


The use of whole-body fluorine-18-fluorodeoxyglucose positron emission tomography integrated with computed tomography for accurate staging and surveillance in the case of mucosa-associated lymphoid tissue

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ABSTRACT

We present the case of a 79-year-old male, who was initially treated for mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) of the right eyelid, and later for disease relapse in the stomach. During follow up, he was noted to have developed left arm nodules just medial to the proximal biceps muscle, which were found to be multiply enlarged lymph nodes on subsequent ultrasound imaging. Excisional biopsy of these nodes revealed MALT lymphoma. He was initially referred for consideration of radiation, but a restaging F-18 fluorodeoxyglucose positron emission tomography integrated with computed tomography (F-18 FDG PET/CT) further identified a focus of suspicious uptake in left calf, which was later also biopsy proven to be MALT lymphoma. His disease was upstaged as the result of this later finding, and the overall recommendation for treatment changed to favor systemic treatment with Rituximab.

CASE REPORT

CASE REPORT

Our patient is a 79-year-old male with a past medical history significant for rheumatoid arthritis and a known diagnosis of MALT lymphoma. He initially presented 10 years ago to his primary care physician with a one-month history of right eyelid swelling. He underwent a CT scan of the orbit with contrast enhancement, which showed a 2.7 cm infiltrating mass in the right upper eyelid extending posteriorly into the extraconal orbital roof. He underwent orbital exploration with biopsy of the mass, which yielded pathology consistent with a diagnosis of MALT lymphoma. Flow cytometry showed

lambda monotypic B cells which represented about 6% of the total leukocytes. For disease staging, he underwent a F-18 FDG PET/CT scan from eyes to thighs. Notably, there was a focus of asymmetric increase in FDG activity with maximum standardized uptake value (SUVmax) of 4.2 in the region of the right orbit, likely related to the biopsied mass. No other focus of FDG activity was noted (Figure 1). His disease was staged as IE per Ann Arbor classification, and he proceeded to undergo external beam radiation therapy at his local radiation center, receiving 3060 cGy in 17 daily fractions to his right orbit.

He was then referred to see the Medical Oncology services at our hospital for his continuing disease surveillance. He was followed with serial imaging studies, which noted the resolution of the aforementioned right orbit mass on CT scan. Three years after his initial presentation, he sought care at an outside hospital after he developed nonspecific gastrointestinal symptoms and underwent diagnostic esophagogastroduodenoscopy. This revealed a 1.5 cm lesion in the gastric cardia. Fine needle aspiration of the lesion was obtained, with pathology consistent with MALT lymphoma. Workup did not find associated *Helicobacter pylori* (*H. pylori*) infection. Re-staging PET/CT scan from eyes to thighs reported increased FDG activity associated with this lesion, which had a SUVmax of 4.6. This was determined to be an isolated distant relapse of his previously treated orbital lymphoma, and he was treated with external beam radiation therapy at his local radiation center. He received 3000 cGy in 20 daily fractions to the whole stomach. Complete disease response was confirmed on post-treatment surveillance PET/CT scan, again from eyes to thighs, which showed resolution of the gastric lesion and the associated FDG activity (Figure 2).

One year ago, during a routinely scheduled follow up appointment with Medical Oncology at our hospital, the patient was noted on clinical examination to have several nodules in the left arm, just below the axilla, medial to the proximal biceps muscle. Subsequent ultrasound imaging of the left arm revealed a group of enlarged lymph nodes at the site of these palpable nodules (Figure 3). The patient underwent excisional biopsy of the suspicious masses, with pathological findings consistent with nodal MALT lymphoma (Figure 4). Re-staging CT scan of the chest, abdomen, and pelvis with intravenous contrast did not find any evidence of additional lymphoma involvement. The patient also underwent bilateral restaging bone marrow biopsy, which were negative for disease involvement.

At the time, he was referred to the Radiation Oncology department at our hospital for consideration of consolidative external beam radiation therapy to his left arm. He had no specific concerns or complaints. A thorough clinical examination noted a 6 cm, well healed linear scar on the anteromedial aspect of his left arm, medial to the biceps, but yielded no other suspicious findings. After detailed discussion with the patient, an agreement was reached to obtain a whole-body PET/CT scan from vertex to feet. We felt the need for a comprehensive evaluation of his disease with extensive field of view, especially given his history of multiple disease relapses. For this reason, we recommended a whole-body PET from vertex through feet and dedicated CT with contrast enhancement. This did not show any abnormal FDG activity in his left arm. However, it did reveal the incidental findings of a group of mildly enhancing masses within the musculature of the left proximal calf. The largest of these masses measured 3.1 x 5.1 x 12.0 cm and was located within the medial aspect of the soleus muscle. These lesions were metabolically active, with SUVmax of 7.4 (Figure 5). This finding was highly suspicious for another focus of MALT lymphoma.

