Role of FDG PET/CT in Diagnostic Evaluation of Granulocytic Sarcomas: A Series of 12 Patients

Piyush Chandra, Sanket Dhake, Nilendu Purandare, Archi Agrawal, Sneha Shah, Venkatesh Rangarajan

Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Mumbai, Maharashtra, India

Abstract

Objective: Granulocytic sarcoma (GS) is a rare extramedullary manifestation in patients with acute myeloid leukemia (AML), which can precede the diagnosis or occur in the posttreatment setting. Unlike its established role in other hematological malignancies like Hodgkin's on non-Hodgkin's disease, the exact role of positron emission tomography/computed tomography (PET/CT) in AML with or without GS remains to be defined. **Materials and Methods:** We retrospectively reviewed PET/CT scans of 12 patients with histologically proven GS. Marrow examination of these patients identified nine patients with isolated GS (without existent leukemia) and three patients with coexistent leukemia. **Results:** PET/CT accurately identified all clinically evident GS in all 12 patients at initial staging and at follow-up with tumors, showing moderate to high 2-deoxy-2-fluoro-D-glucose uptake. Coexistent marrow disease was seen on PET/CT in three patients, which was confirmed on histopathology. In the same patients, PET/CT also detected additional sites of extramedullary disease in 66.6% (n = 8), which was either clinically occult or not evident on routine CT. **Conclusion:** PET/CT appears to be a highly sensitive imaging modality in diagnostic evaluation of GS. The most important indication of using PET/CT in these cases is to identify additional sites of clinically occult extramedullary disease, which can potentially impact treatment decisions and outcomes.

Keywords: *FDG, PET/CT, granulocytic, sarcoma, myeloid, AML, leukemia*

Introduction

Granulocytic sarcoma (GS) or myeloid sarcoma is a rare extramedullary tumor arising from immature granulocytes. It is most commonly seen in association with acute myeloid leukemia (AML) and uncommonly with myelodysplastic syndrome, chronic myeloid leukemia (CML), or myeloproliferative disorders. They may precede the diagnosis of AML or can be a presenting feature of AML or occur during relapse after initial treatment.[1,2] The incidence of GS in AML across all ages is about 9%. It is more common in children, where it is reported in up to 40% of the cases.[3] Rarely, these tumors may not be associated with any hematological malignancy/disease and are termed as primary/nonleukemic GS.[1] Although most patients usually develop AML eventually, 25% of these patients on long-term follow-up never develop acute leukemia. The exact reason for why certain patients do or do not progress is currently unknown.[3] Due to lack of large prospective studies, prognostic significance of GS in AML is uncertain. One study showed median overall survival of 5.4 months and 59.5 months survival (P = 0.002) in AML patients with and without GS, respectively.[4] However, other studies showed no difference in survival in these two groups.[5,6] Certain AML subtypes, such as M2, M4, and M5 subtypes are probably more likely to be associated with GS than other subtypes.[7]

The clinical manifestations in patients with GS are a result of mass effect by the primary tumor. GS can be clinically misdiagnosed as non-Hodgkin's lymphoma, extraosseus Ewing's sarcoma, or embryonic rhabdomyosarcoma due to similar clinical presentation/pathological features. Role of imaging in patients with GS is to facilitate early and accurate clinical diagnosis, guide biopsy, aid in treatment planning, and for evaluation of treatment response. Tumors can be solitary or multifocal with local CT or magnetic resonance imaging (MRI) findings often nonspecific. Numerous sites have been described in literature; among these most

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Address for correspondence:
Dr. Venkatesh Rangarajan, Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India. E-mail: drvrangarajan@gmail.com

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common locations include bone, soft tissue, peritoneum, central nervous system, and lymph nodes.[8-11] Few case reports/series published previously have shown utility of 2-fluoro-deoxy-glucose positron emission tomography/computed tomography (FDG PET/CT) in accurately evaluating the disease burden, by identifying additional sites of disease involvement which may be clinically occult or not identified on conventional imaging.[12-15] We present a retrospective case series to demonstrate the clinical utility of PET/CT performed at baseline and follow-up of patients with biopsy-proven GSs.

