18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in a Rare Case of Epithelioid Hemangioendothelioma – A Diagnostic Challenge

Abstract

Our case highlights the 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scan findings in a rare case of biopsy-proven epithelioid hemangioendothelioma (EHE) in a 66-year-old woman with multi-organ involvement (lung, liver, and bone) who was subsequently treated with palliative radiation therapy and oral pazopanib. Furthermore, follow-up 18F-FDG PET/CT findings are detailed. EHE is a rare malignant vascular neoplasm (<1% of all vascular tumors) with an epithelioid and histiocytoid appearance arising from the vascular endothelial and preendothelial cells.

Keywords: *18F-fluorodeoxyglucose positron emission tomography/computed tomography, epithelioid hemangioendothelioma, pazopanib*

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Case Summary

A 66-year-old woman initially presented with complaints of abdominal pain, vomiting, and backache for 1 year. Contrast enhanced-computed tomography (CE-CT) chest and abdomen study revealed multiple small bilateral pulmonary nodules which were reported as infective/inflammatory in nature and also bilateral liver hypodense lesions with subtle arterially enhancing rim, reported as metastases. Magnetic resonance imaging (MRI) lumbosacral spine showed subtle patchy marrow edema involving L3 vertebra with surrounding edema in the paraspinal muscles, features likely of infective/inflammatory etiology. In view of age of the patient and scan findings of bilateral pulmonary nodules with bilobar liver lesions and skeletal lytic lesions, the clinical suspicion was that of disseminated metastases and hence the patient was referred for fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) to look for unknown primary. Baseline FDG PET/CT [Figure 1a] showed multiple pleural-based, subpleural, and parenchymal irregular nodular lesions in both lungs with no significant FDG uptake in the right lung upper lobe measuring approximately 1.6 cm × 1 cm with pleural tagging [Figure 1c]. Multiple mildly FDG-avid peripherally enhancing hypodense lesions were noted in both lobes of the liver. The largest hypodense lesion in segment VII of the liver measured 2.3 cm × 2.1 cm with SUVmax 1.7 [Figure 1e]. On triple-phase CT images [Figure 2a-c], multiple hypoattenuating lesions were seen in both lobes with predominant peripheral enhancement. Also, noted were mildly FDG-avid lytic lesions in few skeletal sites as follows-in the left scapula [Figure 1g] with soft tissue component (SUVmax: 2.1), proximal shaft of left femur, and spinous process of L3 vertebra. To summarize the 18F-FDG PET/CT findings, there were nonmetabolic bilateral pulmonary nodules, mildly metabolically active bilobar liver lesions, and lytic lesions in few skeletal sites. With no definite lesion to suggest primary, the first differential reported was mild active infective/inflammatory disease (?disseminated tuberculosis) and the second differential was metastatic cancer of unknown primary. Biopsy was advised for confirmation. Ultrasonography-guided liver biopsy and Immunohistochemistry (IHC) showed features of epithelioid

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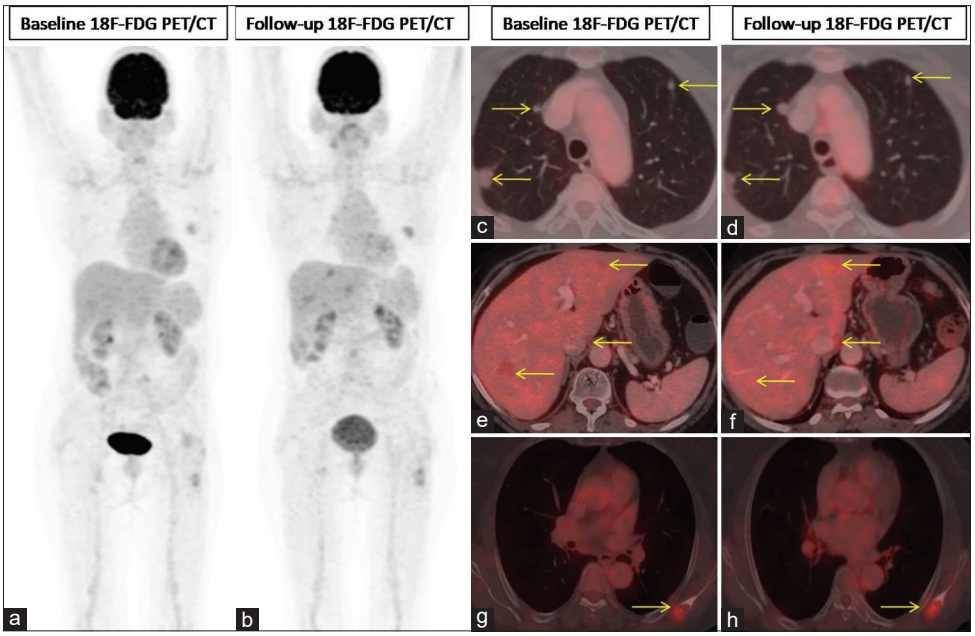