Given the concern that his disease now involves both a lymph node group and a separate extra-nodal site, we abandoned our tentative plan of localized radiation therapy with curative intent. The patient instead underwent ultrasound guided biopsy of the left thigh mass, with pathological findings were consistent with MALT lymphoma. Given his multiply recurrent, multifocal disease, he was started on weekly Rituximab therapy and received 4 treatments under the care of our colleagues from Medical Oncology. Complete disease response was confirmed on post-treatment surveillance PET/CT scan.

DISCUSSION

Etiology & Demographics:

Marginal zone lymphoma originates from memory B lymphocytes resident within the marginal zone of secondary lymphoid follicles. Marginal zones are present in the mucosa-associated lymphoid tissues (MALT), the spleen, and occasionally within lymph nodes. The pathogenesis of marginal zone lymphoma is believed to involve a persistent infectious or autoimmune process, such as chronic gastritis induced by *H. pylori* or rheumatoid arthritis, which in turn induces lymphocyte accumulation [1,2].

MALT lymphoma is the most common marginal zone lymphoma subtype and accounts for 5-8% of all B-cell lymphomas. It presents as lymphomatous infiltration of an extranodal site in organs that normally lack lymphoid tissues [3,4]. The incidence of MALT lymphoma has no gender predilection and is highest in patients between the ages of 50 and 60. The most common site of origin is within the gastrointestinal tract, especially the stomach, but MALT lymphoma can also affect other organs, such as the parotid glands, the ocular adnexa/orbit, and the lungs [5]. MALT lymphoma is an indolent disease, usually confined to its site of origin upon diagnosis and tends to remain localized for a prolonged period. However, localized MALT lymphoma can often be multifocal. Disease dissemination to regional lymph nodes, or other sites upon initial presentation may occur in up to one-third of patients [6,7]. Furthermore, relapse of marginal zone lymphoma after successful treatment is not uncommon, and often occurs in a site distant from the site of origin [8-11].

MALT lymphoma is staged using the modified Ann Arbor staging system, which divides patients into four stages: localized disease (I), multiple sites of disease on one (II) or both sides (III) of the diaphragm and disseminated disease (IV). By definition, a subscript E is included in MALT lymphoma staging in recognition of the disease involvement of extranodal sites [12].

Differential Diagnoses:

The differential diagnoses of MALT lymphoma, which often present as a focus of increased FDG activity on PET/CT scan, may include other malignancies, and non-malignant processes such as reactive inflammatory lymphoid changes. Ultimately, tissue biopsy is critical in establishing the correct diagnosis. The presence of monoclonal neoplastic proliferation of lymphocytes will distinguish MALT lymphoma from

reactive inflammatory changes, which are characterized by polyclonal aggregation of lymphocytes. A combination of clinical history, as well as both histologic and immunophenotypic features allows for the distinction of MALT lymphoma from other malignancies, especially from other small B-cell lymphomas (e.g. follicular lymphoma, mantle cell lymphoma, and small lymphocytic lymphoma) (Table 2).

Clinical & Imaging Findings:

Because of the risk of multi-focal or multi-site disease in newly diagnosed and relapsed MALT lymphoma, accurate evaluation of the extent of disease involvement is essential. In this regard, the role of F-18 FDG PET/CT scan in disease staging, and post-treatment surveillance of MALT lymphomas is less clear when compared to other lymphoma subtypes. Per the clinical guidelines of the National Comprehensive Cancer Network (NCCN), PET/CT scan is an essential part of initial staging for non-gastric MALT lymphoma and can be useful in selected cases of gastric MALT lymphoma [13]. On the other hand, the practice guideline from the European Society of Medical Oncology (ESMO) does not see enough clinical utility in PET/CT scan to warrant its incorporation in initial staging [14]. Neither of these guidelines specify whether there is a role for PET/CT scan in post-treatment surveillance. There are primarily three challenges limiting the utility of PET/CT scan. First, the FDG activity of MALT lymphoma is low, especially in its early stage, due to its indolent nature [15]. As demonstrated in the case we presented, the right orbit region, where the biopsy-proven MALT lymphoma was found, had an associated SUVmax of 4.2 on the initial staging PET/CT. In a recently retrospective study from Memorial Sloan Kettering Cancer Center, Qi et al., analyzed the PET/CT positivity and the intensity of FDG activity of the biopsy proven lesions identified through PET/CT scan in 173 MALT lymphoma patients, and reported a median involved site SUVmax of 6.0 with a range of 0.7-28.0 [16]. Additionally, the FDG activity of a disease focus may be highly heterogeneous and dependent on the site of origin. Finally, the most common site of origin of MALT lymphoma is in the gastrointestinal tract, which has diffuse physiological background FDG activity, making it difficult to discern focal sites of disease. Therefore, the previously reported sensitivity of PET/CT scan varies drastically with sites of origin and disease stage, ranging from 0% to 81% [17-19].