Patients and Results

This is a retrospective cohort of 12 patients with GS who underwent PET/CT at our institute from 2010 to 2016. A total of 14 PET/CT scans were reviewed, eight of these were performed at baseline and six at follow-up/posttreatment setting. In all these patients, the primary site was biopsied within 1–2 weeks of PET/CT scans and was positive for GS. Marrow biopsy to demonstrate coexistent AML was done in all initial staging patients within 1 week of PET/CT scans. All the PET/CTs were done without administration of an intravenous contrast as per the institution protocol.

Detailed profile of patients is presented in Tables 1 and 2. Most of these patients (8/12) were evaluated with PET/CT at initial staging, with no prior history of AML with suspected clinical diagnosis of lymphoma/sarcoma. In remaining four patients, PET/CT was done at follow-up, either for evaluation of treatment response or suspected disease recurrence after receiving chemotherapy with or without radiotherapy. In seven out of eight initial staging, patients were children/adolescents with a mean age of 14 (range 10–19). GS was the presenting clinical symptom in all these seven patients, where biopsy subsequently confirmed coexistent marrow disease in two of them. Out of the four adult patients referred for PET/CT for follow-up evaluation, one patient was a known case of CML on treatment.

PET/CT detected the clinically evident primary/recurrent GS in all 12 patients. The FDG uptake of treatment naïve primary tumors was moderate with mean standardized uptake value (SUVmax) of 7.92 (range 2.5 -16.6). PET/CT detected additional multiple clinically occult lesions in 66% of patients (n = 8/12). In two patients who underwent PET/CT following chemotherapy/radiotherapy showed progressive disease in one and partial response in another. In three follow-up patients, PET/CT confirmed clinical disease relapse.

Discussion

Incidence of GS in AML is probably higher in the era of advanced imaging than previously thought. GS with or without coexistent leukemia can occur at any organ/site in

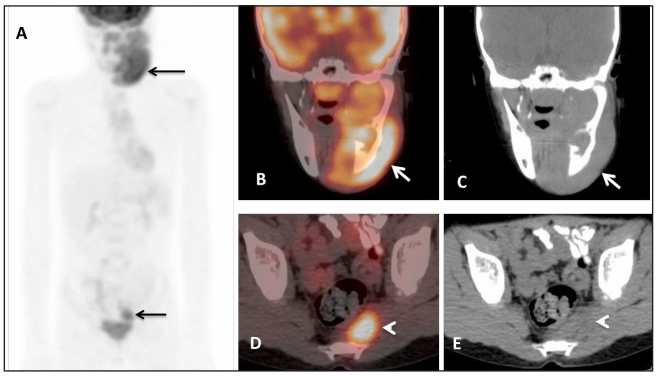

Figure 1: (a) Maximum intensity projection (MIP) image of 14-year-old male patient with FDG avid disease in the left mandible and pelvis. (b and c) Showing coronal PET/CT and CT images, show lytic lesion with soft tissue mass involving the ramus of the left mandible (white arrow), (d) Transaxial PET/CT and CT images, showing FDG avid soft tissue lesion in the presacral region, which is clinically occult and not very evident on CT alone (arrow head).

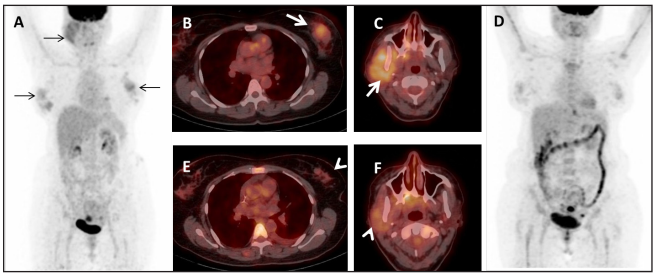

Figure 2: (a) Maximum intensity projection (MIP) image of 50-year-old female patient with FDG avid disease in the right parotid and bilateral breast (thin black arrows). Focal FDG uptake noted in the pelvis (thick black arrow) was confirmed on ultrasound evaluation as fibroid. (b and c): Transaxial PET/CT image showing FDG avid nodule in the left breast and right parotid (small bold white arrows). Follow-up PET/CT postchemotherapy at 2 months showing partial metabolic and morphological response on MIP. (d) Transaxial PET/CT images (arrow heads, E and F).