Figure 1: Baseline and follow-up 18F-FDG PET/CT images. (a and b) show baseline and follow-up 18F-FDG PET/CT maximum intensity projection images, respectively. The transaxial fused image (c) shows few nonmetabolic pleural-based and parenchymal irregular nodular lesions in both lungs. (e) Shows multiple mildly FDG-avid peripherally enhancing hypodense lesions in both lobes of the liver (SUVmax of the caudate lobe lesion 1.7). (g) Shows a FDG-avid lytic lesion with soft tissue component in the left scapula (SUVmax: 2.2). On follow-up 18F-FDG PET/CT post palliative radiotherapy to left femur lesion and oral pazopanib, there is no significant interval change in size and number of the bilateral lung lesions (d). (f and h) show mild interval increase in metabolic activity in few of the liver lesions (SUVmax of the caudate lobe lesion: 2.8) and also in the lytic lesions in multiple skeletal sites (SUVmax: 2.7 in the left scapula). 18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography

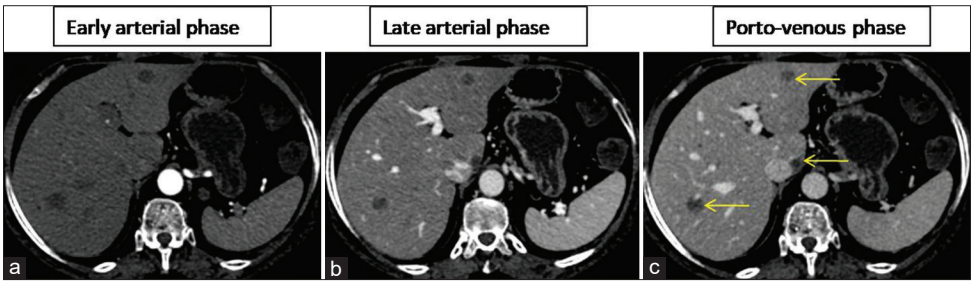

Figure 2: Triple-phase contrast-enhanced computed tomography images of the abdomen. (a-c) show multiple hypoattenuating lesions in both lobes of the liver with predominant peripheral enhancement

hemangioendothelioma (EHE) [Figure 3a-c]. Hence, a final diagnosis of EHE was made in our patient with multi-organ involvement as shown in 18F-FDG PET/CT scan. The patient was treated with palliative radiotherapy to the proximal shaft of the left femur with direct anterior and posterior field (20 Gy/5#/5 days) along with oral pazopanib 400 mg once a day.

Post 3 months of radiotherapy, follow-up 18F-FDG PET/CT [Figure 1b] showed no significant interval change in size and number of the bilateral lung lesions [Figure 1d]. Mild interval increase in metabolic activity in few of the liver lesions was observed in the caudate lobe with SUVmax 2.8 versus previous SUVmax 1.7 [Figure 1f], segment III and IVa lesions. Mild interval increase in metabolic activity of the lytic lesions in multiple skeletal sites was also seen [SUVmax in the left scapula lesion was 2.7 versus previous SUVmax 2.1, Figure 1h].

Discussion

EHE is a rare malignant vascular neoplasm with an epithelioid and histiocytoid appearance arising from the vascular endothelial as well as preendothelial cells. EHE makes up <1% of all vascular tumors.[1] The 5th Edition of the 2020 World Health Organization classification of tumors of soft tissue and bone describes EHE as malignant vascular neoplasm.[2] EHEs have been characterized by tumor-specific WW domain-containing transcription regulator 1-calmodulin-binding transcription activator 1 translocations and Yes-associated protein 1-transcription factor E3 gene fusion.[3,4] Although the median age at diagnosis is reported to be around 38 years, EHE can occur from children to the elderly, with a female preponderance of 1.5–4.5. Although it is difficult to assess the prognosis, studies have revealed that multi-organ involvement, age >55 years, presence of symptoms at the time of

