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CLINICAL–PATIENTS STUDIES

Potential clinical role of FDG-PET in detecting sarcomatous transformation in von Recklinghausen's Disease: a case study and review of the literature

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Abstract
Background The diagnosis of sarcomatous transformation of plexiform neurofibromas in Neurofibromatosis-1 (NF 1) is a clinical and radiological challenge. Considerable overlap exists in the clinical and the radiological characteristics between the benign enlarging neurofibromas and their counterparts undergoing malignant changes. Surgical biopsy to rule out suspicious malignant transformation is often a problem in deep seated lesions.
Methods We, in this paper, explore the clinical utility of FDG-PET in detecting and assessing this life threatening complication of neurofibromas. A case is described with FDG-PET and MRI documentation of such transformation and subsequent histopathological correlation. The case upholds the potential advantages of a FDG-PET over the conventional imaging modalities. A review of the existing literature is also carried out; a total of four published reports on this issue were identified in English literature by searches of Pubmed.
Results and conclusion FDG-PET appeared a reliable as well as sensitive noninvasive technique that might minimize unnecessary deep surgical biopsy to rule out malignant transformation in cases of NF-1 with features of enlargement of a preexisting peripheral nerve sheath tumour, pain or neurodeficit.

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Introduction

NF1 is a multisystem disorder, predominantly with neurocutaneous and orthopedic manifestations, linked to mutation in NF1 gene on band 17q11.2 [1–3], leading to truncations in a protein called neurofibromin (responsible for the negative regulation of Ras and thereby acting as a tumour suppressor). Globally the incidence is approximately 1 of 2,500–3,000 live births, regardless of race, sex, or ethnic background. The disease manifestations are extremely variable even within the affected family members [4, 5], with an unpredictable clinical course. They are histologically composed of Schwann cells, fibroblasts, mast cells, and vascular components [6]. Among the three subtypes of neurofibromas (viz. cutaneous, subcutaneous, and plexiform), the plexiform type is noncircumscribed, thick, and irregular, and regarded as specific for NF-1. Often they infiltrate and encase major nerves, blood vessels and other vital structures. Hence it is difficult to completely resect these lesions. Neurofibrosarcoma is the major cause of death of NF1 patients less than 40 years of age. It may develop de novo or from sarcomatous degeneration of a pre-existing plexiform neurofibroma. The clinical features associated with malignant transformation include increase in the size of the lesion, pain and neurodeficit. This is suspected in patients with new onset of the abovementioned symptoms or patients with changing symptoms.

The case

A 19 year old male presented with a gradually increasing slightly painful recurrent swelling in the left popliteal region, which was operated two times at the same region over the previous 1 year. MRI of the lumbar and cervical spine enlarged exit nerve roots at C5/6 and C6/7 levels bilaterally; scoliosis of the lumbar spinal column with scalloped posterior aspects of bodies of L2, 3, 4 with bright areas on T2 weighted images in the paraspinal levels at L3/4, L4/5 and L5/S1 levels. He also gave a history of multiple subcutaneous nodules and brownish coloured patches throughout the body. General physical examination revealed multiple subcutaneous nodules and numerous café-au-lait spots scattered throughout the body. Local examination revealed 4×4 cm mildly tender, noncompressible firm nodular mass in the left popliteal fossa which was mobile horizontally but not vertically. There was scar of previous two surgeries on the skin of left popliteal region. He had scoliosis in lumbar region, concavity being towards the right. He had decrease in fine touch sensation in L4 and L5 dermatomes, absent left ankle jerk and a grade 4/5 power in left extensor hallucis longus and the left extensor digitorum longus. Rest of the neurological examination is within normal limits. The last surgery was performed 3 months previously in the left popliteal fossa for excision of recurrent plexiform neurofibroma (reported in the first surgery undertaken 1 year back). Intraoperatively the tumor was very vascular, soft and friable encasing the left tibial nerve and bifurcation of the sciatic nerve. The tumor was excised completely except the part, which was adherent to surrounding fascicles. The histopathology impression was that of a malignant schwannoma (high grade neurogenic sarcoma) of the tibial nerve in the background of von Recklighausen's disease. The tumor cells possessed oval nuclei and moderate amounts of cytoplasm. There were also epithelioid nuclei and numerous mitosis and many areas of geographic necrosis. The tumor had a rich network of vessels with a stag horn pattern. He was referred for a whole body FDG-PET (Fig. 1) for disease evaluation 3 months after surgery. This showed a fair sized area of intense FDG uptake in the posterior aspect of left popliteal fossa. Two other foci were observed, one posterior to the midshaft of the femur in the course of the sciatic nerve and the other just left to the convexity of the spine at the level of L2 vertebra. These were subsequently explored surgically and histologically proven to be neurofibrosarcoma. Another tiny focus was noted in the left iliac bone, which was interpreted as metastatic disease focus; however, no histologic correlation could be obtained of this focus. The other numerous palpable subcutaneous swellings and the enlarged exit nerve roots (noted in MRI) did not show enhanced FDG uptake. An MRI of the left leg and thigh (Fig. 2a–c) at this time revealed a nodular tumor along the course of left tibial nerve with local infiltration into the belly of the semimembranosus and biceps femoris terminations. Fibres of the lateral head of gastrocnemius were also infiltrated. The popliteal vessels and soleus muscle were free of the tumor. The sciatic nerve was thickened, lobulated measuring approximately 2 cm in cross section extending from the sacral plexus across the greater sciatic notch and along its course into the popliteal fossa. The thickened sciatic nerve did not enhance, however, the tumor in the popliteal fossa enhanced markedly. There were also numerous scattered nodules in the subcutaneous tissues and muscle bellies. He later on underwent reexcision of the popliteal recurrence followed by local external radiotherapy with an uneventful postsurgical recovery. The histologic section (Fig. 3) demonstrated spindle shaped tumor within foci of necrosis, with cells showing moderate degree of pleomorphism; occasional cells showed nucleoli.