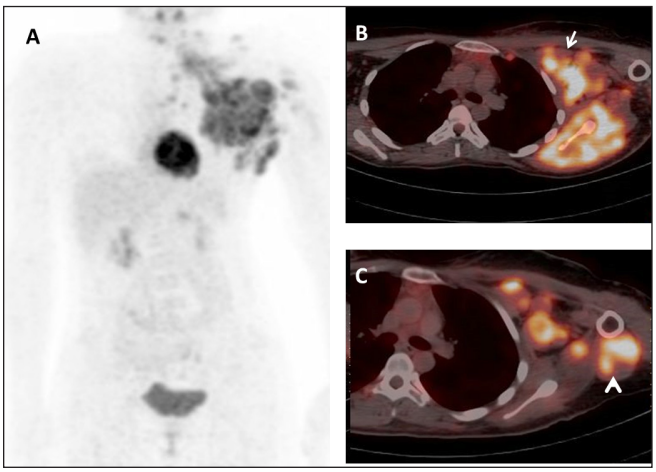

Figure 3: (a) Maximum intensity projection (MIP) image of 20-year-old female patient with FDG avid disease in the left scapular region, axilla, and supraclavicular region. (b) Showing axial PET/CT and FDG avid soft tissue mass arising from the left scapula (long white arrow) with enlarged FDG avid left axillary nodes (small white arrow). (c) Follow-up PET/CT postchemotherapy and radiotherapy at 6 months shows complete response in the scapular mass, however, with new FDG avid nodular lesions posterior to the left humerus metaphysis (arrow head), suggestive of progressive disease.

Table 1: Details of Patients referred for baseline disease status evaluation

Age/ Gender	Clinical Presentation	Primary Site of GS	Marrow disease	PET/CT findings of primary site	Additional PET/CT findings
15/F	Pain in abdomen with intermittent vomiting	Small intestine	Negative	Right pelvic mass involving ileal loops (4.8cm-SUVmax-8.04)	Multiple mesenteric, retrocaval, aortocaval and para-aortic nodes (largest 1cm-SUVmax-5.04)
19/F	Pain in Left shoulder	Scapula	Negative	Large soft tissue mass associated with lytic erosion of the scapula (11.5cm-SUVmax-11.41)	Multiple left axillary and supraclavicular nodes (largest-2.5cm-SUVmax-6.10)
13/M	Bilateral neck swelling with fever	Cervical nodes	Positive- AML-M7	Enlarged discrete bilateral cervical nodes- largest 3cm-SUVmax-4.59	Multiple enlarged mediastinal, retroperitoneal, inguino-pelvic nodes (largest pelvic-2cm-SUVmax-3.34) Diffuse increased FDG uptake in marrow of entire axial and appendicular skeleton
13/M	Swelling in left submandibular region	Mandible	Negative	Large soft tissue mass associated with lytic erosion of the ramus of mandible extending into retromolar trigone and left masseteric space (9cm-SUVmax-11.88)	Pre-sacral soft tissue mass extending into the left S3 and S4 neural foramina (3.5cm-SUVmax-11.11)
10/F	Right eye proptosis	Orbit	Negative	Soft tissue mass in superior aspect of right orbit (3.5cm-SUVmax-2.5)	None
17/M	Swelling in lower back with paraplegia	D-10 vertebra	Negative	Large para-spinal soft tissue mass associated with lytic lesion involving the pedicle/lamina of D10 vertebra (6.1cm-SUVmax-3)	None
11/M	Progressive swelling in the left orbit with loss of vision	Orbit	Positive- AML-M2	Large intra-orbital mass displacing the eye antero-laterally laterally (6.7cm-SUVmax-4.79)	Multiple para-spinal lesions at L1, D3 and L5-S1 level (largest 3.5cm-SUVmax-8.5) Lesion in the S1-S4 neural foramina (SUVmax-4.98) Diffuse increased FDG uptake in marrow of entire axial and appendicular skeleton
48/F	Parotid swelling	Parotid	Negative	FDG avid mass involving the right parotid and infiltrating masseter and pterygoid muscles (6.8cm-SUVmax-6.8)	FDG avid bilateral soft tissue breast lesions (largest on left- 4cm- SUVmax-5.8)

