Pediatr Radiol (1997) 27: 124–129

Ravi Bhargava
David M. Parham
Olga E. Lasater
Radha S. Chari
Gang Chen
Barry D. Fletcher

MR imaging differentiation of benign and malignant peripheral nerve sheath tumors: use of the target sign

Received: 10 January 1996
Accepted: 14 June 1996

R. Bhargava[1] · B. D. Fletcher (✉)
Department of Diagnostic Imaging,
St. Jude Children's Research Hospital,
332 N. Lauderdale St., Memphis, TN 38101,
USA

D. M. Parham
Department of Pathology and Laboratory
Medicine, St. Jude Children's Research
Hospital, Memphis, Tennessee, USA

G. Chen
Department of Biostatistics,
St. Jude Children's Research Hospital,
Memphis, Tennessee, USA

R. Bhargava · B. D. Fletcher
Department of Radiology,
University of Tennessee, Memphis,
Tennessee, USA

D. M. Parham
Department of Pathology,
University of Tennessee, Memphis,
Tennessee, USA

R. S. Chari[2]
Department of Obstetrics and Gynecology,
University of Tennessee, Memphis,
Tennessee, USA

B. D. Fletcher
Department of Pediatrics,
University of Tennessee, Memphis,
Tennessee, USA

O. E. Lasater
Department of Pathology,
Le Bonheur Children's Medical Center,
Memphis, Tennessee, USA

Present addresses:
[1] Department of Radiology,
University of Alberta Hospitals,
Edmonton, Canada

[2] Department of Obstetrics and
Gynecology, University of Alberta
Hospitals, Edmonton, Canada

Abstract *Background.* T2-weighted MR imaging of soft tissue tumors of neural origin may show round lesions with a central hypointensity and a hyperintense rim resembling a target. We define the "target sign" as a mass consisting of a solitary target, or a multicompartmental mass in which the largest component consists of multiple targets.

Objective. The objective of this study was to determine whether the target sign can differentiate benign neurofibromas and their malignant counterparts, malignant peripheral nerve sheath tumors.

Materials and methods. Preoperative T2-weighted MR images of 23 neurofibromas or malignant peripheral nerve sheath tumors were retrospectively reviewed in 16 patients, aged 3 weeks to 20 years (median 15 years), without knowledge of the pathologic diagnosis. The presence or absence of a target sign was noted.

Results. The target sign was seen in all 12 neurofibromas and 1 of the 11 malignant peripheral nerve sheath tumors. Statistical analysis showed good differentiation of benign and malignant tumors using this sign ($\varkappa = 0.91$).

Conclusion. The target sign on T2-weighted MR imaging is helpful in differentiating neurofibromas from malignant peripheral nerve sheath tumors.

Introduction

Malignant degeneration of peripheral neurofibromas is the leading cause of cancer death in patients with neurofibromatosis type 1 (NF1) [1, 2]. However, it is clinically difficult to distinguish benign from malignant neural tumors, especially in patients with neurofibromatosis, in whom tumors may be numerous and/or deeply situated. Optimal treatment of malignant peripheral nerve sheath tumors (MPNST) is surgical excision. However, excision of benign neurofibromas (BN), which contain intermingled neural elements and Schwann cells, usually compromises the affected nerve [3]. Further, blind biopsy of large complex tumors may

be subject to sampling errors [4]. Thus, a test that could differentiate benign from malignant lesions would prevent unnecessary morbidity.

MR imaging is the modality of choice for resolving and anatomically defining the extent of soft tissue tumors [5], and has been widely used to evaluate nerve sheath tumors [6–10]. However, there is overlap between the imaging features of benign and malignant neural tumors as to size, margination, MR imaging signal heterogeneity, contrast enhancement, peripheral edema, and adjacent muscle atrophy [5, 11–13].

Previous reports of BN have described a target (a hyperintense rim with centrally decreased intensity on T2-weighted sequences homogeneously isointense or mildly hyperintense to muscle on T1-weighted sequences) [8–12, 14–16]. Histologically the target comprises a central zone of tightly packed eosinophilic fibers, consisting of collagen or a highly cellular component surrounded by nonfibrillary stromal or myxoid material [8, 11, 12]. According to previous reports, MPNST have a heterogeneous appearance on T2-weighted MR imaging and lack this finding [11, 14]. These studies have not allowed statistical analysis of the target sign as a differentiating feature [8, 11, 14]. The purpose of this study was to determine the value of the target sign in differentiating BN from MPNST.

