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Schwannoma in neurofibromatosis type 1: a pitfall for detecting malignancy by metabolic imaging

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Abstract

Neurofibromatosis type 1 (NF1) is a neurocutaneous syndrome characterized by the development of multiple peripheral nerve sheath tumors, the majority of which are benign neurofibromas. However, malignant peripheral nerve sheath tumors (MPNSTs) occur with a 10 % lifetime risk in patients with NF1, often developing within a neurofibroma. When clinical suspicion for an MPNST arises, imaging with FDG PET and MRI is performed to characterize a peripheral tumor for potential malignancy. In this report, we describe a patient with NF-1 who had two peripheral tumors with similar features by PET, both suspicious for MPNST, but differing features by MRI, one of which was subsequently determined to be an MPNST and the second to be a schwannoma.

Keywords

Neurofibromatosis type 1; Schwannoma; Malignant peripheral nerve sheath tumor; Neurofibroma

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous syndrome characterized by multiple central and peripheral tumors [1]. Typical neoplasms associated with NF1 are benign neurofibromas, but malignancies also occur, such as malignant peripheral nerve sheath tumors (MPNSTs), non-lymphocytic leukemias, and gliomas. An MPNST most often arises within a benign plexiform neurofibroma and patients with NF1 have a 10 % lifetime risk of developing an MPNST [2]. The prognosis of NF 1 patients with MPNST is poor, with an overall 5-year survival of 30 % [3]. Hence, detection of an MPNST among the multiple benign peripheral nerve sheath tumors in patients with NF1 is of paramount importance.

Current algorithms for the work-up of a potential MPNST in patients with NF1 include metabolic imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) [4], for the identification of a metabolically active tumor characteristic of malignancy, and magnetic resonance imaging (MRI), to provide an anatomic assessment of the tumor in question [5]. MRI may also provide information about distinguishing anatomic features [5–7] and functional and metabolic features of the tumor [8–10]. The differentiation of benign from malignant peripheral nerve sheath tumors can be challenging in patients with NF 1 for various reasons, including shared and overlapping imaging features, synchronous benign and malignant lesions, and sampling errors during percutaneous biopsy. We report a patient with NF-1 with clinical signs and symptoms concerning for malignancy who underwent FDG-PET showing two peripheral tumors with suspicious high metabolic activity, one subsequently diagnosed as an MPNST, and the second as a schwannoma. Unlike PET imaging, anatomic and functional MRI features of these two masses differed.

Case description

A 53-year-old man with a history of NF1 and known peripheral tumors complained of new-onset severe left leg and knee pain with progressive numbness that had developed over the 6–8 weeks prior to his clinic visit. Regarding his history of NF1, he was diagnosed in his 20s with a family history of NF1 and had several NF1-associated complications, including an MPNST of the left femoral nerve 25 years prior and a thalamic glioma 19 years prior. No prior relevant studies were available for comparison. Given the progressive pain, the patient underwent imaging with FDG-PET with early and delayed acquisitions, as has been previously described [4]. The PET images showed mild FDG uptake in numerous masses, which were presumed neurofibromas throughout the extremities; however, in the left anterior thigh along the left femoral nerve, a soft tissue mass had PET features that were suspicious for malignant transformation (a maximum standardized uptake value (SUV) of 4 on the early acquisition and 6.4 on the delayed acquisition) (Fig. 1a). A second mass in the distal left thigh along the tibial nerve also exhibited suspicious PET features with an SUV of 6.8 on the early acquisition and 8.4 on the delayed acquisition (Fig. 2a). Subsequently, MRI

for the left lower extremity was performed with anatomic, functional, and metabolic sequences, detailing the location and extent of the two suspicious masses, and providing additional metrics for characterization of these masses. The suspicious proximal anterior mass showed MRI features concerning for malignancy (Fig. 1b–e), including heterogeneous signal and enhancement and markedly restricted diffusion. The suspicious distal left thigh mass had similar MRI features of heterogeneity, although diffusion weighted imaging showed less restriction (Fig. 2b–e). A third mass for comparison in the field of view, was located in the proximal posterior thigh and had anatomic features of homogeneous T2 hyperintensity, T1 hypointensity, and mild contrast enhancement, with no restricted diffusion (minimum ADC value of $2.1 \times 10^{-3} \text{ mm}^2/\text{s}$ and average ADC value of $2.6 \times 10^{-3} \text{ mm}^2/\text{s}$); consistent with a benign neoplasm. Given the suspicious nature of the two masses by PET and the clinical need, eventual complete resection of each of these masses was performed, yielding a histo-logic diagnosis of MPNST for the proximal anterior thigh mass, schwannoma for the distal posterior thigh mass and neurofibroma for the proximal posterior thigh mass (Fig. 2f–i).