Discussion

The diagnostic criteria [7, 8] for NF-1 include presence of two or more of the following: (a) six or more café au lait macules, (b) two or more neurofibromas of any type or one plexiform neurofibroma, (c) freckling in the axillary or inguinal regions, (d) optic glioma, (e) two or more lisch nodules, (f) osseous lesions like sphenoid dysplasia or thinning of the long bone cortex, (g) first-degree relative with NF-1 according to the above criteria. Malignant transformation of neurofibromas (usually the plexiform subtype) to a neurofibrosarcoma is the most important cause of mortality in adult patients with NF1. Riccardi [9] analysed the risk of malignancy in NF1 and estimates a lifetime risk of about 5% above and beyond the general population risk of approximately 20%. Malignant peripheral nerve sheath tumours (neurofibrosarcomas) are exceedingly rare in the general population; the sex- and age-adjusted risks for this malignancy in the context of NF1 are higher than the general population [9–11]. Loss of heterozygosity (LOH) has been shown to occur in NF1-associated malignancies [12]. Macroscopically it appears as poorly circumscribed, fleshy, frequently necrotic and hemorrhagic lesion. Neurofibrosarcomas are microscopically hypercellular with giant cells, increased mitotic count and vascular proliferation.

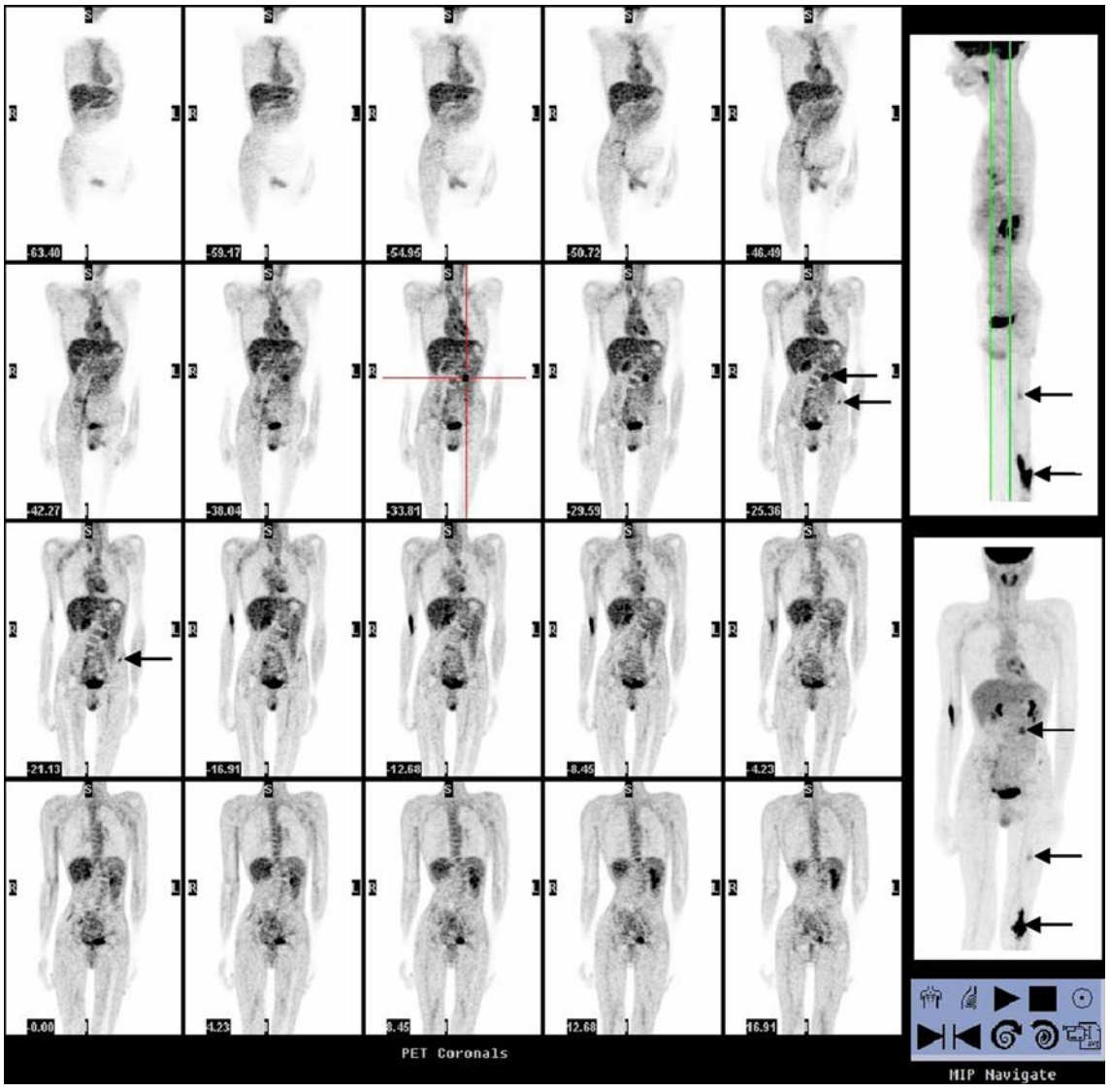

Fig. 1 Whole body FDG-PET showing a focus of intense FDG uptake in the posterior aspect of left popliteal fossa. Two other foci are observed, one posterior to the midshaft of the femur in the course of the sciatic nerve and the other just left to the convexity of the spine at the level of L2 vertebra. Another tiny focus is noted in the left iliac bone

The optimal management and probably final prognosis depends upon early accurate identification of sarcomatous transformation. Clinical suspicion of malignant degeneration in neurofibromas is raised if there is progressive enlargement, pain or neurological deficit. At conventional imaging, it is characterized by a large heterogeneous tumor invading adjacent structures. All these are also observed in the benign infiltrating plexiform neurofibromas. While CT and MRI are useful in assessment of the extent and vascularity of these and thereby help in planning surgical biopsies and resection, they are at times unreliable in accurately characterizing their nature as benign or malignant. Surgical resection of the entire tumour is often not feasible due to associated morbidity and biopsies may often be false negative due to sampling error. Collections of malignant cells may be present between larger masses of benign cells in a plexiform neurofibromas; hence, examining a plexiform tumor carefully (i.e. taking samples from multiple regions to confirm that it is indeed benign) is extremely important. FDG-PET, being a whole body technique and by its ability to reflect glucose metabolism is potentially useful in determining malignant change in plexiform neurofibromas. It can also serve as a guide to obviate the sampling error while biopsying a heterogeneous tumour admixed with benign tissue. In our case, among the numerous enlarged exit nerve roots in the cervical and lumbar region FDG-PET showed uptake in just left to the convexity of the spine at the level of L2