Materials and methods

The records and images of all patients at our institution who had a pathologically proven nerve sheath tumor (BN or MPNST) excised after preoperative MR imaging were studied. Postoperative MR imaging in all cases confirmed that the lesions seen preoperatively had been removed. There were 23 tumors in 16 patients. Six of the tumors were present in one patient. Twenty-two of these were situated within the soft tissues, while one also involved the adjacent bone (calcaneus). Three patients had multiple tumors. The median age at imaging was 15 years (range, 3 weeks to 20 years). There were ten males and six females. Nine of the 16 patients had NF1 by standard clinical criteria [17].

Preoperative T2-weighted MR images of the 23 tumors were retrospectively reviewed in order to determine the presence or absence of the target sign. The size of the largest target in patients with the target sign and the presence of targets in satellite tumors adjacent to the largest component of the mass were noted. The greatest diameter of the entire tumor mass was also measured.

Preoperative MR imaging was performed in our, or referring institutions using a variety of systems with field strength of 0.5 ($n = 2$), 1.0 ($n = 11$), and 1.5 ($n = 10$) T. TR (repetition time) and TE (echo time) for conventional spin-echo T2-weighted images ($n = 12$) ranged from 1800–2500 ms and 80 to 100 ms respectively. Four patients had fast or "turbo" T2-weighted spin-echo imaging with TR/TE of 2500–4250/90–104. Fields of view ranged from 15 to 50 cm, and matrix sizes were 160, 192, 216 or 256 × 256.

Histologic diagnosis of peripheral nerve sheath tumors was accomplished by experienced pathologists using standard histologic criteria [18]. MPNST was distinguished by the presence of high cellularity, mitoses, and/or geographic areas of necrosis [18].

The excised BN were re-reviewed by light microscopy to identify the structures that comprised the target. The periphery and the central core of these lesions were histologically characterized and compared with those of MPNST.

A univariate logistic regression model was fitted first to identify those significant factors related to pathologic diagnosis of the tumor [19]. The kappa statistic was then used to measure the agreement between these significant factors and the pathologic diagnosis of the tumor. This test indicates strong agreement when kappa was > 0.75, fair to good agreement for values of 0.40–0.75, and poor agreement when kappa values were < 0.40 [19].

Results

There was agreement in all cases as to the presence or absence of the target sign. Clinical, imaging, and pathologic data are shown in Table 1. Histologically there were 11 MPNST and 12 BN.

All 12 BN had a positive target sign. Four of 12 tumors consisted of a solitary target (Fig. 1), and the remaining eight benign tumors were composed of multiple targets (Fig. 2). Histologically, 2 of the 12 tumors were plexiform neurofibromas. On MR imaging, plexiform neurofibromas appeared identical to BN, with the presence of multiple target signs. The largest individual target lesion within each BN had a median diameter of 10 mm (range 5–24 mm). The entire BN had a median diameter of 30 mm with a range of 10–110 mm.

Histologically, the target sign was found to represent either myxoid tissue encircling a cellular matrix containing Schwann cells, fibroblasts, and perineurial cells; myxoid tissue encircling collagen; or myxoid tissue encircling a mixed collagen and cellular matrix (Fig. 3).

Ten of the 11 MPNST did not contain targets as the largest component of the mass (negative target signs). These masses had a variable signal that was predominantly hyperintense, with no distinguishing features on T2-weighted MR imaging (Fig. 4). One MPNST (a triton tumor) consisted of a large heterogeneously hypointense lobulated region surrounded by hyperintense muscle edema on T2-weighted MR imaging. Five of the 10 malignant tumors had one or more satellite target signs on the periphery of the mass (Fig. 4). One calcaneal and retrocalcaneal soft tissue MPNST was composed of multiple targets. The histologic features representing the target sign were found in the initial biopsy of this tumor. The MPNST had a median diameter of 50 mm with a range of 20–110 mm.

