



Type 1 neurofibromatosis and adult extremity sarcoma A report of two cases

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We report two cases of malignant soft-tissue tumours - one myxoid malignant fibrous histiocytoma and one pleomorphic rhabdomyosarcoma- which were diagnosed in two young adult patients with type 1 neurofibromatosis (NF 1). The patients were evaluated with criteria for Neurofibromatosis 1 and NF 1 gene analysis was performed. Four of seven criteria were found in both patients. The tumours were stage II and III respectively. Both patients were treated with radiotherapy or chemotherapy and surgical intervention. Diagnoses of myxoid malignant fibrous histiocytoma and pleomorphic rhabdomyosarcoma in adult NF 1 patients are exceedingly rare. Thus detection of subtypes of rhabdomyosarcoma and malignant fibrous histiocytoma with immunohistochemistry may be helpful for the management of these tumours among other pleomorphic sarcomas that may occur in type 1 Neurofibromatosis.

Keywords : neurofibromatosis type 1 ; rhabdomyosarcoma ; malignant neurofibromatosis fibrous histiocytoma.

are malignant peripheral nerve sheath tumour (approximately half of the cases), optic glioma, malignant astrocytoma, rhabdomyosarcoma (RMS), nonlymphoid leukemia, Wilms' tumour and neuroblastoma (1, 2). We report the cases of two young adults who presented with a large thigh mass and who also revealed the signs and symptoms of NF1. The tumours were diagnosed as myxoid malignant fibrous histiocytoma (MMFH) in one patient and pleomorphic rhabdomyosarcoma (PRMS) in the other. Patients were evaluated with NIH (National Institutes of Health) consensus development criteria for NF1.

INTRODUCTION

As a well defined genetic disorder, type 1 neurofibromatosis (NF1) has an incidence of 1 in 3000-4000 individuals. This autosomal dominant disorder has high penetrance but 50% of cases result from a new mutation. Malignancy in NF1 is the major life-threatening complication of this genetic disease. The malignant tumour development rate is 5% (4). Common malignancies in NF1 patients

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CASE REPORTS

Case 1

A 21-year-old male patient complained of a large mass in his right thigh, which had developed over the past few months. Physical examination revealed a firm, painless thigh mass. The patient underwent complete staging and evaluation on suspicion of malignancy. Magnetic resonance imaging (MRI) showed a soft-tissue mass ($12 \times 9 \times 5$ cm) in the posterolateral part of the thigh, between the vastus lateralis and biceps femoris muscle. On T1-weighted images the tumour appeared heterogeneous isointense and on T2-weighted images heterogeneous hyperintense. After Gd-DTPA enhancement, obvious heterogenic paramagnetic contrast uptake was observed (fig 1 A-B).

Case 2

A 22-year-old male patient complained of a rapidly growing large thigh mass. On physical examination, a firm, painful, immobile mass in the whole aspects of the thigh was detected. MRI revealed a $20 \times 12 \times 10$ cm soft tissue tumour that invaded the anterior, lateral and posterior compartments of the thigh (fig 2). The mass appeared heterogeneous, isointense and contained central necrotic areas on T1-weighted images and heterogeneous hyperintense on T2-weighted images. All structures in the thigh were pushed medially by the mass (fig 3 A-B).

Pathological findings : High-speed needle biopsy was performed in both patients and pathological and immunohistochemical stainings were performed. The diagnoses were myxoid malignant fibrous histiocytoma (MMFH) in case one and pleomorphic rhabdomyosarcoma (PRMS) in case two. The immunoprofiles of the tumours were as follows : in the MMFH case, it revealed CD 68 expression without S-100, EMA and cytokeratin expression by tumour cells ; the PRMS tumour was desmin and vimentin positive ; staining for S-100 protein was negative.

