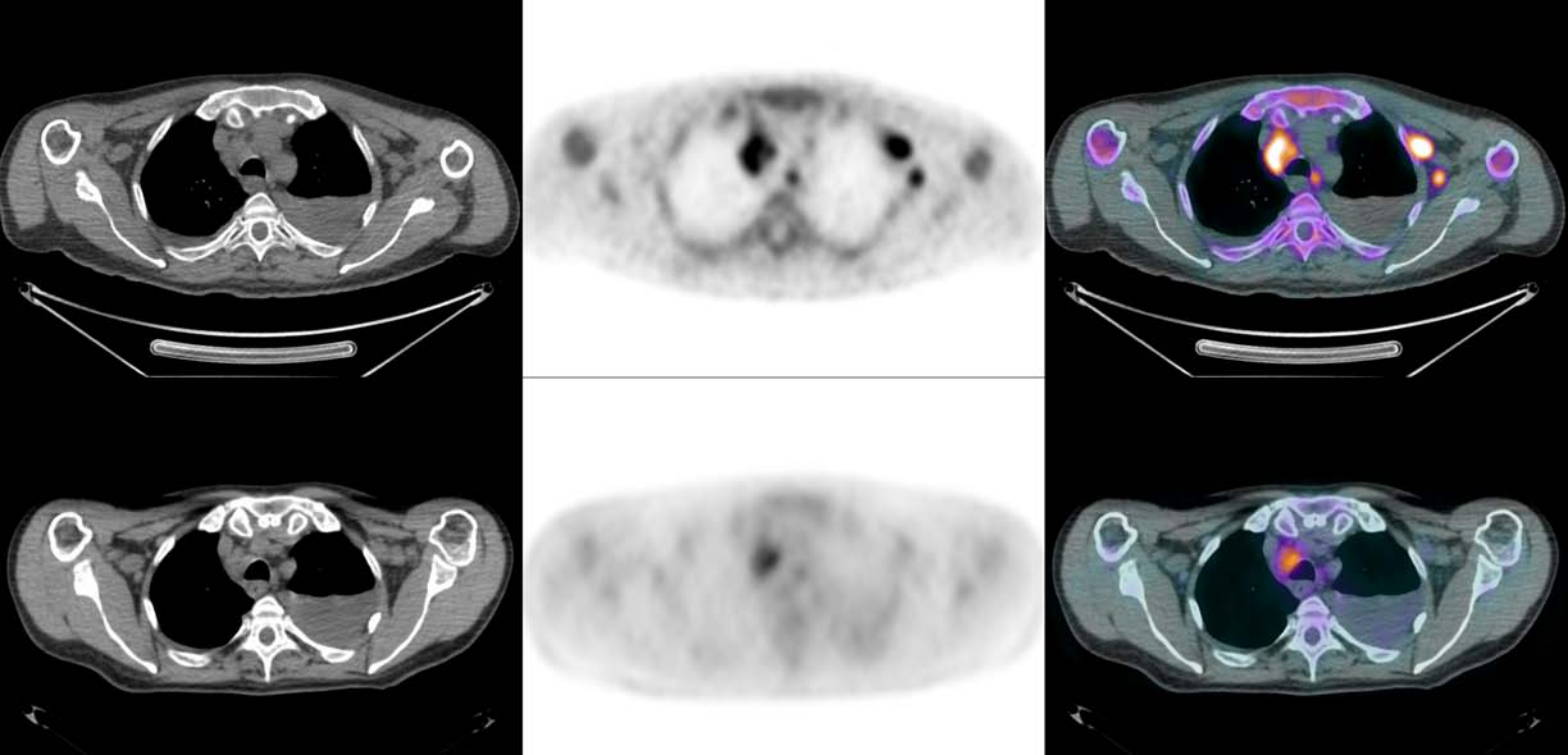
Figure 2

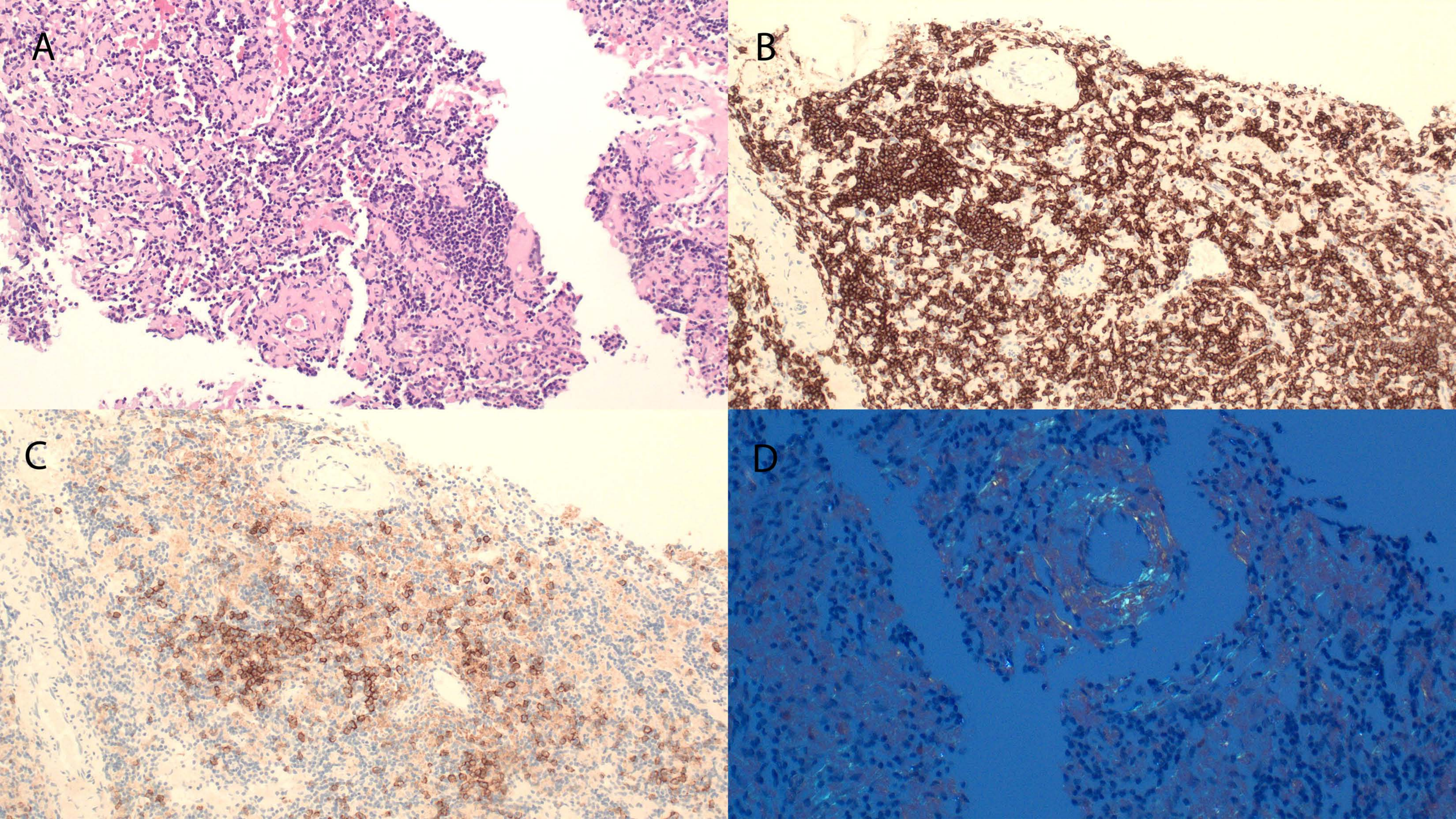
Axial image sections. From left to right: axial CT, PET and fused images of [^{18}F]florbetaben (top row) & FDG (bottom row) PET-CT. These are representative images taken at the axial level of axilla. Most avid and largest left axillary node at this level measured 1.4x2.3cm on both studies, with SUVmax of 18.6 on [^{18}F]florbetaben & 2.7 on FDG PET-CT. Mediastinal nodes have SUVmax of 15.6 on [^{18}F]florbetaben & 12.1 on FDG PET-CT respectively. Bilateral pleural effusion is also evident.

Figure 3

Histology sections. (A) H&E - The lymph node is effaced by a lymphoid infiltrate with amyloid deposition and thickening of the blood vessel walls; Immunohistochemistry demonstrates CD20 staining (B) and the plasmacytic CD138+ component (C). Amyloid stains positive with Congo red with apple green birefringence under polarised light (D)



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