The NCCN and ESMO guidelines are consistent with regards to the utility of PET/CT scan in assessing disease extent when there appears to be localized MALT lymphoma and a plan to proceed with radiotherapy. Neither guideline, however, has defined a standardized field of view. Understandably, providers who do not see the value of scanning more extensively will opt for a PET/CT scan from eyes to thighs. Nevertheless, the case we present here illustrates the pitfalls of performing a limited scan that does not include the full extent of the extremities. First, it is difficult to know when our patient's left calf lesions developed, since the distal lower extremities were never included in the field of views during initial staging and early restaging. This begs the question of whether the calf disease could have been detected earlier, prompting timelier initiation of systemic treatment. Second, the disease extent would have again been underestimated if we had relied solely on the

staging CT scan of the chest, abdomen, and pelvis, or if we were to have repeated a PET/CT scan from eyes to thighs only. The patient would have received a misguided localized approach to treatment. Finally, it is quite likely that these lesions would have remained undetected until a later time point, as the patient had thus far remained asymptomatic.

Treatment & Prognosis:

Radiation is an option for definitive treatment of early stage localized/organ-confined MALT lymphoma, i.e. IE and selected IIE, and can result in complete response in greater than 95% of the patients, which translates into excellent long-term local disease control and a 5-year overall survival of more than 90% [20-23]. In the event of disease dissemination, or when the patient is not an appropriate candidate for radiation, Rituximab monotherapy is often offered initially and confers a 5-year overall survival of approximately 90% [24].

TEACHING POINT

It can be challenging to stage and monitor an indolent disease such as MALT lymphoma, which can sometimes present in multiple sites, anywhere in the body, and can relapse at distant locations years after completion of local treatment. Staging of patients with MALT lymphoma and the use of a whole-body scanning protocols covering vertex to feet, when FDG PET/CT scan is being utilized, is recommended to accurately determine optimized treatment approaches.

