



FDG-PET in two cases of neurofibromatosis type 1 and atypical malignancies

P. de Blank MD MSCE, K. Cole MD PhD,^{†‡} L. Kersun MD MSCE,^{†‡}
A. Green MD,^{†‡} J.J. Wilkes MD,^{†‡} J. Belasco MD,^{†‡}
R. Bagatell MD,^{†‡} L.C. Bailey MD,^{†‡} and M.J. Fisher MD^{†‡}*

ABSTRACT

Patients with neurofibromatosis type 1 (NF1) are at increased risk for both benign and malignant tumours, and distinguishing the malignant potential of an individual tumour is a common clinical problem in these patients. Here, we review two cases of uncommon malignancies (Hodgkin lymphoma and mediastinal germ-cell tumour) in patients with NF1. Although ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET) has been used to differentiate benign neurofibromas from malignant peripheral nerve sheath tumours, FDG-PET characteristics for more rare tumours have been poorly described in children with NF1. Here, we report the role of PET imaging in clinical decision-making in each case. In NF1, FDG-PET might be useful in the clinical management of unusual tumour presentations and might help to provide information about the malignant potential of uncommon tumours.

KEY WORDS

Neurofibromatosis type 1, pediatric oncology, Hodgkin lymphoma, germ-cell tumours, Klinefelter syndrome

1. INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common genetic syndrome associated with both benign and malignant tumours. Affected individuals have an increased risk of malignancy, most commonly malignant peripheral nerve sheath tumour (MPNST). Positron-emission tomography with ¹⁸F-fluorodeoxyglucose (FDG-PET) has been useful in differentiating MPNST from benign neurofibroma¹⁻⁴, but few reports of FDG-PET in the evaluation of other NF1-associated malignancies have been published. Here, we report FDG-PET characteristics of two unusual malignancies in NF1 and discuss the utility of PET in the management of atypical tumour presentations.

2. CASE DESCRIPTIONS

2.1 Case 1

A 6-year-old boy was referred for evaluation of a non-tender 4-cm left axillary mass, which had recently increased in size. On examination, 6 café-au-lait macules more than 5 mm in diameter were noted, as well as axillary freckling, meeting the clinical diagnostic criteria for NF1.

Chest radiography revealed no active disease in the thorax; a complete blood count was normal; and the erythrocyte sedimentation rate was not elevated. Magnetic resonance imaging using multiplanar short T1 inversion recovery sequences revealed a 3×1.6×5-cm mass within the left axilla abutting the chest wall (Figure 1). Imaging characteristics were consistent with benign neurofibroma, MPNST, or lymph node expansion from other malignancy. Because of the tumour's rapid growth, imaging by combined FDG-PET and computed tomography (CT) was obtained to evaluate the lesion's malignant potential. Images revealed a hypermetabolic focus with a maximum standardized uptake value (SUV_{max}) of 5.8 that corresponded with the soft-tissue mass.

Because of the increased FDG uptake and recent growth, excisional biopsy was performed. Pathology was consistent with nodular lymphocyte-predominant Hodgkin lymphoma (HL). Imaging of neck, chest, abdomen and pelvis by CT with intravenous contrast showed no other tumours, and the child received no further therapy at that time.

He returned 3 months after surgery for surveillance FDG-PET-CT, which revealed no increased FDG uptake in the left axilla, but a new focus of abnormal activity in the left chest wall with an SUV_{max} of 5.4, corresponding to a 1.9×1.2-cm soft-tissue mass under the pectoralis major muscle that had not been present during the earlier study. Based on the imaging, a second surgical resection was performed, and histologic evaluation confirmed recurrence of nodular lymphocyte-predominant HL.

The patient received 3 cycles of chemotherapy with doxorubicin, vincristine, prednisone, and cyclophosphamide, achieving a complete response. He remained disease-free at 9 months after completion of therapy.

2.2 Case 2

A young man (15 years of age) followed for known sporadic *NF1* (diagnosed clinically at a young age) and with a large abdominal–pelvic–lumbar spine plexiform neurofibroma diagnosed by magnetic resonance imaging, presented with a 1-week history of fevers, intractable cough, and shortness of breath. Chest CT and multiplanar short T1 inversion recovery magnetic resonance imaging (Figure 2) revealed a 17.8×11.8×14-cm heterogeneous mass in the anterior mediastinum, with internal foci of calcifications and fat, separate from his known plexiform neurofibroma. The mass caused rightward deviation of the heart and compression of the left main pulmonary artery and left mainstem bronchus. Lymph nodes in the paratracheal and prevascular regions measured up to 1.3×3.0 cm. Differential diagnosis included MPNST, germ-cell tumour, lymphoma, thymoma, or metastatic disease. Laboratory evaluation was significant for mild anemia (hemoglobin 12.9 g/dL), but no elevation in lactic dehydrogenase or uric acid was found. Alpha-1-fetoprotein was elevated [59.7 ng/mL

(normal range: 0.6–3.9 ng/mL)], and the beta subunit of human chorionic gonadotropin was undetectable (<1.0 mIU/mL).

