

Myxoid Spindle Cell Sarcoma with *LMNA-NTRK* Fusion: Expanding the Morphologic Spectrum of *NTRK*-Rearranged Tumours

Yik Ka So, MBBS¹, Chit Chow, PhD², Ka Fai To, FHKCPATH², John K.C. Chan, FHKCPATH¹, and W. Cheuk, FHKCPATH¹

¹ Queen Elizabeth Hospital, Kowloon, Hong Kong SAR, China

² Department of Anatomical and Cellular Pathology, the Chinese University of Hong Kong, Shatin, Hong Kong

Introduction

Neurotrophic tyrosine receptor kinase (*NTRK*)-rearranged spindle cell neoplasm is an emerging entity involving frequently soft tissue and rarely visceral organs. It shows a wide morphologic spectrum of spindle cell proliferation resembling lipofibromatosis, low-grade malignant peripheral nerve sheath tumour or myopericytoma. The tumour frequently shows CD34 and S100 co-expression in the absence of SOX10 expression. The clinical course varies from being indolent, locally aggressive to metastasizing. Recognition of these tumours has become clinically relevant due to the recent availability of FDA-approved TRK inhibitors.

Case Report

A 40 year-old female presented with 2 weeks' history of left calf mass. MRI imaging showed a 4.4 cm contrast-enhancing mass involving the left soleus and tibialis posterior muscles. Core biopsy revealed a low-grade myxoid spindle cell sarcoma. Local excision was performed, followed by radiotherapy. The diagnosis rendered for the excised specimen was 'unclassified spindle cell sarcoma, low-grade' after expert consultation. The patient developed lung metastases at 2, 3.5 and 5 years after initial presentation, which were treated by wedge resections. At 6 years after initial presentation, multiple metastases were found in the left lung, left pleura, intrapulmonary lymph nodes and hilar lymph nodes on PET-CT. One of the previously resected specimen was sent to a private laboratory for comprehensive genomic profiling, and *LMNA-NTRK1* fusion was detected. After taking TRK inhibitor, PET-CT scan showed near-complete resolution of lung nodules and lymph nodes at 1 year follow up.

Pathologic Findings

Grossly, the lower limb tumour had a fleshy tan cut surface and several reddish areas. Histologically, it comprised spindle cells of low to moderate cellularity with pushing invasive borders and focal vascular invasion (Figure 1A). The monomorphic spindle cells formed streaming fascicles and reticular networks, within abundant myxoid stroma (Figure 1B, Figure 1C). The tumour cells had oval to elongated nuclei, fine chromatin, indistinct nucleoli and a moderate amount of eosinophilic cytoplasm (Figure 1D). There were some interspersed narrow to ectatic blood vessels. In some areas, keloid-like or hyalinized stromal and perivascular fibrosis was found (Figure 1B, Figure 1C). The mitotic count was 8 per 10 high-power fields (22 mm eyepiece). No tumour necrosis was seen. The morphologic features of the subsequent lung metastases were similar to the primary tumour, except in the latest resected lung metastasis, increased cellularity, presence of epithelioid cells and multinucleated tumour giant cells and increased mitotic counts were observed.