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FIGURES

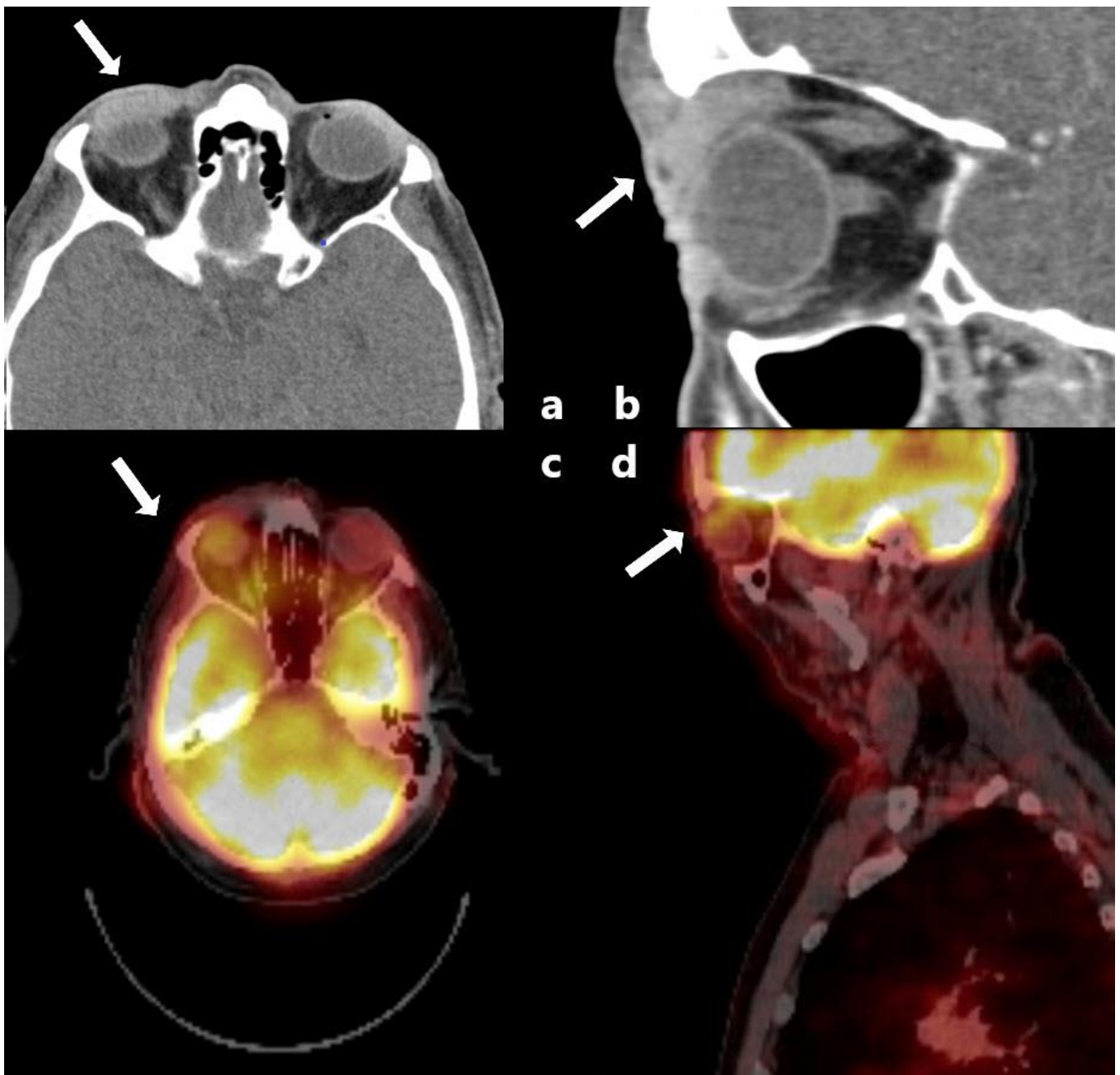


Figure 1: 70-year-old male with mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) of the right eyelid.

When this patient was 70 years old, he presented with a newly diagnosed with MALT lymphoma of the right orbit.

FINDINGS: CT scan of the orbit with contrast enhancement demonstrated a 2.7 x 2.3 x 1.8 cm infiltrative mass in the right upper eyelid, extending posteriorly into the extraconal orbit along the orbit roof (Figure 1a, axial view; Figure 1b, sagittal view, arrow); on a staging PET/CT scan from eyes to thigh that was obtained shortly after biopsy, there was a focus of asymmetric increase in FDG activity with a SUVmax of 4.2 in the region of the right orbit, likely related to the biopsied mass. (Figure 1c, axial view; Figure 1d, sagittal view, arrow).

TECHNIQUE: Figure 1a, b: Axial CT scans with 67 mAs, 120 kV in 2 mm slice thickness and coronal reformations without and with 100ml IV nonionic iodinated contrast material. Figure 1c, d: Initial non-contrast whole body CT axial scan with 71 mAs, 130 kV in 3 mm slice thickness was performed for attenuation correction purposes. Patient is then injected intravenously with 15.3 mCi of F-18 fluorodeoxyglucose followed by a delayed PET scan 60 minutes afterwards from the skull base through the mid thigh. Blood glucose 95 mg/dL.