Discussion

Neurofibromatosis type 1 (NF1) is a disorder characterized by the development of benign peripheral neurofibromas. However, patients with NF1 are at increased risk for developing a variety of malignancies, with a 100-times-greater risk of developing an MPNST than in the general population [11]. Clinical clues to the presence of an MPNST include the development of new onset pain, the intensification of existing pain, and the rapid enlargement of a peripheral tumor. Imaging with PET and MRI is utilized in an attempt to distinguish benign neurofibromas in a growth phase from an MPNST.

By PET, multiple studies have demonstrated good separation between neurofibromas and MPNSTs by their FDG uptake. Bredella et al. retrospectively reviewed 44 patients with NF1 who underwent whole-body PET for a suspected MPNST, with a single 45–60 min acquisition, and showed a sensitivity of 95 % and specificity of 72 % for detecting an MPNST by SUV values [12]. In 2008, Ferner et al. [13] studied 105 patients with NF1 who had symptomatic neoplasms, using early (60–90 min) and delayed (240 min) FDG-PET acquisitions, and reported a sensitivity and specificity of 89 and 95 %, respectively for diagnosing an NF-1-associated MPNST. In the latter study, there were three false-negative results, all in low-grade MPNST, although the sensitivity for a high-grade MPNST was 100 % with a maximum SUV (SUVmax) cut-off of 2.5 at 4 h. Three of the false-positive cases occurred in presumed benign peripheral tumors that exhibited an SUV greater than 3.5, but a pathological diagnosis for these three neoplasms was not provided. Subsequently, Warbey et al. [4] evaluated the use of FDG-PET with early and delayed acquisitions in patients with symptomatic neurofibromas to further clarify the role of PET for detecting an MPNST and to examine the relationship between SUV and tumor grade. For 62 patients in the study, a cut-off SUVmax of 3.5 on delayed imaging classified tumors as malignant with a sensitivity of 97 % and specificity of 87 % [4]. In the tumors with histological correlation, Warbey et al. reported significant differences between SUVmax measures in neurofibromas, atypical neurofibromas, low-grade MPNSTs, and high-grade MPNSTs, using early and delayed imaging. Finally, in 2010, Benz et al. [14] examined the utility of FDG-PET/CT to

distinguish histologically proven MPNSTs from benign peripheral nerve sheath tumors, including both neurofibromas and schwannomas. As in other studies, for 40 peripheral nerve sheath tumors (17 MPNSTs, nine neurofibromas and 14 schwannomas), the SUVmax was significantly higher in MPNSTs compared with all benign PNSTs (12 ± 7 vs. 3.4 ± 1.8 , respectively). Although the latter study did not report the presence of any schwannomas in patients with NF1, interestingly, the difference in SUVs observed in MPNSTs compared with that of schwannomas was not as striking as the difference between SUVs of MPNSTs and neurofibromas, with 3/14 schwannomas exhibiting an SUVmax greater than 5. Such investigations suggest that although PET is useful for differentiating an MPNST from a neurofibroma, PET is less specific for distinguishing an MPNST from a schwannoma.

The incidence of schwannomas in the setting of NF-1 is not known; a search of the world literature only shows two case reports [15, 16]. However, Feany et al. reported nine cases of rare “hybrid” nerve sheath tumors showing histologic features of both neurofibroma and schwannoma [17], with distinct, often nodular regions of classical schwannomatous differentiation within neurofibromas [17]. Harder et al. reported the incidence of these “hybrid” lesions in patients with tumor syndromes and found NF1 in 9 % of cases (two out of 23 patients) [18]. In addition, atypical neurofibromas may occur and these refer to neurofibromas with unusual pathologic features such as degenerative cytological atypia (neurofibroma with ancient change, atypical neurofibroma) and/or increased cellularity (cellular neurofibroma) [19]. Neurofibromas with ancient change feature degenerative nuclear atypia containing scattered cells with markedly enlarged, hyperchromatic nuclei; however, they lack increased cellularity, or mitotic activity. Similar changes may be seen in so-called ancient schwannomas [19]. Fortunately, in patients with NF-1, schwannomas are a rare occurrence; hence, PET is still used as a mainstay for detecting malignancy. In the case reported here, the schwannoma exhibited high metabolic activity, in a pattern similar to the level found for the patient’s concurrent MPNST, while other peripheral tumors and one histologically proven neurofibroma exhibited significantly lower SUVs (in the benign range), consistent with findings of the published investigations to date. In the current diagnostic algorithm for patients with NF-1, PET/CT plays a central role. In case of PET/CT non-availability, one would proceed to tissue diagnosis with biopsy based on anatomic imaging in conjunction with the clinical picture.