the body with varied clinical presentation.[3] Accordingly, the true extent of such a systemic disease would be better characterized with whole body PET/CT rather than conventional local imaging (CT/MRI) alone. The higher sensitivity of PET/CT compared with conventional imaging in tumor imaging can partly be attributed to whole body coverage in PET/CT, where identification of clinically occult distant metastases, changes treatment decisions in a significant number of patients. The evidence supporting the use of FDG PET in diagnostic evaluation of GS is promising as suggested by several case reports and multiple retrospective case series.[12-15] In one study including 10 patients with histologically proven GS, where PET/CT identified all of the 52 untreated or recurrent lesions, CT alone was false negative for 13 of these lesions.[12] Results of a large observational study to evaluate the diagnostic utility of PET/CT in AML patients, with GS before and after induction chemotherapy, is being awaited (*ClinicalTrials.gov Identifier: NCT01278069*).

In our series, PET/CT accurately detected the clinically evident primary/recurrent GS in all 12 patients. The FDG uptake of primary tumors was moderate with mean SUV max of 7.92 ranging from 2.5 to 16.6. High FDG uptake by the tumor makes PET/CT a very sensitive tool in diagnosis, staging, and following up patients with GS. Apart from the identifying clinically evident disease, PET/CT detected multiple additional lesions which were clinically occult in 66% of patients (8/12); in five patients at initial staging and in three patients at follow up. These sites included nodes,

Table 2: Details of patients referred for follow up evaluation

Age/ Gender	Primary Site of GS	Marrow disease	Treatment received	Initial PET/CT findings	Follow up PET/CT post treatment
19/F	Scapula	Negative	Chemotherapy	FDG avid large soft tissue mass associated with lytic erosion of the scapula (11.5cm-SUVmax-11.41) with multiple enlarged left axillary and supra-clavicular nodes	At 3 months of treatment- Near complete regression of the scapula mass, with new FDG avid nodules in the muscles of the left shoulder and left arm
48/F	Parotid	Negative	Chemotherapy and Radiotherapy	FDG avid mass involving the right parotid and infiltrating masseter and pterygoid muscles (6.8cm-SUVmax-6.8) FDG avid bilateral soft tissue breast lesions (largest on left- 4cm- SUVmax-5.8)	At 2 months of treatment- Partial regression in the FDG avid right parotid gland mass (3.6cm , SUV max-3.64). Partial regression in the bilateral breast lesion (left -1.2cm SUV ma × 2.31)
28/F	Orbit	Negative	Chemotherapy	Not available	At 1 year of treatment-Non FDG avid 1.5 cm residual lesion in the right upper eyelid
55/F	Mandible	Negative	Chemotherapy	Not available	At 2 years of treatment- Nodular thickening in the right breast (SUVmax-3.60). Subcutaneous soft tissue mass- noted anterior to the right lobe of the thyroid (2cm- SUVmax-4.30)
45/M	Humerus and pleura	CML	Chemotherapy and radiotherapy	Not available	At 1 year of treatment-Lytic lesion with minimal left sided paravertebral soft tissue thickening is seen involving L3 vertebra (SUV max 9.26)
33/M	Parotid	Negative	Chemotherapy and Radiotherapy	Not available	At 1 year of treatment- Mass in the right nasal cavity extending into the ipsilateral orbit and maxillary sinus (max SUV 16.6) and left level Ib node (1.1cm-max SUV 6.8)