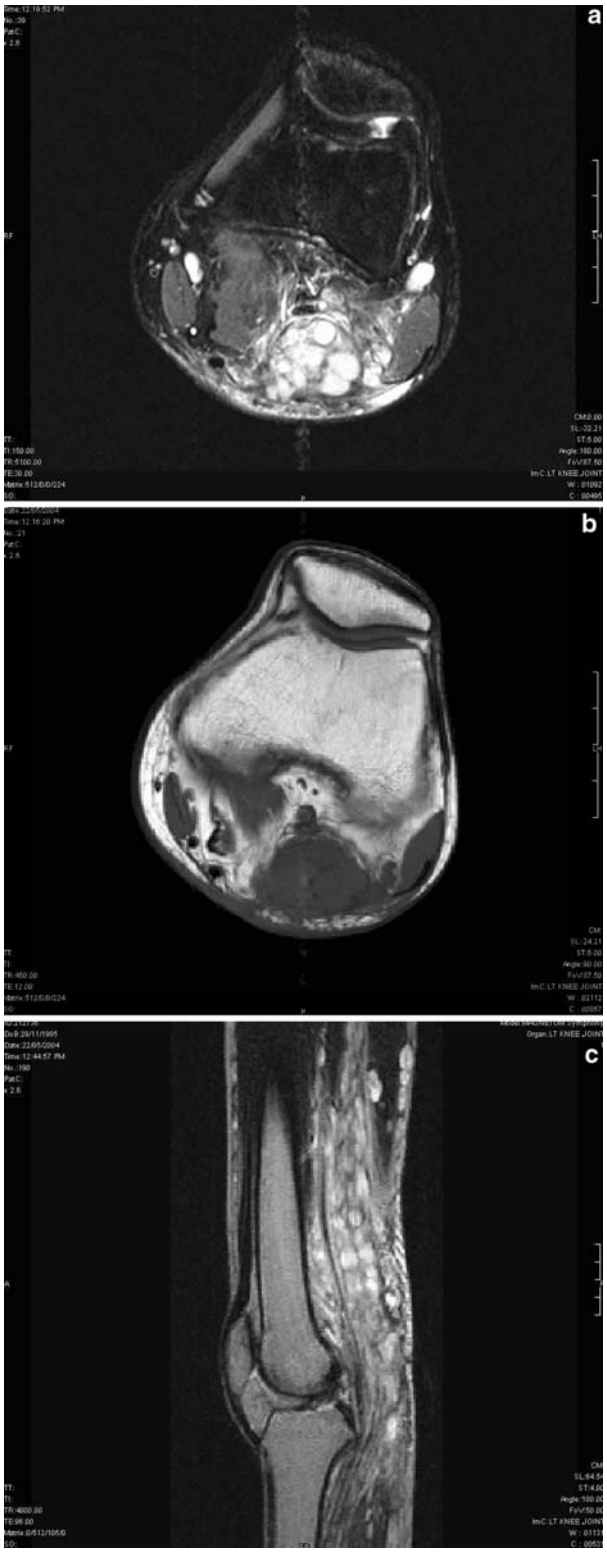

Fig. 2 (a–c) MRI of the left leg and thigh (axial and sagittal views) showing a nodular tumor in the popliteal fossa along the course of left tibial nerve with local infiltration into the belly of the semimembranosus and biceps femoris terminations. Fibres of the lateral head of gastrocnemius were also infiltrated. The popliteal vessels and soleus muscle were free of the tumor. The tumor showed marked contrast enhancement

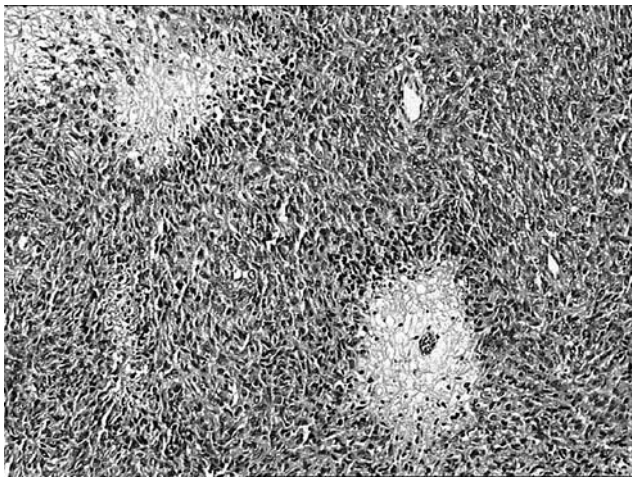

Fig. 3 The histologic section of the nodular tumour in the left popliteal fossa demonstrating spindle shaped tumor within foci of necrosis, with cells showing moderate degree of pleomorphism

vertebra; this was later proven to be malignant. It also identified a clinically silent focus in sciatic nerve. Qualitative assessment was sufficient for characterizing and correlating the lesions as the other clinically and radiologically proven lesions did not show any FDG uptake; hence a standardized uptake value (SUV) was not attempted.

A total of four published reports [13–16] in English literature dealing with sarcomatous transformation in NF1 were identified by searches of Pubmed. Ferner et al. [13] investigated eighteen NF1 patients who presented with pain, increase in size, or neurological deficit associated with a plexiform neurofibromas. While no malignant tumours were classified as benign, two benign tumours were reported as malignant. Chander et al. [14] reported a 14-year-old girl with a history of NF1 right iliac wing showed increased FDG uptake and PET was useful in therapy planning and subsequent follow up. Otsuka et al. [15] reported FDG-PET/CT in identification of sarcomatous change in a patient of NF1. Brenner et al. [16] showed that tumour SUV was an important predictor for survival. Their study found that patients with an SUV >3 had a shorter survival compared to those with an SUV <3. Tumour SUV, according to them, was better correlated with ultimate survival than histological grading. Not restricting to NF1, Cardona et al. [17] examined 25 neurogenic soft tissue tumours and found FDG-PET distinguished between MPNST and benign neurogenic tumours with 100% sensitivity and 83% specificity. The present case reaffirms the notion that FDG-PET is the most sensitive noninvasive probe to diagnose malignant transformation in NF1 and hence likely to appear as the screening procedure of choice in their follow up to rule out malignant transformation.

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