Analysis of age, sex, size greater than 3 cm, and size greater than 5 cm by the univariate logistic regression model did not show any significant association with the presence or absence of malignancy ($P = 0.21$, 0.07, 0,51, and 0.32 respectively). The presence of either the target sign or clinical evidence of NF1 was positively correlated with BN. The kappa statistic of 0.91 [95 % confidence in-

Table 1 Clinical, imaging and histologic findings in patients with benign and malignant peripheral nerve sheath tumors (*NF1* neurofibromatosis type 1, *MPNST* malignant peripheral nerve sheath tumor, *BN* benign neurofibroma, *N/A* not available, + present, – not present)

Patient no.	Age at imaging (years)	Sex	NF1	Tumor site	Tumor size (mm)	Target size (mm)	Target sign	Target in a satellite lesion near mass	Pathology diagnosis	Pathology target	Center	Periphery
1	9	M	Yes	Left neck	80	20	Yes	+	BN	Yes	Collagen and cells	Myxoid tissue
2	15	M	Yes	Left arm	55	10	Yes	+	BN	Yes	Collagen	Myxoid tissue
3	10	F	Yes	C1 nerve root	10	5	Yes	+	BN	Yes	Collagen and cells	Myxoid tissue
4	12	F	Yes	Orbit	25	25	Yes	–	BN	No		
5	15	M	Yes	Scalp	10	10	Yes	–	BN	Yes	Collagen and cells	Myxoid tissue
6	15	F	Yes	Lower extremity	25	5	Yes	+	BN	Yes	Collagen and cells	Myxoid tissue
7	16	F	Yes	Left posterior femoral cutaneous nerve	35	10	Yes	+	Plexiform BN	N/A		
7	16	F	Yes	Right sciatic nerve	35		No	+	MPNST	N/A		
7	16	F	Yes	Left sciatic nerve	35	10	Yes	+	BN	N/A		
7	19	F	Yes	Right chest wall	110	5	Yes	–	BN	Yes	Collagen	Myxoid tissue
7	19	F	Yes	Right intercostal nerve	25	5	Yes	–	BN	Yes	Collagen	Myxoid tissue
7	19	F	Yes	Left chest wall soft tissue	10	5	Yes	+	Plexiform BN	Yes	Increased cellularity	Myxoid tissue
8	19	M	Yes	Presacral	50	10	Yes	+	BN	Yes	Collagen	Myxoid tissue
8	19	M	Yes	Left sciatic nerve	65		No	+	MPNST	No		
9	13	F	Yes	Abdominal mass	60		No	+	MPNST	No		
10	15	M	No	Right popliteal	110		No	–	MPNST	No		
10	13	M	No	Right calcaneus	50	5	Yes	+	MPNST	Yes	Increased cellularity	Cells
11	3	M	No	Left C8 nerve root	25		No	–	MPNST	No		
12	11	M	No	Right clavicle soft tissues	20		No	–	MPNST	No		
13	20	M	No	Right thigh	55		No	–	MPNST	No		
14	10	M	No	Right axilla	80		No	+	MPNST	N/A		
15	18	M	No	Left calf	20		No	–	MPNST	No		
16	3/52	F	No	Right back	20		No	+	MPNST	No		