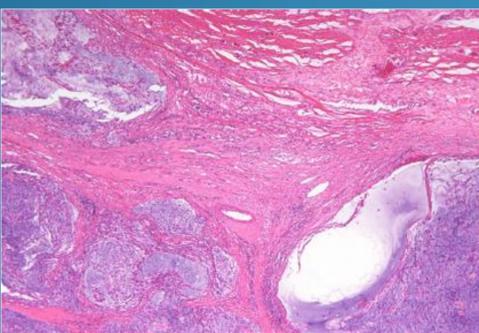


Figure 1A

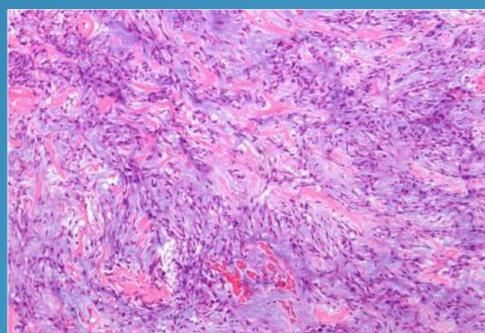


Figure 1B

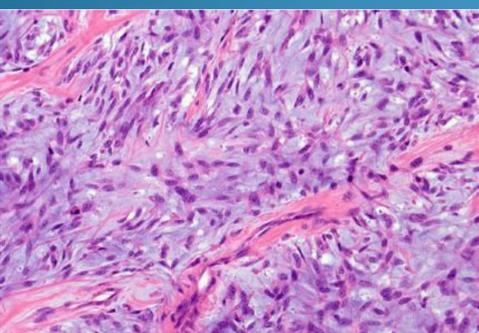


Figure 1C

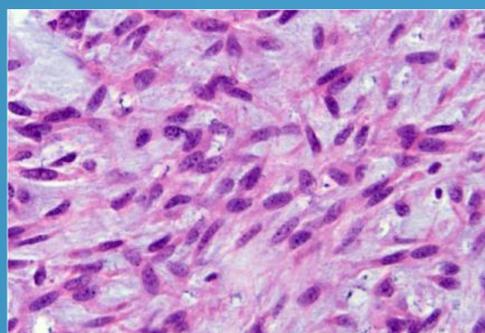


Figure 1D

Immunohistochemistry

Immunohistochemically, the tumour cells showed patchy expression of CD34 and S100 (Figure 2A, Figure 2B), with weak focal staining for smooth muscle actin. They are negative for SOX10, STAT6, GFAP, calponin, desmin, MUC4, CD56, CDK4, CD31, epithelial markers and melanocytic markers. Stainings for H3K27me3, Rb and INI1 were retained, and p53 staining was wild-type. Nuclear membrane and cytoplasmic staining for pan-TRK monoclonal antibody was observed (Figure 2C).

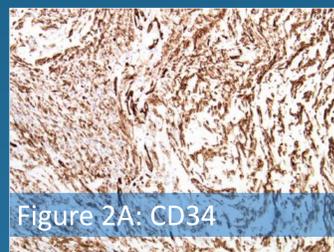


Figure 2A: CD34



Figure 2B: S100

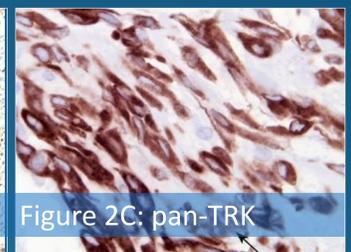


Figure 2C: pan-TRK

Molecular studies

Fluorescence in situ hybridization revealed 1 fused signal and 1 red telomeric signal of *NTRK1* gene break-apart probes, consistent with *LMNA-NTRK1* fusion due to intrachromosomal interstitial deletion as *LMNA* gene was located centromeric to *NTRK1* gene (Figure 3). In-house next generation sequencing with hybrid capture target enrichment was performed using the RNA extracted from a lung specimen. Pair-ended sequencing confirmed a fusion transcript joining the exon 2 of *LMNA* gene and exon 11 of the *NTRK1* gene (Figure 4).

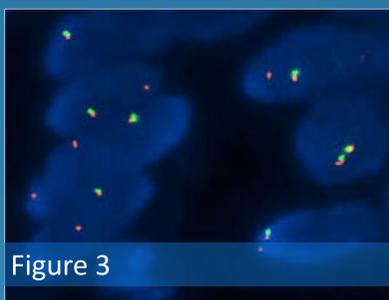


Figure 3

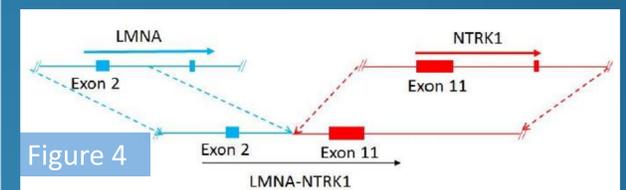


Figure 4

Discussion

NTRK family members *NTRK1*, *NTRK2* and *NTRK3* are critical in the development and maintenance of the nervous system. Oncogenic *NTRK* fusions lead to production of chimeric oncoproteins with constitutive TRK activation. The previously described morphologic spectrum of *NTRK*-rearranged spindle cell tumours includes lipofibromatosis-like, myopericytoma-like, low-grade malignant peripheral nerve sheath tumour-like, fibromatosis-like, herringbone growth and inflammatory myofibroblastic tumour-like patterns. This case further expands the morphologic spectrum of *NTRK*-rearranged spindle cell tumours. Differential diagnoses include myoepithelial neoplasm, low-grade fibromyxoid sarcoma and low-grade myxofibrosarcoma. A helpful morphologic clue typical for tumours with *NTRK1* gene fusions seen in this case is the presence of keloid-like stromal and perivascular fibrosis. The co-expression of CD34 and S100 is another helpful feature. *NTRK*-rearranged sarcoma should be included in the differential diagnoses of low-grade myxoid spindle cell tumours in young patients. Pan-TRK immunostain is a useful screening tool to enable more patients to benefit from targeted therapy.

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