NF1 criteria : Both patients were found to exhibit typical neurocutaneous signs of NF1. However the diagnosis of neurofibromatosis had

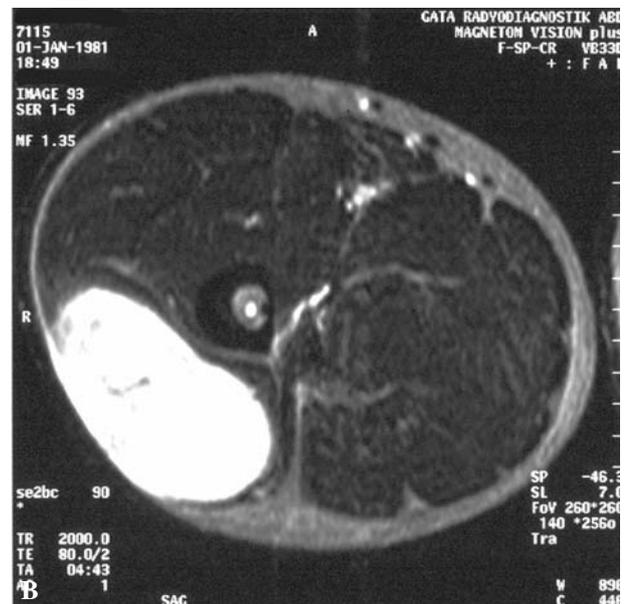
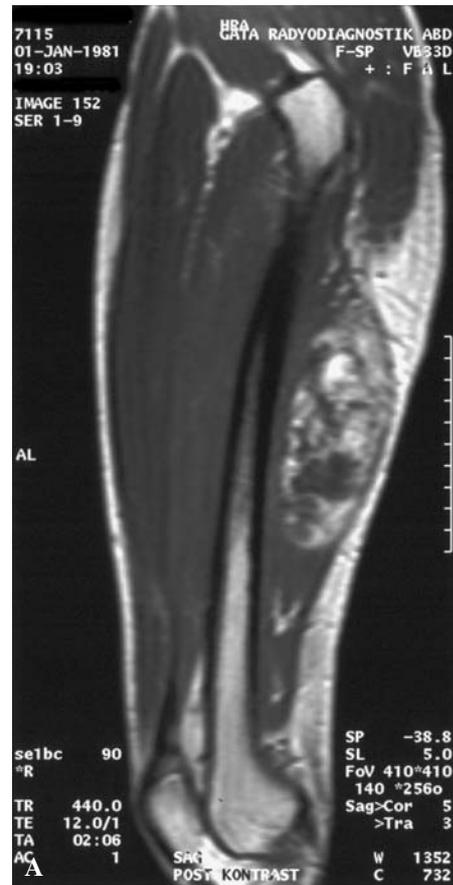


Fig. 1A-B. — MRI scans showing a soft tissue mass on the lateral aspect of thigh. Note the heterogeneity of the mass (Case 1).



Fig. 2. — Clinical appearance of the patient in Case 2

not been made previously in either of them. Therefore both patients underwent complete dermatological, ophthalmological, and neurological evaluation and they were evaluated according to the NIH consensus development criteria for NF1 (4). Four of seven criteria were positive in both patients. They had learning disability. Case 2 also had unidentified brain objects (table I).

These findings revealed that patients had soft tissue sarcomas coexisting with NF 1. According to the criteria of the American Joint Committee on Cancer the tumours were stage IIA and grade III, respectively.

Treatment : In order to achieve local control of the MMFH in case one, a wide resection was performed included removal of the vastus lateralis and biceps femoris muscle with their fascia and part of tensor fasciae latae. Adjuvant radiotherapy was performed with 3500 cGy, over 25 days. During 32 months of follow-up no evidence of local recurrence and/or systemic disease has been noted. In Case 2, chemotherapy and hip disarticulation were suggested, due to the extent of the lesion, but the patient refused disarticulation and therefore underwent wide resection. After the operation wound necrosis and recurrent infections occurred. Hyperbaric oxygen therapy and repetitive wound debridement were unsuccessful and hip disarticulation was eventually made. Adjuvant chemotherapy was initiated but multiple lung metastases were detected during the course and the patient died 15 months after the operation.