Percutaneous needle biopsy of the mediastinal mass before FDG-PET was nondiagnostic. Subsequent FDG-PET–CT identified a hypermetabolic focus with a SUV_{max} of 5.6 within the chest mass, but no other areas of significantly increased FDG uptake. Because of the size of the focus, the elevated germ-cell markers, and increased metabolic activity inconsistent with typical neurofibroma, a malignant component of the tumour was suspected. A decision to attempt a complete resection was therefore made.

The mass was successfully resected; pathology revealed immature teratoma with intermixed yolk sac tumour with moderate-to-strong staining for alpha-1-fetoprotein. Analysis of the tumour tissue by single nucleotide polymorphism array demonstrated whole-chromosome gains of X and 7. Subsequent cytogenetic analysis of whole blood revealed a karyotype of XXY, consistent with Klinefelter syndrome. Testing for *NF1* mutation was not performed because clinical criteria for *NF1* had already been met.

Chemotherapy with bleomycin, etoposide, and cisplatin was started. Serum alpha-1-fetoprotein subsequently normalized, and the patient remained disease-free at 16 months from completion of therapy.

3. DISCUSSION

The autosomal-dominant disorder *NF1* is caused by a mutation of the *NF1* gene at chromosome 17q11.2. It affects approximately 1 in 3000 individuals⁵. The *NF1* gene is a tumour suppressor encoding the protein neurofibromin, a GTPase inactivator for the Ras pathway⁶. Lack of neurofibromin results

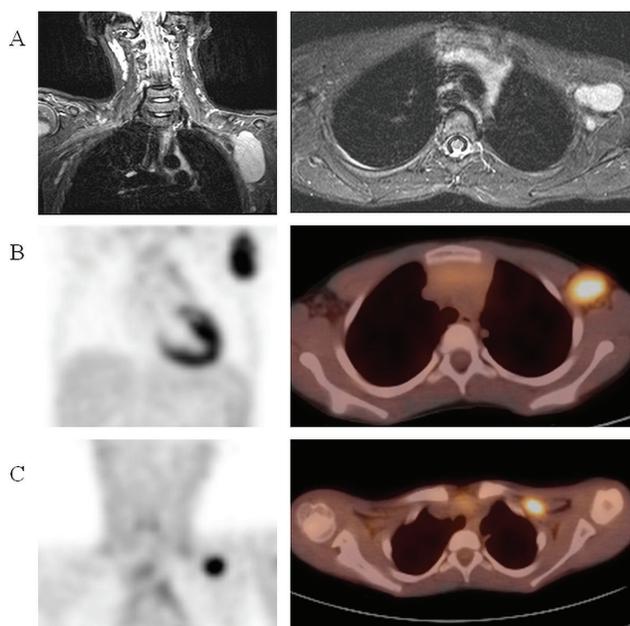


FIGURE 1 Case 1. (A) Initial coronal and axial magnetic resonance short T1 inversion recovery images of left axillary Hodgkin lymphoma, (B) with corresponding coronal fluorodeoxyglucose (FDG) positron-emission tomography (PET) image and axial FDG-PET–computed tomography (CT) image. (C) Coronal FDG-PET and axial FDG-PET–CT images 3 months after surgery show a new focus of FDG uptake in the left pectoralis major muscle.

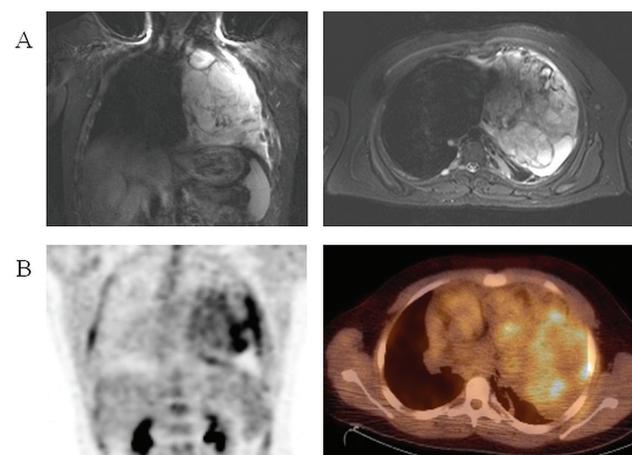


FIGURE 2 Case 2. (A) Axial and coronal magnetic resonance short T1 inversion recovery images of the left thorax tumour with mass effect on the mediastinum. (B) Corresponding coronal fluorodeoxyglucose (FDG) positron-emission tomography (PET) and axial FDG-PET–computed tomography images of the same mass.

in stimulation of mitogen-activated protein kinases and phosphoinositide 3 kinases, leading to cellular proliferation and increased cell survival⁷.