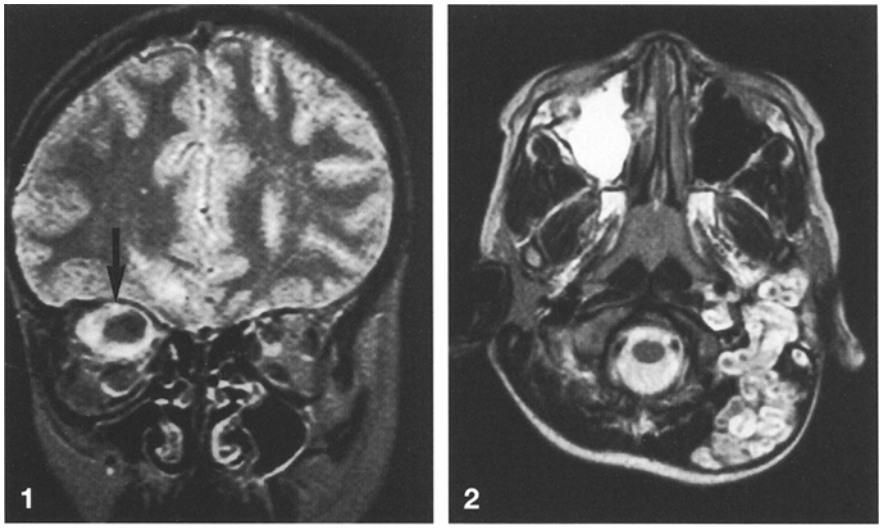

Fig. 1 A 12-year-old girl (patient 4) with NF1 and proptosis caused by an orbital neurofibroma. T2-weighted [2300/80 (TR ms/TE ms)] coronal image shows a 2.4-cm diameter target sign *(arrow)* consisting of a large central hypointense region surrounded by a hyperintense rim

Fig. 2 A T2-weighted (2500/104) transverse image through the neck and skull base of a 9-year-old boy (patient 1) shows multiple target signs in a plexiform neurofibroma on the left

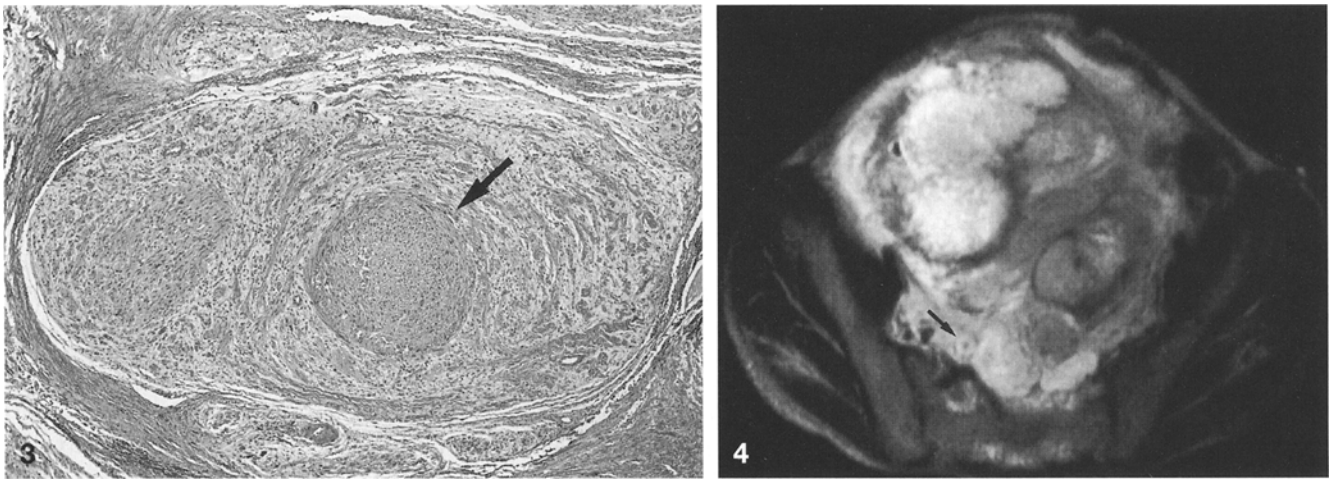

Fig. 3 Histologic section of a benign neurofibroma of the lower extremity in a 15-year-old girl shows a 4-mm target sign composed of compactly packed neurofibroma cells and collagen *(arrow)* surrounded by a less compact region containing an abundant myxoid stroma (H & E, original magnification 40 ×)

Fig. 4 A 13-year-old girl with a heterogeneous multilobulated retroperitoneal malignant peripheral nerve sheath tumor shown on a transverse turbo spin-echo T2-weighted (4250/90) MR image of the pelvis. There is a target sign *(arrow)* anterior to the right sacral wing suggesting the neural origin of the tumor. The largest compartment of the tumor does not contain targets, and thus the mass has a negative target sign

terval (0.74, 1.0), $P < 0.001$] indicates strong agreement between the target sign and a benign pathologic diagnosis. The sensitivity of the target sign for a BN is 100 % [95 % confidence interval (78 %, 100 %)] and the specificity is 92 % [95 % confidence interval (59 %, 100 %)]. The kappa statistic of 0.74 [95 % confidence interval (0.47, 1.0), $P < 0.001$], indicates fair agreement between NF1 and a benign pathologic diagnosis.