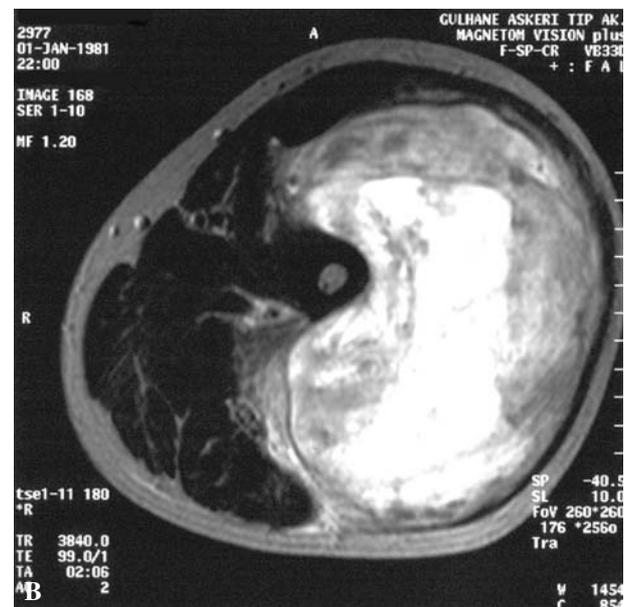
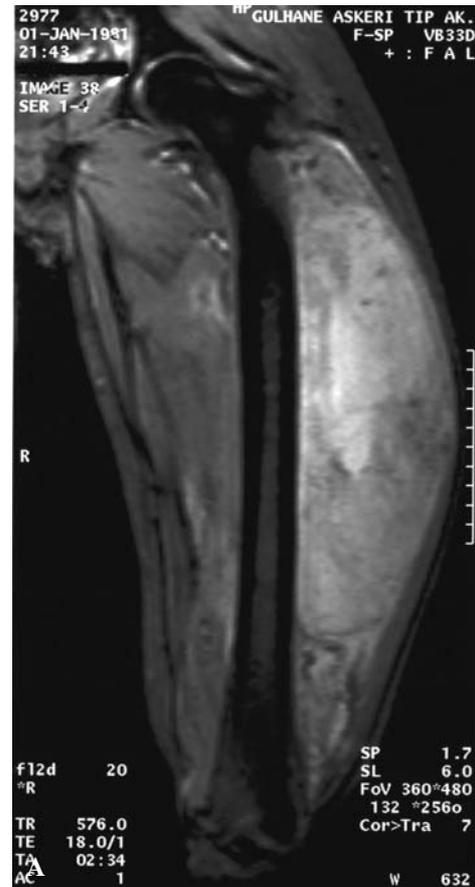


Fig. 3A-B. — MRI scans showing a very large soft tissue mass surrounding the vicinity of the femur and containing necrotic areas (Case 2).

Table 1. — Summary of findings in our patients according to the diagnostic criteria of the NIH consensus development conference.

	NIH Criteria							Additional Findings	
	Café au lait spots	Neurofibromas	Freckling	Optic Pathway Tumour	Lisch Nodules	Bone Dysplasia	First degree relative	Learning Disability	MRI abnormalities in brain
Case 1 (MMFH)	+	+	–	–	+	–	+ Paternal	+ IQ 72	–
Case 2 (PRMS)	+	+	–	–	+	–	+ Paternal	+ IQ 70	+ UBO

UBO : Unidentified brain objects.

MMFH : Myxoid malignant fibrous histiocytoma.

PRMS : Pleomorphic rhabdomyosarcoma.

The data of patients, blood samples and biopsy materials were referred to the National Neurofibromatosis Committee for registration and further genetical analysis for NF 1 gene.

DISCUSSION

As the most important life threatening complication of NF1, malignancies deserve attention because of their high incidence in these patients. Several malignant tumour types have been encountered associated with NF1. The majority of these malignancies are peripheral and central nervous system tumours (2, 9). About 42% of the NF1 patients who have malignancy are under the age of 19 at the time of diagnosis (2).

Rhabdomyosarcoma has a well known association with NF 1 in children, with a 2% incidence. Embryonal and alveolar RMS are the most prominent subtypes in NF 1 and most of these tumours are localized in the genitourinary tract rather than in the extremities (9). A diagnosis of RMS in adult NF1 patients is rarely made (0.4%) (3, 9). As a rare subtype of RMS, pleomorphic RMS (PRMS) is a high-grade aggressive sarcoma which occurs in the normal adult population with a mean age of 49 years (3). Aggressive progression, extremity predominance and poor prognosis are major clinical features of PRMS like in our case (3, 5). We found no single case of PRMS in association with NF 1 in adults reported before in English literature.