Complimentary to metabolic information obtained by PET imaging, MRI, typically with anatomic T1-weighted, T2-weighted, and contrast-enhanced sequences, is performed for the assessment of NF1 patients with a symptomatic peripheral tumor. By MRI, neurofibromas and MPNSTs frequently share anatomic MRI features. A few studies, however, have described some distinguishing features for benign and malignant peripheral nerve tumors [5–7]. Matsumine et al. assessed MRI features of 18 neurofibromas and 19 MPNSTs in 37 patients with NF1 [7] and showed that although irregular tumor shape, indistinct margins, and heterogeneous enhancement were important factors, only intra-tumoral lobulation and the presence of T1 hyperintense areas were considered diagnostic indicators of malignancy [7]. Li et al. assessed 26 patients (one schwannoma, 16 neurofibromas, and nine MPNSTs) and showed the absence of a split fat sign as an additional feature of malignancy [6]. Recently, four specific MRI features were reported, which can be used to distinguish MPNSTs from neurofibromas with a sensitivity and specificity of 61 and 90 %, respectively

(when two or more of the following features were observed: large size, peripheral enhancement pattern, perilesional edema, and intratumoral cystic changes) [7]. An important limitation of these latter studies is that their case populations did not include schwannomas, entities which may present with cystic degeneration and complex internal signal, similar to features described for an MPNST on conventional MRI sequences [5]. There is still considerable overlap between the imaging features of benign and malignant PNSTs, with benign lesions occasionally demonstrating heterogeneous enhancement [6]. In the patient described in this report, the anatomic features of the MPNST and schwannoma were similar in that heterogeneous contrast enhancement was shown in both tumors, but were different in that the signal characteristics by T1- and T2-weighted imaging showed different degrees of heterogeneity and signal increase. Although there are studies that show large size (>5 cm) as a feature of malignancy, there was only a small difference in lesion size in our patient with the anterior MPNST measuring 4.4 cm in longest dimension and the posterior schwannoma measuring 2.9 cm [6, 7].

Functional and metabolic MRI sequences have also been described for the assessment of nerve sheath tumors. Unlike T1-weighted and fluid-sensitive-type anatomic imaging, diffusion-weighted (DW) imaging is a method of functional imaging. DW imaging is sensitive to changes in the diffusion of water within the intracellular and extracellular space. Restricted diffusion of water is noted in tumors due to increased cellularity [8]. The ADC is an established marker of tumor cellularity with regions of high cellularity demonstrating restricted diffusion or low ADC value and regions of low cellularity demonstrating unrestricted diffusion or high ADC value [8]. Quantitative DW imaging with ADC mapping has been reported to be of questionable value for distinguishing benign and malignant soft tissue tumors in several studies that have included peripheral nerve sheath tumors [20–25]. In our subject, lower ADC values were observed in the anterior thigh MPNST (minimum ADC $0.2 \times 10^{-3} \text{ mm}^2/\text{s}$, average ADC $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$) than in both the pathologically proven neurofibroma (minimum ADC $2.1 \times 10^{-3} \text{ mm}^2/\text{s}$, average ADC $2.6 \times 10^{-3} \text{ mm}^2/\text{s}$) and the schwannoma (minimum ADC of $1 \times 10^{-3} \text{ mm}^2/\text{s}$, average ADC of $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$). Finally, metabolic MRI with MR spectroscopy has been studied for the characterization of musculoskeletal lesions for malignancy, and both benign and malignant nerve sheath tumors have shown detectable levels of the metabolite choline, a marker of malignancy in the musculoskeletal system [26–29]. However, malignant lesions tend to have higher choline levels than their benign counterparts [9]. In our case, detectable choline content was found in the MPNST, but the schwannoma was not studied with MR spectroscopy.