breast nodules, and soft tissue deposits in the paravertebral region and in sacral neural foramina. Similar results were seen in studies done by Aschoff et al and Stölzel *et al.* who reported additional sites of disease on PET/CT in 80% and 60% cases, respectively [Figures 1 and 2].[12,13] These high proportion of cases showing additional sites of clinically occult extramedullary disease on PET/CT is in accordance with another study done by Cribe *et al* which showed that PET/CT detected 55 sites of extramedullary disease compared with 15 sites diagnosed by clinical examination alone.[14] Earlier and accurate detection of these additional extramedullary sites of disease at baseline or posttreatment using whole body PET/CT appears to be of potential clinical benefit, where a local therapy (like radiotherapy/ surgery) can boost the systemic chemotherapy and thereby improving treatment outcomes.[3]

In three patients, where bone marrow biopsy was positive for leukemia, we detected diffuse increased FDG uptake throughout marrow of axial skeleton and extremities. In rest of the nine patients without coexistent leukemia, the FDG uptake in the marrow was normal. This finding of increased FDG uptake in leukemia may not only facilitate early clinical diagnosis of coexistent marrow disease, but can also be used as a noninvasive tool for assessing treatment response.[16,17] Though PET/CT is sensitive in identification of leukemic infiltration of marrow, its specificity is poor as similar distribution of increased FDG uptake can also be seen in reactive marrow hyperplasia due to anemia, infections, following chemotherapy, or administration of colony-stimulating factors. Hence, whether increased or normal FDG uptake is noted in red marrow of patients with GS, it does not obviate the need for bone marrow biopsy for initial diagnosis of coexistent leukemia or at follow up.

As discussed earlier, GS can occur before diagnosis of AML, during treatment, or present as relapse, postsystemic chemotherapy/transplant. AML indeed should not be considered purely as a "liquid tumor'' and monitoring the blood/bone marrow response to therapy without use of imaging be questioned.[3] Assessing response and early identification of patients at risk for relapse will help reduce the treatment-related morbidity and planning appropriate treatment. Studies have shown that radiological response seen in GS by PET/CT scans is concordant with the pathological examination of bone marrow response.[12-14] In our series, six patients had done PET/CT following chemotherapy with or without radiotherapy. Out of these, two were for response evaluation after induction chemotherapy and radiotherapy, which showed progressive disease in one and partial response in another, consistent with the clinical examination [Figure 2, Figure 3]. In one patient, PET/CT was done for routine surveillance of an eyelid mass which was treated with chemotherapy. In rest of the three patients, PET/CT was done to evaluate

suspected disease relapse. In all three patients, PET/CT confirmed disease relapse and also identified additional clinically occult extramedullary lesions in two of these patients.

PET/CT is a powerful translational imaging tool in oncology that bridges the long time gap between research at molecular level and its final clinical application. Recently, a serum metabolomics study demonstrated that AML is associated with enhanced glycolysis, increased purine synthesis, and increased fatty acid utilization, as previously observed in other malignancies. The same study also showed that this enhanced glycolysis may be associated with reduced sensitivity to chemotherapy drugs.[18] Such studies can form the basis of using molecular imaging in AML patients with GS, using radiotracers, such as FDG or ^{18}F-fluorothymidine, which demonstrates *in vivo* glucose metabolism or cellular proliferation, respectively. Tumor characterization through such precision imaging would not only be diagnostically more accurate, but also can help provide further prognostic information and aid in developing novel chemotherapeutic targets.

Conclusion

PET/CT appears to be a highly sensitive imaging tool in diagnosis of GSs. PET/CT can also be used for treatment response evaluation in high-risk patients and for early identification of suspected disease recurrence. Performing PET/CT at baseline would help assess the exact extramedullary tumor burden by identifying clinically occult multifocal disease. This would then potentially alter disease management and/or improve treatment outcomes. Given these promising results from our case series and multiple case series reported in the past, it would be worthwhile that larger prospective trials are undertaken to integrate whole body PET/CT to routine work up of patients with myeloid/GSs.

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Conflicts of interest

There are no conflicts of interest.

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