Myeloid Sarcoma and Acute Myelomonocytic Leukemia in an Adolescent with Tetrasomy 8: Staging with ^{18}F -FDG PET/CT

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Abstract Tetrasomy 8 is a relatively rare chromosomal abnormality that has been reported in only 33 cases in hematologic disorders. It is known for its association with aggressive acute myeloid leukemia (AML) and myeloid sarcoma and is considered a very poor prognostic factor. Myeloid sarcoma is a rare hematologic malignancy characterized by tumor masses consisting of immature myeloid cells, presenting at an extramedullary site. We present a case of a 17-year-old boy referred for an ^{18}F -FDG PET/CT for the evaluation of pleural masses and spinal bone lesions seen on CT, after presenting with a 4 month history of chest pain. The PET/CT revealed extensive FDG-avid extramedullary disease in the soft tissues of the chest, abdomen, and pelvis, which were biopsy-proven to be myeloid sarcoma, as well as extensive intramedullary disease biopsy proven to be AML. This is the first report of the use of ^{18}F -FDG PET/CT to stage a subset of aggressive AML and myeloid sarcoma in a patient with an associated chromosomal abnormality (tetrasomy 8).

Keywords Tetrasomy 8 · Extramedullary AML · Myeloid sarcoma · Granulocytic sarcoma · Fluorodeoxyglucose · FDG · PET/CT

Introduction

Numerical and structural abnormalities of chromosome 8 are seen frequently in tumors of hematopoietic and lymphoid tissues. Trisomy 8 is one of the most common recurring aberrations in acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS). Tetrasomy 8, on the other hand, has been reported in only 33 cases in hematological disorders, the majority of them AML and MDS. It is considered a poor prognostic factor and is associated with very aggressive disease [1–7]. In many cases, it is associated with other chromosomal aberrations, including 11q23 rearrangements [8, 9].

Myeloid sarcoma has been referred to in the literature under various names, including granulocytic sarcoma, extramedullary AML, and chloroma. Myeloid sarcoma may develop de novo, concurrently with AML, or as a relapse of leukemia. It occurs in 2% of AML patients, and median survival time is only 7 months [10–13]. Although ^{18}F -FDG PET/CT is not used routinely in the evaluation of leukemias, scattered reports suggest it can be very useful in determining the extent of disease in leukemic diseases such as AML, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, and myeloid and histiocytic sarcomas [14–21]. This rare report highlights the usefulness of ^{18}F -FDG PET/CT in determining the extent of extramedullary and intramedullary disease in a subset of particularly aggressive AML and myeloid sarcoma. The use of PET/CT in the staging and evaluation of response to therapy in these aggressive leukemias warrants further investigation.

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Fig. 1 ^{18}F -FDG PET/CT maximum intensity projection (MIP) images with **a** anterior and **b** posterior views show extensive FDG-avid disease in the soft tissues of the chest, abdomen, and pelvis; in the lymph nodes in the axillae, mediastinum, and upper abdomen; as well as FDG-avid intramedullary disease in the axial and appendicular skeleton

Case Report

A 17-year-old boy with no significant past medical history presented with a 4 month history of increasing left-sided chest wall pain radiating laterally and posteriorly, along with a 2 week history of dyspnea and increasing shortness of breath. A CT of the chest and abdomen showed multiple large pleural-based and pelvic masses, as well as abnormal spinal bone lesions and enlarged abdominal lymph nodes. He was referred for an ^{18}F -FDG PET/CT to assess the extent of the suspected malignancy.

An ^{18}F -FDG PET/CT (Discovery ST, GE Healthcare, Waukesha, WI, USA) was performed. The patient fasted overnight prior to the examination and waited in a quiet dark room the morning of the exam. No muscle relaxants were administered, and no urinary bladder catheterization was performed. Oral contrast (900 cc of barium) was administered. An ^{18}F -FDG emission scan extending from the head to the mid-thigh was obtained 60 min after intravenous injection of 0.22 mCi/kg of ^{18}F -FDG. The emission scan was acquired for 5 min per field of view, each covering 14.9 cm, at an axial sampling thickness of 3.75 mm/slice. The 16-slice helical CT

Fig. 2 Transaxial **a** CT portion of the PET/CT, **b** PET, **c** PET/CT fusion, and **d** contrast-enhanced CT images of the left chest wall mass and extensive upper abdominal lymphadenopathy

Fig. 3 Transaxial **a** CT portion of the PET/CT, **b** PET, **c** PET/CT fusion images, and **d** MRI T2-weighted fat saturation image show a mass involving the left iliopsoas muscle

acquisition was performed prior to a full-ring dedicated PET scan of the same axial range. The CT component was operated with an X-ray tube voltage peak of 140 kVp, 80 mA, a 1.75:1 pitch, a slice thickness of 3.75 mm, and a rotational speed of 0.8 s per rotation. The patient was allowed to breathe normally during the PET and CT acquisitions. PET images were reconstructed with CT-derived attenuation correction using ordered subset expectation maximization software (20 subsets,

2 iterations). Only the maximum standardized uptake value (SUV_{max}) was reported, corrected for body weight.