Individuals with NF1 have an increased risk of malignancy that predominantly affects children and youths. The overall incidence of cancer in NF1 patients is 2.7 times that in the general population; in NF1 patients less than 20 years of age, it is 27.8 times the incidence in the age-matched general population⁸. The most common tumours in NF1 are MPNST and gliomas; however, other malignancies have been associated with NF1, including rhabdomyosarcoma⁹, pheochromocytoma¹⁰, breast cancer⁸, and leukemia¹¹. A review of previously published cohorts and population-based studies of individuals with NF1 described an incidence of malignancy between 4% and 52%, but identified only a single case of germ-cell tumour (malignant teratoma of the retroperitoneum in a Japanese registry¹²) and no cases of HL among 535 NF1-associated malignancies reviewed¹³. Although individuals with NF1 are at increased risk for non-Hodgkin lymphoma¹¹, only one prior report describes HL in a patient who had segmental NF1¹⁴. In addition to the germ-cell tumour already mentioned, a single case report of a peripheral germ-cell tumour in an individual with NF1 was previously described¹⁵. Germ-cell tumours are rarely associated with NF1, but are more common in adolescents with Klinefelter syndrome, as occurred with our second patient¹⁶.

In our cases, NF1 might have influenced the timing and appearance of the malignancies. Case 1 describes a common tumour (HL) presenting unusually early (in a 6-year-old), illustrating the increased incidence of malignancy in young children with NF1, given that 90% of childhood HL occurs in children more than 9 years of age¹⁷. Case 2 describes a child with NF1 and a new mediastinal mass. Although mediastinal germ-cell tumours are associated with Klinefelter syndrome, NF1 might have additionally influenced its appearance. A single patient having both NF1 and Klinefelter syndrome is unusual. However, both genetic syndromes are common in the general population (1:1000 for Klinefelter syndrome) and could overlap. Hatipoglu *et al.* reported another case of a patient with NF1 and Klinefelter syndrome not associated with malignancy¹⁸. These cases are reminders of the diversity of the tumours that present in patients with NF1.

Many tumours in patients with NF1 are benign, but distinguishing those tumours from malignancy is a common clinical problem. Most studies of FDG-PET in NF1 have investigated its ability to differentiate benign neurofibromas from MPNSTs¹⁻⁴. In the largest study of 116 lesions in 105 patients with NF1 and symptoms concerning for MPNST, the mean SUV_{max} was significantly lower for plexiform neurofibromas than for MPNSTs (1.5 vs. 5.7)⁴. Overall sensitivity of FDG-PET to identify MPNST in subjects with NF1 ranges from 75% to 100%, with specificity between 72% and

100%¹⁹. However, a comparison of studies is difficult because of inconsistencies in the cut-off values used to identify malignant tumours, and variability in the type and timing of SUV measurements.

The range of SUV_{max} seen in benign lesions and MPNSTs often overlap, and individual lesions can be misidentified^{3,4,20,21}. Although studies of the use of FDG-PET in children with NF1 demonstrated results similar to those seen in adults²², further prospective studies are warranted in the pediatric population. Imaging by FDG-PET has the potential to distinguish benign from malignant lesions in NF1; however, methods must be standardized, and larger prospective trials that include less common malignancies must be conducted before FDG-PET is routinely recommended for the evaluation of symptomatic lesions.

Here, we describe the PET imaging characteristics of two such malignancies uncommonly seen in NF1. Only two earlier studies described FDG-PET results in patients with NF1 and non-MPNST malignancies. Ferner *et al.*⁴ described 2 other malignant tumours (of thyroid and esophagus) discovered incidentally. Bredella and colleagues³ reported 3 additional tumours (2 gastrointestinal stromal tumours and 1 poorly differentiated carcinoma of the colon). Although no quantitative measurements were described, and methods of testing varied, all non-MPNST tumours were considered tracer-avid on FDG-PET except for the carcinoma of the colon.

Imaging by FDG-PET is not without risk or cost, and screening for new tumours with FDG-PET in children with NF1 is not routinely recommended²³. Unnecessary radiation exposure should be avoided, especially in individuals with NF1, because of the risk of secondary malignancy²⁴ and other potential complications²⁵ seen with higher doses of radiation therapy. However, FDG-PET might be useful for the assessment of malignant potential (as in our case 1) and for clinical and surgical planning of unusual presentations (our cases 1 and 2).

4. CONCLUSIONS

Imaging by FDG-PET has been used to distinguish benign plexiform neurofibromas from MPNST²⁶. It is also promising for predicting the likelihood of growth in plexiform neurofibroma²⁷. However, PET should be reserved for situations in which it might contribute to clinical decision-making. Here, we report two unusual malignancies (HL and germ-cell tumour) in patients with NF1 in whom PET imaging helped with identification and guided surgical management and clinical care.

5. ACKNOWLEDGMENTS

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6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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Correspondence to: Peter de Blank, Division of Pediatric Hematology/Oncology, Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, Cleveland, Ohio 44106 U.S.A.

E-mail: Peter.deBlank@UHHospitals.org

* Department of Pediatrics, Division of Pediatric Hematology and Oncology, Rainbow Babies and Children's Hospital, Cleveland, OH, U.S.A.

† Division of Oncology and Center for Childhood Cancer Research, The Children's Hospital of Philadelphia, Philadelphia, PA, U.S.A.

‡ Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, U.S.A.