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ANATOMICAL PATHOLOGY

Lipofibromatosis-like neural tumour: a clinicopathological study of ten additional cases of an emerging novel entity

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Summary

We present our experience with ten cases of lipofibromatosis-like tumour (LPF-NT) to further characterise this newly described neoplasm. There were six males and four females with a mean age of 12.8 years (range 2–37 years). Tumours occurred in the neck ($n = 3$), buttock ($n = 2$), chest wall, flank, hip, hand and foot ($n = 1$). Histologically, they were composed of cellular fascicles of mildly to moderately atypical spindle cells displaying an infiltrative pattern reminiscent of lipofibromatosis or dermatofibrosarcoma protuberans. Immunohistochemically, all cases co-expressed S100 protein and CD34. FISH analysis revealed *NTRK1* gene rearrangement in four of five cases tested. Clinical follow-up showed local recurrence in three cases but no evidence of metastasis. This study further supports that LPF-NT represents a novel entity of *NTRK1*-associated neoplasms. Awareness of its clinicopathological features, immunophenotypes and cytogenetic abnormalities helps pathologists arrive at the correct diagnosis.

Key words: Lipofibromatosis; neural tumour; biphenotype; *NTRK1*.

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INTRODUCTION

In 2016, Agaram *et al.* described a unique soft tissue tumour bearing a close resemblance to lipofibromatosis (LPF).[1] However, the tumour differed from LPF by exhibiting a mild degree of nuclear atypia, co-expression of S100 protein and CD34, and recurrent neurotrophic tyrosine kinase receptor 1 (*NTRK1*) gene rearrangement. Based on the morphology and S100 protein positivity, they proposed a descriptive term of lipofibromatosis-like neural tumour (LPF-NT) to define this particular type of mesenchymal tumour. Before the description of LPF-NT, we also encountered several cases with identical morphology and immunophenotype but found it difficult to further catergorise using the existing classification systems of soft tissue tumours. At that time, we made a tentative diagnosis of a low grade spindle cell tumour of possibly neurogenic or fibrogenic origin. Of note, we even made a diagnosis of low grade CD34+/S100+ spindle cell tumour/sarcoma in a few cases. However, interphase fluorescence *in situ* hybridisation (FISH) analysis in four recent cases with available materials verified recurrent *NTRK1* gene rearrangement, consistent with that of LPF-NT reported by Agaram *et al.* To the best of our knowledge, LPF-NT has not been widely recognised, possibly due to its rarity and a lack of awareness of the entity. We present here our own experience with ten additional cases of LPF-NT in support of a distinctive novel entity.

MATERIALS AND METHODS

Nine cases of LPF-NT were collected from the consultation files of the Department of Pathology, Fudan University Shanghai Cancer Center, and one in-house case was retrieved from the Department of Pathology, Zhejiang Provincial People's Hospital. All cases were diagnosed between January 2015 and February 2017. Of consultation cases, the diagnosis provided by the referring pathologists included congenital fibrosarcoma, solitary fibrous tumour (SFT) and spindle cell tumour not otherwise specified in two cases each, infantile fibromatosis, neurofibroma versus dermatofibrosarcoma protuberans (DFSP) versus lipomatous tumour, and fibroma in one case each. Our initial diagnosis in six consultation cases included low grade neural tumour in two cases, peripheral nerve sheath tumour, borderline spindle cell tumour of fibrogenic or neurogenic origin, CD34+/S100+ spindle cell sarcoma of possibly neurogenic origin, and low grade CD34+/S100+ spindle cell tumour in one case each. The primary tumour of the in-house case was originally diagnosed as low grade malignant peripheral nerve sheath tumour (MPNST), whereas the diagnosis of the recurrent tumour was amended to LPF-NT based on subsequent FISH analysis. The clinical and follow up data were obtained from the medical records and hospital discharge summary, or by direct telephone inquiry. All available haematoxylin and eosin (H&E) slides were reassessed.

Immunohistochemistry was performed on 4 μm thick unstained sections on the Ventana Benchmark XT autostainer (Ventana Medical Systems, USA) using antibodies against CD34 (1:100; Dako, Denmark), S100 protein (1:300; Dako), SOX10 (ready to use; Celerus Diagnostics, USA), CD99 (1:50; Dako), STAT6 (ready to use; Abcam, UK), alpha-smooth muscle actin (SMA) (1:200; Dako), calponin (1:150; Maxin, China), h-caldesmon (1:300; Dako), desmin (1:200; Dako), myogenin (1:500; Novacastra, UK), MyoD1 (1:50; Dako), pancytokeratin (AE1/AE3) (1:50 Dako), epithelial membrane antigen (EMA) (1:200; Dako), CD31 (1:30; Dako), ERG (ready to use; Roche Diagnostics, USA) and Ki-67 (MIB1) (1:150; Dako). Antigen retrieval was performed in a pressure cooker. Appropriate positive and negative controls were run simultaneously for all antibodies tested. Interphase FISH analysis was carried out on 5 μm thick sections of formalin fixed, paraffin embedded tissues. Five recent cases were tested for the presence of *NTRK1* gene rearrangement using NTRK1 dual-colour break-apart probe (Linked-Biotech Pathology, China). Another five cases were not tested for the presence of *NTRK1* rearrangement as there was no *NTRK1* probe available then and spare unstained slides are no longer available. Two cases were tested for *ETV6* and one case was tested for *PDGFB* gene rearrangement using corresponding dual-colour break-apart probes (Abbott Molecular and Vysis, USA)

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respectively. The fluorescence signals were analysed using an Olympus BX51 fluorescence microscope (Olympus, Japan). A total of 200 nuclei were evaluated from each specimen. A positive score was interpreted as more than 20% of the nuclei showing a break-apart signal.