In conclusion, this case demonstrates an important pitfall to be aware of regarding metabolic imaging with PET when used for the detection of MPNST in patients with NF1. Schwannomas, while rare in NF1, may occur and mimic malignancy by PET features. Conventional anatomic MRI features may occasionally help distinguish an MPNST from benign peripheral tumors, but commonly, there is overlap in the anatomic MRI features of benign and malignant peripheral tumors, such that a confident distinction is not possible by MRI. With further study, functional and metabolic MRI techniques may prove complimentary to PET for the purpose of distinguishing benign peripheral nerve tumors from MPNSTs in NF1.

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Fig. 1.

FDG-PET and MRI of left anterior thigh malignant peripheral nerve sheath tumor. **a** Delayed axial attenuation corrected FDG PET image showed a soft tissue mass along the left anterior thigh involving the left femoral nerve (*short arrow*) measuring 4.4 cm with PET features that were suspicious for malignant transformation (a maximum standardized uptake value (SUV) of 4 on the early acquisition and 6.4 on the delayed acquisition). Note the posterior proximal thigh mass for comparison (*long arrow*), which demonstrated low-level FDG uptake and no increased uptake on delayed images. **b** Axial T2-weighted image (SPAIR, TR 4060/TE 71) showed heterogeneous intermediate signal within the anterior MPNST (*short arrow*) and homogeneous hyperintensity in the posterior neurofibroma (*long arrow*). **c** Axial T1-weighted image (TR 961/TE 9.4) showed T1 heterogeneous signal of the anterior femoral MPNST (*short arrow*) and T1 homogeneous hypointensity of posterior sciatic nerve neurofibroma (*long arrow*). **d** Axial apparent diffusion coefficient map (TR 7600/TE 40) of the anterior MPNST (*short arrow*) showed restricted diffusion with low ADC values (minimum ADC value of $0.2 \times 10^{-3} \text{ mm}^2/\text{s}$ and average ADC value of $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$). Note posterior sciatic nerve neurofibroma (*long arrow*) with no restricted diffusion on ADC map (minimum ADC value of $2.1 \times 10^{-3} \text{ mm}^2/\text{s}$ and average ADC value of $2.6 \times 10^{-3} \text{ mm}^2/\text{s}$). **e** Coronal contrast-enhanced VIBE subtraction images (TR 4.02, TE 1.52) showed heterogeneous enhancement of the anterior left femoral nerve MPNST (*arrow*)

Fig. 2.

FDG-PET and MRI of left distal posterior thigh schwannoma. **a** Delayed axial attenuation corrected FDG PET image showed a second mass in the distal left thigh along the tibial nerve (*arrow*), measuring 2.9×2.7 cm, also exhibiting suspicious PET features concerning for malignancy (an SUV of 6.8 on the early acquisition and 8.4 on the delayed acquisition). **b** Axial T2-weighted image (SPAIR, TR 3600/TE 70) showed distal left thigh schwannoma (*arrow*) with mildly heterogeneous high signal. **c** Axial T1-weighted image (TR 961/TE 9.4) showed homogeneous internal T1 hypointensity of the distal thigh schwannoma (*arrow*). **d** Axial ADC map (TR 7600/TE 80) showed higher ADC values (minimum of 1.0×10^{-3} mm^2/s and average of 1.1×10^{-3} mm^2/s) within the schwannoma (*arrow*) than that observed with the MPNST. **e** Coronal post-contrast T1-weighted image (VIBE, TR 6.35/ TE1.44) demonstrate heterogeneous enhancement within the schwannoma (*arrow*), similar to the contrast enhancement pattern of the MPNST. **f** Schwannoma displaying Antoni A (more cellular) cells in the top half of the field and looser Antoni B zones in the bottom half of the field. Note the characteristic thick-walled vessels in both zones. Original magnification 10 $\times$. **g** High magnification of an Antonio A zone. There is enlarged hyperchromatic nucleus in the lower portion of the image; such changes are considered degenerative rather than malignant. Original magnification 40 $\times$. **h** Diffuse strong S100 protein expression in both the cytoplasm and nuclei (*red*) is a characteristic feature of benign nerve sheath tumors. Original magnification 20 $\times$. **i** The proliferative index in this lesion is low using ki-67 immunolabeling. Note that the enlarged atypical nuclei are negative (*not brown*). Original magnification 40 $\times$