There is strong agreement between having a benign pathologic diagnosis when the patient has NF1 and a target sign within the largest component of the mass. The sensitivity in our population of having NF1 and a target sign for a BN is 100 % [95 % confidence interval (76 %, 100 %)] and the specificity is 100 % [95 % confidence interval (78 %, 100 %)].

Discussion

BN is the most common benign tumor to arise from the peripheral nerves [4, 18, 20, 21]. BN may occur alone or in association with NF1, a condition that affects 1/2000 to 1/4000 individuals [4, 17, 18, 22]. MPNST are the principal malignancy of peripheral nerves and account for 10 % of all soft tissue sarcomas, with one-half occurring in patients with NF1 [18, 23]. Of patients with NF1, 2 %–13 % may develop a MPNST [18, 23].

The target-like appearance of BN on MR images reflects the mode of tumor formation. Endoneurial myx-

omatous matrix proliferates, progressively separating myelinated and non-myelinated axons [4]. Schwann cells and collagen fibers proliferate and become embedded in unorganized intercellular material [4]. This nonfibrillary myxomatous tissue accounts for the hyperintense appearance of the peripheral zone on T2-weighted sequences, while the central zone of dense collagen is hypointense [7, 8].

Clinical differentiation of benign from malignant tumors can be difficult, and a delay in diagnosis of malignant tumors adversely affects prognosis [18]. This differentiation is especially important in patients with NF1, who often have many neural tumors. BN may be symptomatic; increasing pain in patients with BN may be a symptom of malignant degeneration. However, patients with MPNST may have minimal discomfort or even be asymptomatic, making clinical diagnosis difficult.

Plexiform neurofibromas have been demonstrated by CT as bilateral symmetric, low-attenuation masses in parapsoas or presacral locations [24]. Asymmetry in size and/or attenuation of these bilateral masses suggested malignant degeneration of the larger mass. However, there were no other characteristics identified that could differentiate a benign from a malignant unilateral mass. In our series, tumor size was not a reliable discriminating feature between BN and MPNST.

This study showed fair agreement between clinical evidence of NF1 and the presence of a benign soft tissue tumor. The combination of having NF1 and a target sign comprising the largest component of the mass was indicative of a benign lesion. One patient without NF1 had a MPNST composed of multiple target signs. Since this was the only patient without NF1 whose tumor showed a positive target sign, we cannot form a conclusion about the specificity of this sign in the absence of NF1. However, since the MR appearance reflects histologic findings of a neurofibroma, we expect that the target sign will be useful in patients without NF1. To our knowledge schwannomas are the only other published lesion to sometimes have a target on MR imaging [14].

Care must be taken in evaluating masses with targets, as MPNST may be adjacent to BN. MPNST may even appear as a gradual regional histologic transition from a BN [4]. In these complex cases we found the absence of a target as the largest component of the mass to be the most accurate predictor of malignancy. A presumptive radiologic diagnosis of MPNST could be made in five of the ten malignant tumors in our study by noting absence of targets as the largest component of the mass, in spite of smaller satellite target lesions adjacent to the periphery. In these cases our findings suggested that the target sign comprised benign neurofibromas and the adjacent larger component devoid of target lesions was caused by sarcomatous degeneration. The remaining five malignant tumors had a nonspecific heterogeneous appearance on T2-weighted MR imaging with areas of hyperintensity and no target signs. Although some tumors may display heterogeneous imaging characteristics or may not have a single dominant mass, recognition of the target as a likely indicator of a benign lesion may help direct biopsy of heterogeneous tumors to portions of tumor devoid of targets, thus increasing the likelihood of sampling malignant cells.

Since the target sign may not be appreciated due to improper instrument window and level settings that can obscure the dark center, we use a wide window to allow characterization of the internal architecture of a mass. Also, the matching of matrix size and field of view to provide high spatial resolution is important so as to adequately resolve the dark centers, which were as small as 1.0 mm in diameter. These factors may explain the unexpectedly high sensitivity of the target sign as an indicator of BN in our series. In our study, targets were readily apparent on images made by a variety of instruments and were visualized on both conventional and fast spin-echo sequences.