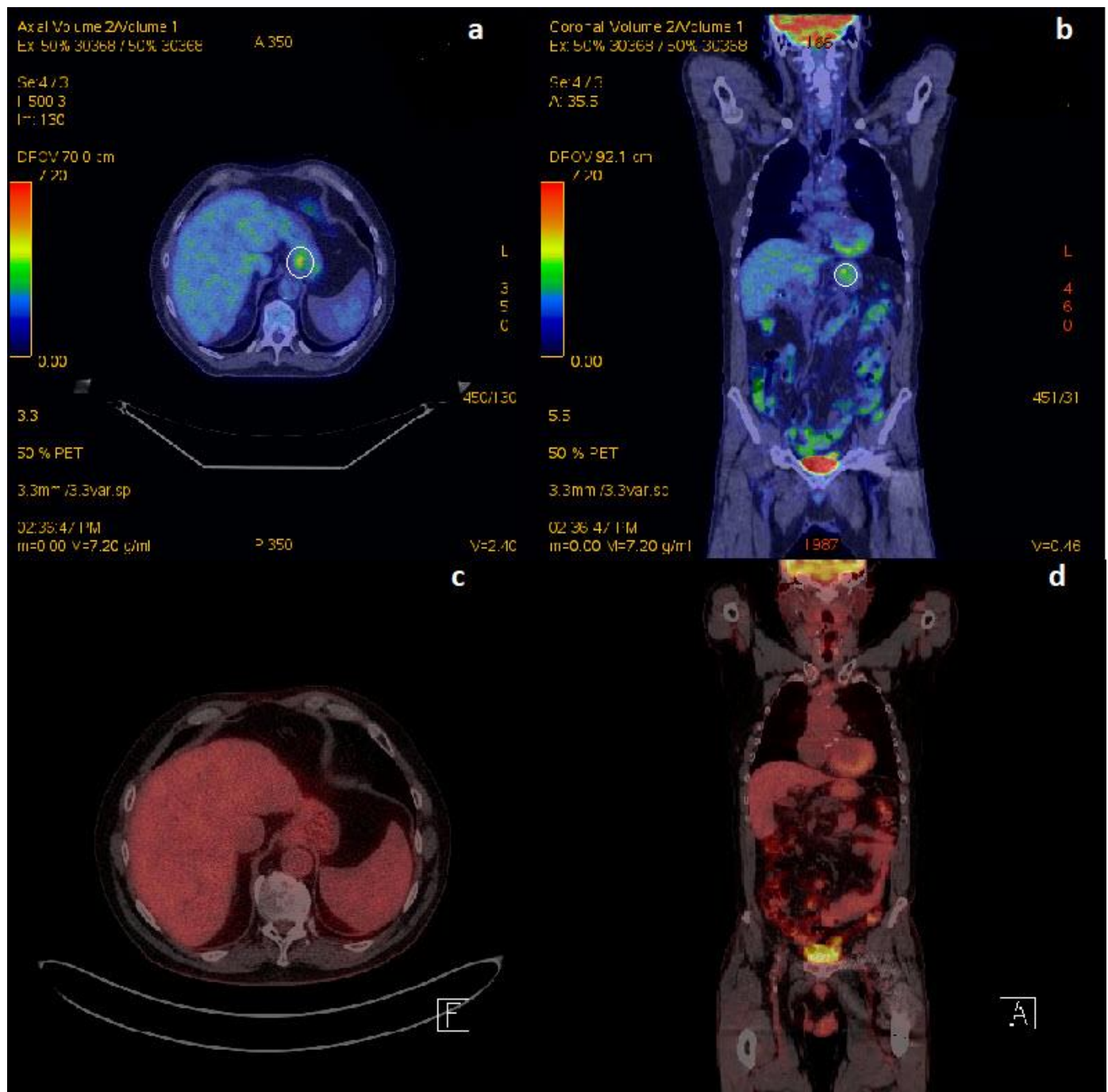


Figure 2: 73-year-old male with mucosa-associated lymphoid tissue lymphoma (MALT lymphoma).

Three years later (after figure 1), this patient was diagnosed with relapsed MALT lymphoma of the gastric cardia.

FINDINGS: On the re-staging PET/CT scan from eyes to thighs, there is a new focus of increased FDG activity in the proximal stomach adjacent to the gastroesophageal junction with SUV Max of 4.6, corresponding to the biopsied lesion (Figure 2a, axial view; Figure 2b, coronal view, circle). A post-treatment PET/CT scan from eyes to thighs was obtained after completion of radiation to the stomach, which showed resolution of the previous focus of increased FDG activity in the gastric cardia (Figure 2c, axial view; Figure 2d, coronal view).

TECHNIQUE: 2a, b: Initial non-contrast whole body CT axial scan with 12 mAs, 120 kV in 3.75 mm slice thickness was performed for attenuation correction purposes. Patient is then injected intravenously with 14.92 mCi of F-18 fluorodeoxyglucose followed by a delayed PET scan from the skull base through the mid thigh 60 minutes afterwards. Blood glucose 90 mg/dL. 2c, d: Initial non-contrast whole body CT axial scan with 94 mAs, 130 kV in 2 mm slice thickness was performed for attenuation correction purposes. Patient is then injected intravenously with 14 mCi of F-18 fluorodeoxyglucose followed by a delayed PET scan from the skull base through the mid thigh. Blood glucose 85 mg/dL.

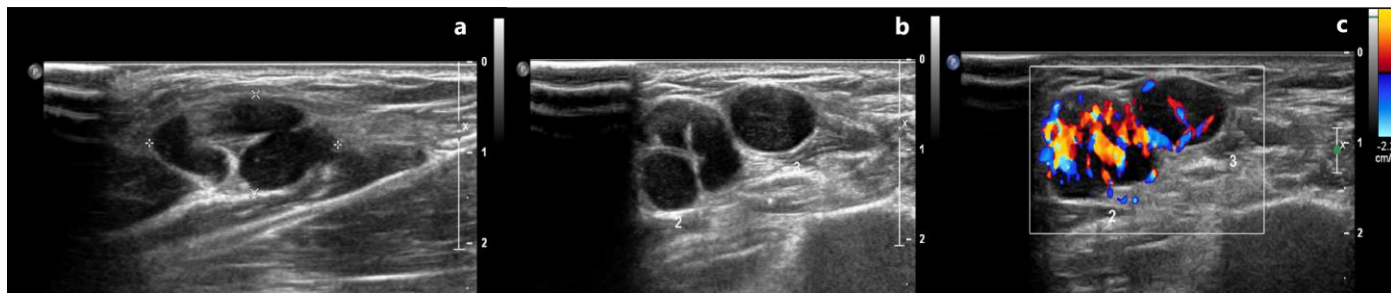


Figure 3: 79-year-old male with mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) who was found to have several nodules in the left arm, just below the axilla, medial to the proximal biceps muscle.