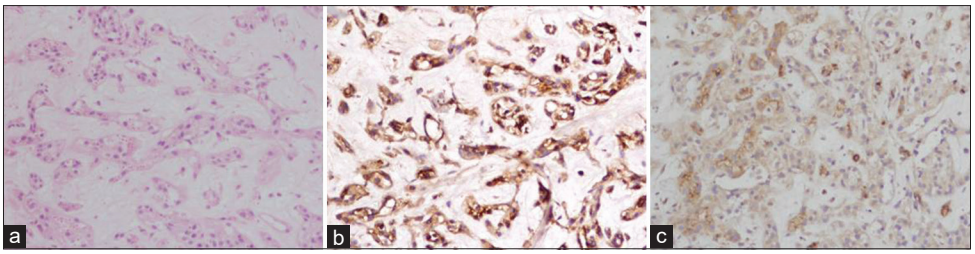

Figure 3: Liver biopsy images show features of epithelioid hemangioendothelioma. (a) shows an infiltrative neoplasm composed of rounded to spindled tumor cells arranged in short strands and solid nests. The tumor cells appear epithelioid and have round to oval nuclei with mild nuclear atypia, inconspicuous nucleoli, and moderate eosinophilic cytoplasm. Background stroma appears myxoid with scanty mixed inflammatory infiltrate. On immunohistochemistry, tumor cells show membranous positivity for CD 31 (b), focally positive for EMA (c) and TFE-3. EMA: Epithelial membrane antigen , TFE-3: Transcription factor E3

diagnosis, pulmonary lesions, high Ki-67 index, and mitotic activity indicate poor prognosis.[4] There is very limited literature regarding EHE, and majority are case reports or case series describing solitary organ involvement.

Pathologic findings are a must for the final diagnosis; nevertheless, the imaging techniques are useful in determining the sites of involvement and extent of the disease and potentially guide the treatment. A review of literature by Mehrabi *et al.* reported that approximately 60%–80% of patients with EHE were misdiagnosed.[5] Pulmonary involvement in EHE mimics metastases and locally advanced lung cancer.[6] Hepatic EHEs are most commonly misdiagnosed with cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma, metastatic carcinoma, and sclerosing hemangioma.[7] While, skeletal EHE involvement is often misdiagnosed as multiple myeloma, metastatic tumor, or brown tumor.[8] Xu *et al*. observed increased tracer uptake mostly in the lesion margins and defect inside lesions on technetium 99m-methyl diphosphonate bone scintigraphy with single-photon emission computed tomography/CT which they attributed to active bone dissolution and concluded high sensitivity of whole-body bone scintigraphy can help detect silent lesions.[8,9]

Limited literature is available citing the role of 18F-FDG PET/CT in evaluation of EHE. 18F-FDG PET/CT may play an important role in detection of multi-organ involvement in EHE and help guide the site for biopsy and also for assessing treatment response. Frota Lima *et al*. evaluated the imaging characteristics of EHE on staging 18F-FDG PET/CT. The authors conducted a retrospective review on 35 patients and observed 18/35 patients (52%) had more than one organ affected, the most common sites reported were liver (60%), lung (54%), bone (14%), lymph nodes (11%), and vasculature (11%).[10] In EHE with multiple organ involvement, it is difficult to conclude if the tumor is multicentric or there is a primary lesion with metastases to other tissues. It is reported observed that metastatic lesions may show less differentiation and loss of expression of epithelial markers.[1] EHE is generally reported to have mild-to-moderate FDG uptake. Frota Lima *et al*., in their study, demonstrated a broad range of FDG avidity in the EHE lesions with an average SUVmax of 5.3 ± 3.3 (range: 1.2–17).[10] Normal physiological FDG uptake in the liver may mask few of the hepatic EHE lesions and also few lesions may be too small for accurate SUV assessment; 21% of the patients had non-FDG-avid nodules.[10] Hence, combination with CE-CT or MRI is recommended. Few additional nuclear medicine diagnostic tracers reported in literature in evaluation of EHE are 68Ga-DOTATATE and 68Ga-PSMA.[11-13] It will be interesting to study the role of diagnostic PET tracers targeting vascular endothelial growth factor (VEGF) and integrin $\alpha v\beta 3$ which are angiogenic markers in EHE.

Therapy options in EHE with multi-organ involvement are limited. Most often combination treatment protocols are tried. Treatment options reported in literature include chemotherapy (carboplatin and paclitaxel), bevacizumab (VEGF inhibitor), radiation therapy, and pazopanib (tyrosine kinase inhibitor).[1,7,13,14] Given the propensity of EHE patients to present with multiple organ involvement rather than a solitary organ, imaging with 18F-FDG PET/CT seems a better alternative in comparison to region-specific conventional imaging techniques such as CT or MRI. An added advantage of whole-body imaging with PET/CT in EHE patients is to assess posttreatment response.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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