The ^{18}F -FDG PET/CT maximum intensity projection (MIP) images (Fig. 1) showed extensive FDG-avid extramedullary disease throughout the soft tissues of the thorax, abdomen, and pelvis (including multiple FDG-avid lymph nodes in the axillae, celiac trunk, and para-aortic regions), as well as intramedullary disease in the axial and appendicular

Fig. 4 Transaxial **a** and **d** CT portion of the PET/CT, **b** and **e** PET, **c** and **f** PET/CT fusion images show infiltration of the pleura bilaterally, an FDG-avid left axillary lymph node that was biopsied, and infiltration of the intramedullary space, most intensely FDG-avid in the left intertrochanteric region

skeleton. There was a large FDG-avid pleural/chest wall mass surrounding the left fifth and sixth ribs (Fig. 2) with SUV_{max} of 5.7, a 7 cm left iliopsoas mass with SUV_{max} of 4.7 (Fig. 3), and extensive FDG-avid celiac and para-aortic lymphadenopathy (Fig. 2). There was also extensive intramedullary uptake in the axial and appendicular skeleton, most intensely FDG-avid in the left intertrochanteric region with SUV_{max} of 7.6 (Fig. 4).

Biopsy of a left axillary node, evaluation of the left pleural fluid, and bone marrow biopsy of the right iliac crest revealed acute myelomonocytic leukemia and myeloid sarcoma. Immunohistochemistry showed positivity of CD45, CD68, myeloperoxidase, and lysozyme. Karyotype analysis revealed a highly abnormal, clonal karyotype. All 25 G-banded metaphases assessed had tetrasomy of chromosome 8, loss of chromosome Y, additional material of unknown origin attached to the short arm of chromosomes 7 and 17, an isochromosome for the long arm of chromosome 10, and a translocation between the short arm of chromosome 19 and the long arm of chromosome 11 (Fig. 5). Fluorescence in situ hybridization studies using a dual color break-apart probe for the MLL gene locus at 11q23 were consistent with translocation involving chromosomes 11 and 19 and provided evidence for the rearrangement of this locus. Four metaphases had, in addition to the previously mentioned anomalies, a

derivative chromosome 14 generated from a translocation with chromosome 17.

The patient was started on induction chemotherapy with hyperCVAD chemotherapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine).

Discussion

Chromosome number 8 is one of the most consistently involved chromosomes in malignant transformation. It is involved in translocations such as t(8;21) in acute myeloblastic leukemia (AML), and the t(8;14) and its variant translocations in lymphomas and lymphocytic leukemias [1, 2]. Trisomy and tetrasomy 8 are clonal aberrations seen mainly in myeloid disorders such as AML and myelodysplastic syndromes (MDS). While trisomy 8 is the most frequent aneuploidy present in AML and MDS, tetrasomy 8 is a very rare chromosomal aberration which has been reported in only 33 cases in hematologic disorders (of which 25 have been AML patients). The median age of diagnosis of tetrasomy 8 is 54 years (range 14–82), and it tends to preferentially affect males in a 2:1 ratio. While trisomy 8 can be found in all subtypes of AML and MDS, tetrasomy 8 seems to be preferentially associated with AML of the

Fig. 5 G-banded karyotype of the mainline at diagnosis: 47, X,-Y, +8, +8. Vertical arrow shows tetrasomy 8, horizontal arrow shows absence of chromosome Y

monocytic lineage (AML-M4 and AML-M5), occurring in 68% of the cases [3, 4]. Cytogenetic studies suggest that a high level of chromosome 8 aneuploidy confers proliferative advantages to cells, which may partially explain the aggressive nature of the leukemias associated with tetrasomy 8 [3, 5], as well as the poor prognosis, with a median survival of less than 6 months [6, 7].

Myeloid sarcoma occurs in approximately 2% of AML patients and median survival time from diagnosis is 7 months [11]. Most patients with myeloid sarcoma present with concurrent AML [12, 13], as did our patient. Tetrasomy 8 has been described in AML with extramedullary manifestations in only a handful of cases in the literature, with myelosarcomatosis of the skin being the most common extramedullary manifestation [1, 2, 8–10]. Abnormalities of 11q23 leading to MLL gene (a gene that codes for histone-lysine N-methyltransferase HRX) rearrangements, as detected in our patient, have been reported in a number of patients with myeloid sarcoma [12]. Interestingly, many cases with tetrasomy 8 and extramedullary disease also had abnormalities of chromosome 11 [2, 9, 10, and our case]. Although the presence of other chromosomal aberrations, including 11q23 rearrangements, does not appear to modify median survival in cases with polysomy 8, status of the MLL gene locus should be documented [8].

^{18}F -FDG PET/CT imaging is not routinely used in the evaluation of leukemias, however scattered reports have described its successful use in the evaluation of a wide variety of leukemias, including acute lymphoblastic leukemia [14], AML [15, 16], chronic myeloid leukemia [17], chronic lymphocytic leukemia [18], myeloid sarcoma [19], and histiocytic sarcoma [20]. One review of 10 patients with granulocytic sarcomas showed a high sensitivity for ^{18}F -FDG PET/CT, with a mean SUV_{max} of 5.1 in 52 lesions, and also demonstrated the usefulness of PET/CT in monitoring response to therapy and follow-up [21]. The use of ^{18}F -FDG PET/CT in the evaluation of aggressive AML and myeloid sarcoma in patients with cytogenetic abnormalities including tetrasomy 8 has not been previously described in the literature. In this case, ^{18}F -FDG PET/CT was very useful in determining the extent of both intramedullary and extramedullary disease, which could not be otherwise accomplished unless the patient had a whole body MRI (not possible in most institutions) or a whole body CT (resulting in excessive radiation exposure, especially for a young patient).

In conclusion, referring physicians and PET/CT readers should be aware of the usefulness of ^{18}F -FDG PET/CT in determining the extent of intra- and extramedullary disease in aggressive AML and myeloid sarcoma associated with a chromosomal abnormality such as tetrasomy 8. Demonstrating the usefulness of PET/CT in the staging of these aggressive leukemias will hopefully invite further research into the use of PET/CT in assessing early response to therapy or follow-up after completion of therapy, to better guide treatment decisions

with the ultimate goal of improving long term outcomes in these patients.

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