FINDINGS: Directed sonography over the palpable nodules revealed several hypoechoic nodules (3a, 3b). Color Doppler image demonstrated hypervascularity (3c) They are consistent with enlarged lymph nodes. The largest one measures 0.9 x 3.0 cm.

TECHNIQUE: Gray scale and color Doppler images obtained using linear 5-18 MHz transducer (frequency 15 MHz) on Phillips Epiq7® scanner).

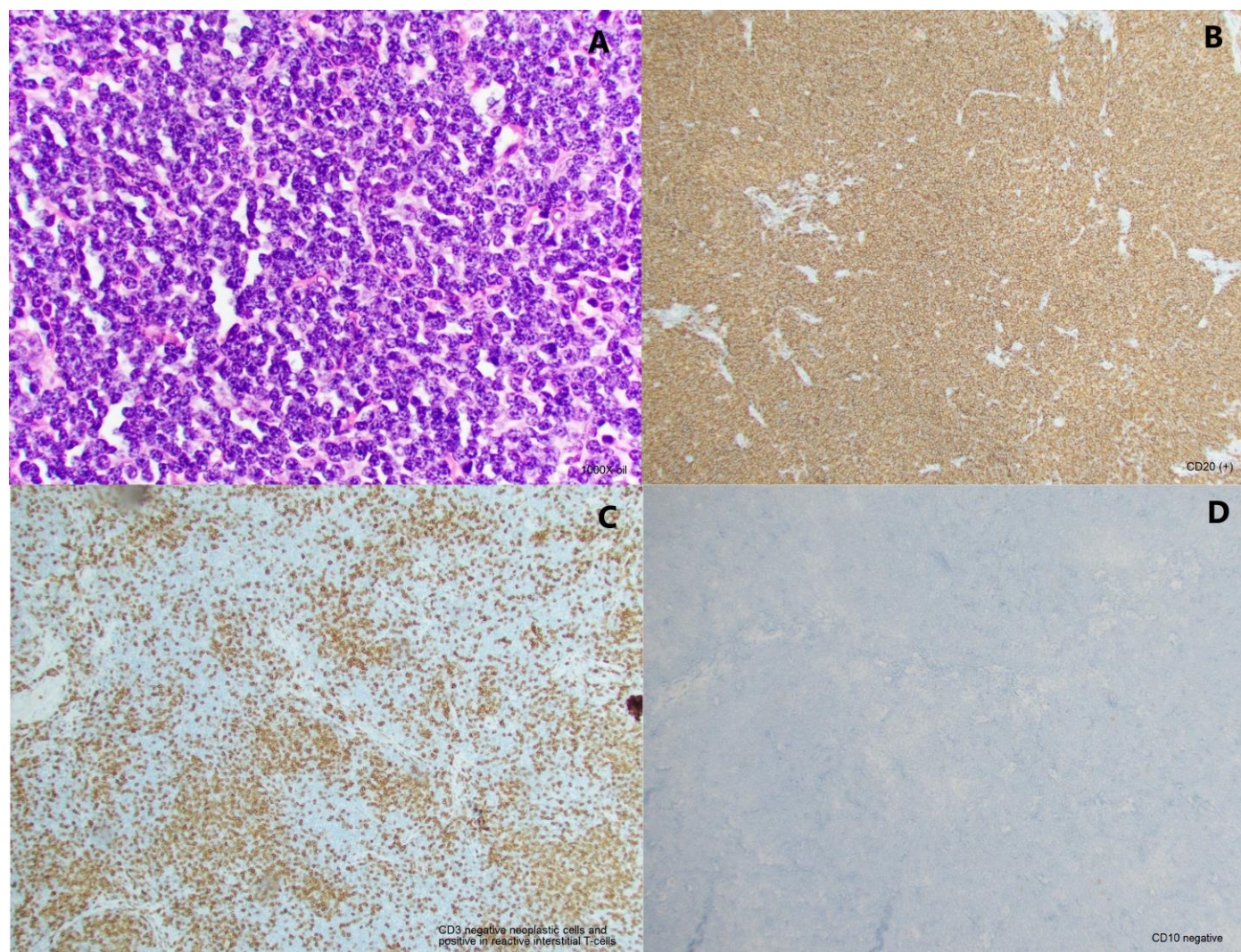


Figure 4: 79-year-old male with mucosa-associated lymphoid tissue lymphoma (MALT lymphoma)

The patient underwent excisional biopsy of the palpable left axillary masses, which confirmed the diagnosis of nodal MALT lymphoma.