Acknowledgements This study was supported in part by the National Cancer Institute, Cancer Center Support (CORE) grant P30CA21765 and the American Lebanese Syrian Associated Charities (ALSAC).

References

1. Elster AD (1992) Radiologic screening in the neurocutaneous syndromes: strategies and controversies (comment). AJNR 13: 1078–1082
2. Shearer P, Parham D, Kovnar E, Kun L, Rao B, Lobe T, Pratt C (1994) Neurofibromatosis type I and malignancy: review of 32 pediatric cases treated at a single institution. Med Pediatr Oncol 22: 78–83
3. Holder TM, Snyder CL (1993) Miscellaneous tumors. In: Ashcraft KW, Holder TM (eds) Pediatric surgery. Saunders, Philadelphia, p 898
4. Harkin JC, Reed RJ (1969) Tumors of the peripheral nervous system. Armed Forces Institute of Pathology, Washington, DC
5. Moore SG, Bisset GS, Siegel MJ, Donaldson JS (1991) Pediatric musculoskeletal MR imaging. Radiology 179: 345–360
6. Guz BV, Wood DP Jr., Montie JE, Pontes JE (1989) Retroperitoneal neural sheath tumors: Cleveland Clinic experience. J Urol 142: 1434–1437
7. Glasier CM, Williamson MR, Lange TA (1989) MRI of peripheral neurofibromas in children. Orthopedics 12: 269–272
8. Suh JS, Abenoza P, Galloway HR, Everson LI, Griffiths HJ (1992) Peripheral (extracranial) nerve tumors: correlation of MR imaging and histologic findings. Radiology 183: 341–346

9. Li MH, Holtas S (1991) MR imaging of spinal neurofibromatosis. Acta Radiol 32: 279–285
10. Breidahl WH, Khangure MS (1991) MRI of lumbar and sacral plexus nerve sheath tumours. Australas Radiol 35: 140–144
11. Burk DL Jr, Brunberg JA, Kanal E, Latchaw RE, Wolf GL (1987) Spinal and paraspinal neurofibromatosis: surface coil MR imaging at 1.5 T. Radiology 162: 797–801
12. Verstraete KL, Achten E, De Schepper A, Ramon F, Parizel P, Degryse H, Dierick AM (1992) Nerve sheath tumors: evaluation with CT and MR imaging. J Belge Radiol 75: 311–320
13. Stull MA, Moser RP Jr, Kransdorf MJ, Bogumill GP, Nelson MC (1991) Magnetic resonance appearance of peripheral nerve sheath tumors. Skeletal Radiol 20: 9–14
14. Varma DG, Moulopoulos A, Sara AS, Leeds N, Kumar R, Kim EE, Wallace S (1992) MR imaging of extracranial nerve sheath tumors. J Comput Assist Tomogr 16: 448–453
15. Shonnard KM, Jelinek JS, Benedikt RA, Kransdorf MJ (1992) CT and MR of neurofibromatosis of the bladder. J Comput Assist Tomogr 16: 433–438
16. Hughes PM, Hawnaur JM, Jenkins JP, Isherwood I (1990) Craniospinal magnetic resonance imaging in neurofibromatosis (Abstract). Br J Radiol 63: 2
17. Anonymous (1988) Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol 45: 575–578
18. Enzinger FM, Weiss SW (1995) Soft tissue tumors, 3rd edn. Mosby, St Louis
19. Fleiss JL (1981) Statistical methods for rates and proportions. Wiley, New York, pp 217–225
20. Woodruff JM (1993) The pathology and treatment of peripheral nerve tumors and tumor-like conditions. CA Cancer J Clin 43: 290–308
21. Kransdorf MJ (1995) Benign soft-tissue tumors in a large referral population: distribution of specific diagnoses by age, sex, and location. AJR 164: 395–402
22. Smirniotopoulos JG, Murphy FM (1992) The phakomatoses. AJNR 13: 725–746
23. Lott IT, Richardson EP Jr (1981) Neuropathological findings and the biology of neurofibromatosis. Adv Neurol 29: 23–32
24. Bass JC, Korobkin M, Francis IR, Ellis JH, Cohan RH (1994) Retroperitoneal plexiform neurofibromas: CT findings. AJR 163: 617–620