RESULTS

Clinical data

The clinical features of ten cases are summarised in Table 1. There were six males and four females. The age at diagnosis ranged from 2 to 37 years, with a mean and median age of 12.8 years and 7 years, respectively. All tumours occurred in the superficial soft tissues, including the neck ($n = 3$), buttock ($n = 2$), chest wall, flank, hip, hand and foot ($n = 1$). The most common presentation was a subcutaneous mass or nodule (Fig. 1A), with a duration of 2 weeks–3 years (median 6 months). Ultrasonograpy usually showed a low or medium echo-level mass located in the subcutaneous adipose layer with uneven internal echo. Computed tomography (CT) and magnetic resonance imaging (MRI) examinations revealed a circumscribed ovoid mass of low density with varying amount of adipose component (Fig. 1B).

Pathological features

Grossly, the resected tumours measured from 2.5 to 8.0 cm in maximum diameter (mean 4.4 cm; median 4.5 cm). On the cut surface they had a grey-pinkish or grey-whitish colour and soft to firm consistency with no areas of necrosis or haemorrhage.

Histologically, the tumour was predominantly located in the subcutis (Fig. 2A). In seven cases, it was composed of streaming fascicles of spindle cells that infiltrated the subcutaneous adipose tissue in a fashion closely reminiscent of LPF (Fig. 2B). A honeycomb infiltrative pattern was also present in some areas, resembling that of DFSP (Fig. 2C). There were also solid areas composed of dense fascicles or compact sheets of spindle cells showing infiltration of fat in varying degrees (Fig. 2D). In three cases, the LPF-like or DFSP-like infiltrative pattern was not prominent. The tumour was composed mainly of fascicles of spindle cells separated by collagen fibres (Fig. 2E). On higher power, the spindled tumour cells displayed a mild to moderate degree of nuclear atypia with indistinct nucleoli and pale to slightly eosinophilic cytoplasm (Fig. 2F). Mitotic figures were rarely encountered in eight tumours [<1/10 high power field (HPF)]. However, two tumours had a mitotic activity of 4/10 HPF (Fig. 2G). In addition to the spindle cell component, scattered pleomorphic polygonal cells were discerned in one primary tumour and one recurrent tumour, respectively (Fig. 2H). Areas of necrosis or haemorrhage were absent in all tumours in this series. Recurrent tumours in three cases showed similar features to the primary tumours, except infiltrating of skeletal muscle in one case.

Immunohistochemical and molecular findings

Immunohistochemically, spindle cells in all tumours showed dual expression of CD34 (Fig. 3A) and S100 protein (Fig. 3B). Scattered pleomorphic cells in one primary tumour and one recurrent tumour were also positive for these two markers (Fig. 3C). Four tumours also showed immunoreactivity for CD99. They were all negative for SOX10, STAT6, SMA, calponin, h-caldesmon, desmin, myogenin, MyoD1, AE1/AE3, EMA, CD31 and ERG. Ki-67 index was about 5–10%. FISH analysis showed rearrangement of *NTRK1* in four of five cases tested (Fig. 3D). There was no *ETV6* gene rearrangement in two cases and no *PDGFB* gene rearrangement in one case analysed, respectively.

Treatment and follow up

All ten patients were treated with surgery. Among them, one patient was first treated with propranolol, pingyangmycin and bleomycin as it was initially considered a vascular malformation clinically. However, the treatment was shown to be ineffective as the mass enlarged progressively. Clinical follow-up information has thus far shown local recurrence in three cases. No patient has evidence of regional or distant metastasis.

DISCUSSION

We described an additional series of LPF-NT that showed clinical and pathological features identical to those reported by Agaram *et al.* Prior to their report, we had already noted the unique co-expression of CD34 and S100 protein in some

Table 1 Clinicopathological features of ten cases of lipofibromatosis-like neural tumour

Case no.	Age, years/Sex	Location	Size, cm	Original diagnosis	Our initial diagnosis and FISH result	Follow-up, months
1	2/F	Left foot	3.2	Infantile fibrosarcoma	Low-grade neural tumour	NED, 32
2	3/M	Left buttock	5	Spindle cell tumour	Peripheral nerve sheath tumour	NED, 17
3	6/F	Right hip	4.5	Infantile fibrosarcoma	Borderline spindle cell tumour of fibroblastic or neural tumour	NED, 15
4	15/M	Left neck	4.7	Infantile fibromatosis	Low-grade neural tumour	NED, 18
5	22/M	Right chest wall	5.9	SFT	CD34+/S100+ spindle cell sarcoma of possibly neurogenic origin	NED, 12
6	7/M	Hand back	2.5	SFT	Primary: low grade CD34+/S100+ spindle cell tumour; Recurrent: LPF-NT (*NTRK1*+)	LR, 12
7	5/F	Left neck	3	Neurofibroma, DFSP, lipomatous neoplasm	LPF-NT (*NTRK1*+)	NED, 7
8	24/M	Left flank	3	Fibroma	LPF-NT (*NTRK1*−)	LR, 3
9	37/M	Left neck	8	Low grade MPNST	LPF-NT (*NTRK1*+)	LR, 27
10	7/F	Buttock	4.4	Spindle cell tumour	LPF-NT (*NTRK1*+)	Recent case

ALK, anaplastic lymphoma kinase; DFSP, dermatofibrosarcoma protuberans; FISH, fluorescence *in situ* hybridisation; LPF-NT, lipofibromatosis-like neural tumour; LR, local recurrence; NED, no evidence of disease; *NTRK1*, neurotrophic tyrosine kinase receptor 1; SFT, solitary fibrous tumour.

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