FINDINGS: Left axilla lymph node pathologic specimen. H & E 1000x (4A) - showed monomorphic small cell proliferation with a slightly vague nodular architecture without significant nuclear irregularity. Immunohistochemical staining was positive for CD 20 (4B), and negative for CD 3 (4C), CD 10 (4D).

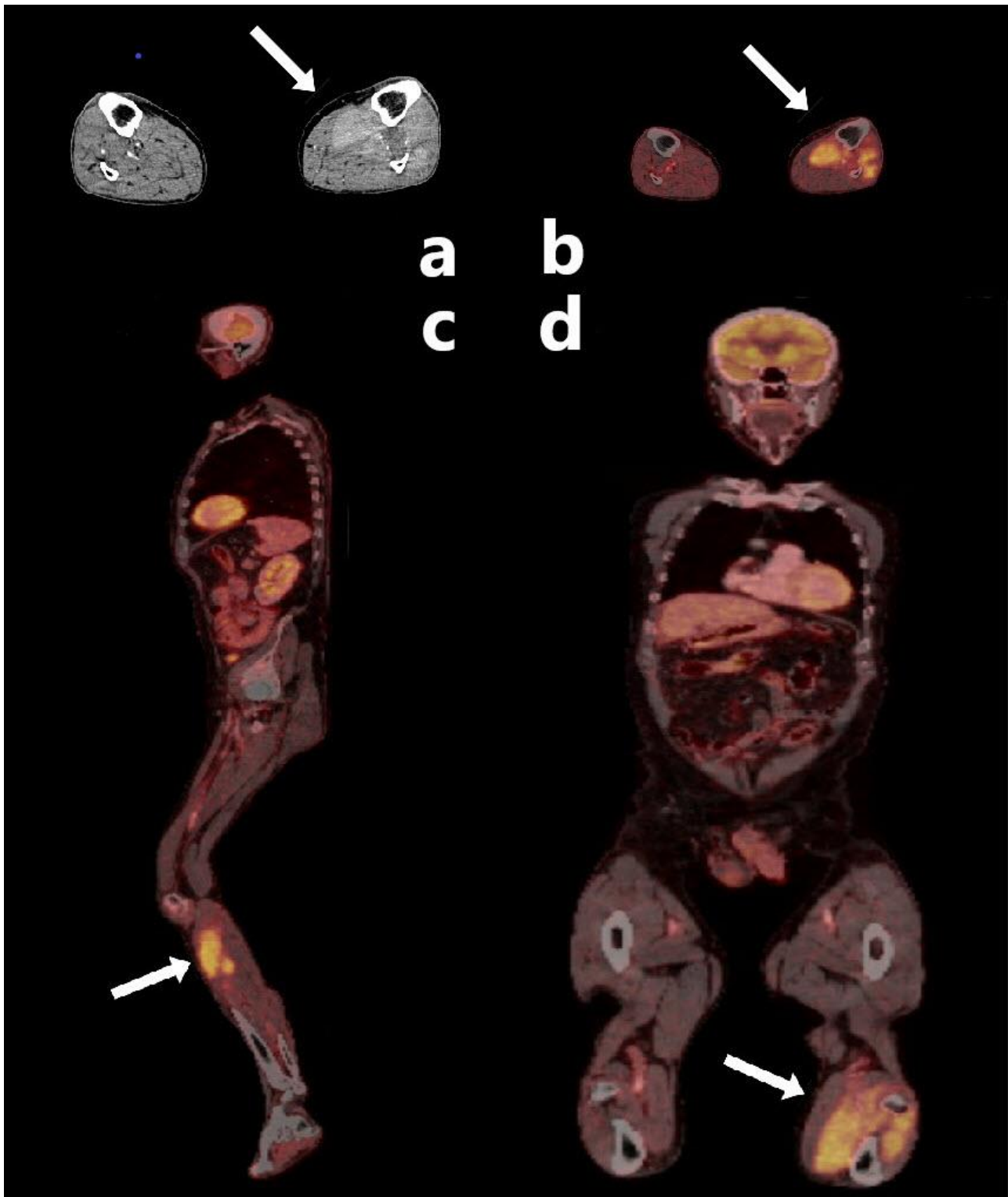


Figure 5: 79-year-old man with relapsed MALT lymphoma of the left axilla, which was excised for biopsy.

FINDINGS: On the re-staging PET/CT scan from vertex to feet, there is no suspicious focus of increased FDG activity in either upper extremity. However, there is a group of intramuscular masses in the proximal left lower leg that showed increased FDG activity, with a SUV Max of 7.4 (Figure 5a, CT axial view, arrow; Figure 5b, PET axial view; Figure 5c, sagittal view; Figure 5d coronal view, arrow). This finding turned out to be lymphomatous involvement. Previous PET/CT scans do not include this area in field-of-view.