Malignant fibrous histiocytoma (MFH) is an exceedingly rare tumour type in NF1. Only four cases have been reported in the literature (1, 6, 7, 10). Of the reported tumours, three were localized in the thigh, which is correlated with classic MFH features, and three patients had a family history of NF 1. But not any subtype of MFH is determined in these cases. Myxoid MFH is a member of the myxoid soft tissue sarcoma family, which is included in a group of intermediate tumours. As was the case with our patient, myxoid MFH has better prognosis among other MFH subtypes.

Accurate histopathological diagnosis of the tumour type is mandatory for optimal patient management of the dedifferentiated or myxoid malignancies occurring in NF1. Klijanienko *et al* revealed that many pathological specimens of RMS and MFH have been misinterpreted as malignant peripheral nerve sheath tumour in previous pathological reports; hence they concluded that broad immunohistochemical tests should be performed in these tumours for accurate diagnosis (8). Additionally identification of subtypes in the sarcoma family will provide characteristic behavioral patterns of each tumour, which may help selecting the best definitive treatment modality and provide valuable clinical information for both pathologist and surgeon.

The gene responsible for NF 1 is located on the long arm of chromosome 17 (4). However, the wide diversity of pathogenic mutations and the large size

of the gene have impeded the development of a clinical diagnostic test. It has been suggested that the NF 1 gene and its protein product (neurofibromin) may initiate some specific clinical features of NF 1 during the course of the disease. Matsui *et al* note that the NF 1 mutant gene is prone to promote the development of a specific type of rhabdomyosarcoma in urogenital organs in childhood (9). However there is not enough evidence for such an association between NF 1 gene and adult RMS.

Finally despite the complex genetic basis of NF 1, the diagnosis is mainly clinical (NIH consensus for NF 1) (6). Determining specific subtypes of RMS and MFH may be helpful for better management of these tumours among other pleomorphic sarcomas occurring in NF 1. It is obvious that the sarcomas diagnosed in our patients were related with the tendency to develop malignancies in NF 1, but further efforts are needed to distinguish the clinical effect of NF1 beyond the simple coexistence of sarcomas with NF1. Therefore physicians must be aware of the neurocutaneous signs of the NF 1 in those patients who have soft tissue tumours, and registration to the national neurofibromatosis committee is mandatory for collecting clinical and genetic data of each patient.

REFERENCES

1. **Ben Izhak O, Groisman GM.** Anal malignant melanoma and soft tissue malignant fibrous histiocytoma in neurofi-

bromatosis type 1. *Arch Pathol Lab Med* 1995 ; 119 : 285-288.

2. **Friedman JM, Birch PH.** Type 1 neurofibromatosis : A descriptive analysis of the disorder in 1728 patients. *Am J Med Genet* 1997 ; 70 : 138-143.

3. **Furlong MA, Mentzel T, Fanburg-Smith JC.** Pleomorphic rhabdomyosarcoma in adults : A clinicopathologic study of 38 cases with emphasis on morphologic variants and recent skeletal muscle specific markers. *Modern Pathology* 2001 ;14 :495-603.

4. **Gutmann DH, Aylsworth A, Carey JC, et al.** The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997 ; 278 : 51-57.

5. **Hulse N, Raja S, Kumar A, Paul AS.** Rhabdomyosarcoma of the extremities in adults. *Acta Orthop Belg* 2006 ; 72 : 199-203.

6. **Johnson PS, Katz DA, Pester J, Penn R.** Malignant fibrous histiocytoma arising in a patient with multiple neurofibromatosis : a case report and literature review. *J Surg Oncol* 1979 ; 12 : 97-105.

7. **Katz RN, Waye JD, Batzel EL et al.** Malignant fibrous histiocytoma of the gastrointestinal tract in a patient with neurofibromatosis. *Am J Gastroenterol* 1990, 85 : 1527-1530.

8. **Klijanienko J, Caillaud JM, Lagace R, Vielh P.** Cytohistologic correlations of 24 peripheral nerve sheath tumors (MPNST) in 17 patients : The Institut Curie Experience. *Diagn Cytopathol* 2002 ; 27 : 103-108.

9. **Matsui I, Tanimura M, Kobayashi N et al.** Neurofibromatosis type 1 and childhood cancer. *Cancer* 1993 ; 72 : 2746-2754.

10. **Warrier RP, Kini KR, Raju U et al.** Neurofibromatosis and malignancy. *Clin Pediatr* 1985 ; 24 : 584-585.