TECHNIQUE: Initial non-contrast whole body CT axial scan with 59 mAs, 120 kV in 2 mm slice thickness was performed for attenuation correction purposes. The patient then received 11.2 mCi of F-18 fluorodeoxyglucose followed by a delayed PET scan 60 minutes afterwards. Images were acquired from vertex to feet. Blood glucose 140 mg/dL.

Etiology	Induced by chronic inflammation in extranodal sites.
Gender ratio	No gender predilection.
Age predilection	Most frequently diagnosed between 5th and 6th decade.
Risk factors	Persistent infectious or autoimmune process.
Treatment	H. pylori associated gastric MALT lymphoma is treated with antibiotics. Other localized MALT lymphoma: radiotherapy
Prognosis	This is an indolent disease, usually confined to its site of origin upon diagnosis and remained localized for years, so the prognosis is generally favorable.
Findings on imaging	The role of PET/CT scan in staging and surveillance of MALT lymphoma remains ill-defined due to the indolent nature of this disease and the high variability of associated FDG activity amongst different disease sites. When PET/CT scan is indicated, we recommend obtaining a PET/CT scan from vertex to feet, as MALT lymphoma has been found in virtually all tissues and organs both upon initial diagnosis and later with disease relapse.

Table 1: Summary table of MALT Lymphoma.

Diagnosis	History/clinical features	Histological features	CT scan	MRI	PET/CT scan
MALT lymphoma	-Commonly presents with a slow growing mass. -May develop symptoms due to localized disease involvement of the glandular epithelial tissues of the site of origin. -Stomach: heart burn, gastroesophageal reflux disease, anorexia, weight loss and occult gastrointestinal bleeding. -Ocular adnexa: eye redness, and epiphora in ocular adnexa. -Skeletal muscle: may presents with pressure and neuropathic symptoms due to mass effect.	Monoclonal proliferation of extrafollicular B-cells, typically with the morphology of marginal zone cells.	-Gastric MALT lymphoma: diffuse, nodular, or segmental wall thickening, mild to modest enhancement. -Ocular adnexal MALT lymphoma: diffuse infiltration of ocular adnexa with homogenous attenuation, mild to modest enhancement. -Skeletal muscle MALT lymphoma: homogenous attenuation, isodense or slightly hyperdense in muscle, mild to modest contrast enhancement.	-Gastric MALT lymphoma: no specific indication. -Ocular adnexal MALT lymphoma: isointense to hyperintense on T2 images slightly hypointense on T1-weighted images. -Skeletal muscle MALT lymphoma: intensity between muscle and fat on T2-weighted images and isointense to slight hyperintense on T1-weighted images	Variable FDG activity
Other B-cell lymphomas	-Commonly presents with asymptomatic enlargement of lymph nodes in the neck, axilla, groin, or femoral canal. -Can sometimes present in extranodal sites and causes symptoms, similar to MALT lymphoma. -Aggressive B-cell lymphomas can also present with systemic B symptoms of weight loss, night sweat, fevers, and weight loss.	Monoclonal proliferation of B-cells, which can be distinguished from marginal zone B-cells with further analysis of the histologic characteristics and immunophenotypic features.	-Lymphatics involvement, isodense to slightly hyperdense, variable enhancement. -Extranodal involvement is location dependent.	-no specific indication.	Variable FDG activity -indolent lymphomas may present with modest increase in FDG avidity -aggressive lymphomas are typically high in FDG avidity.
Reactive inflammatory processes	-Commonly presents with asymptomatic enlargement of various organs. -May be associated with a history of chronic local irritation or trauma, especially in the oral cavity.	Hyperplasia of polyclonal lymphocytes	-Hypodensity with heterogeneous enhancement	-no specific indication.	Low FDG activity

Table 2: Differential diagnosis table for MALT Lymphoma.

ABBREVIATIONS

CT = Computed tomography
ESMO = European Society of Medical Oncology
F-18 FDG PET/CT = F-18 fluorodeoxyglucose positron emission tomography integrated with computed tomography
FDG = Fluorodeoxyglucose
H. pylori = Helicobacter pylori
MALT lymphoma = Mucosa-associated lymphoid tissue lymphoma
NCCN = National Comprehensive Cancer Network
PET/CT = Positron emission tomography-computed tomography

KEYWORDS

Extranodal marginal zone B-cell lymphoma; mucosa-associated lymphatic tissue (MALT) lymphoma; Marginal zone lymphoma of MALT; field of view; PET/CT

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