QUIZ SECTION

MJS PUBLISHING

A 4-year-old Boy with a Red Nodule on His Hand: A Quiz

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A 4-year-old boy was noticed by his mother to have a red nodule on the dorsum of his left hand. The nodule gradually increased in size. He was referred to a local clinic 3 months later, when the red nodule was 2 mm in diameter. The decision at that time was to keep him under observation. At a visit to our department 1 month later, the nodule had enlarged further. Physical examination revealed a 9×8 mm dome-shaped red nodule on the dorsum of the left hand (Fig. 1). The nodule had clear borders, was not adherent to the base, and was not tender. Echographic examination showed a well-defined, well-developed tumour extending from the epidermis to the dermis, with a homogeneous interior and abundant blood flow. There was no bleeding from the mass during treatment. The patient was otherwise in good health, with no history of any other medical problems other than allergic rhinitis, and he had no growth or developmental abnormalities.

What is your diagnosis?

Differential diagnosis 1: Atypical Spitz tumour with *ALK* fusions

Differential diagnosis 2: Haemangioma

Differential diagnosis 3: Pilomatrixoma

Differential diagnosis 4: Cutaneous lymphoid hyperplasia

See next page for answer.

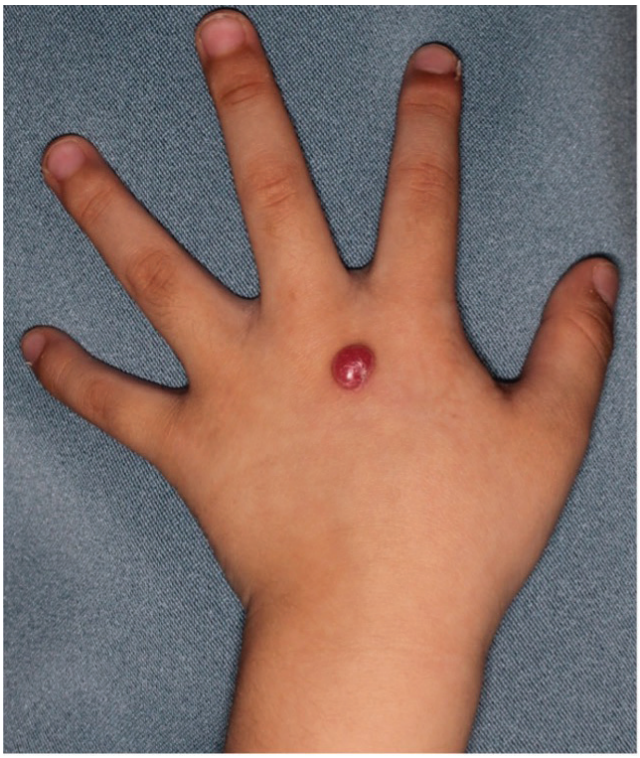

Fig. 1. A 9×8-mm dome-shaped red nodule on the dorsum of the left hand.

ANSWERS TO QUIZ

A 4-year-old Boy with a Red Nodule on His Hand: A Commentary

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Diagnosis: Atypical Spitz tumour with *ALK* fusions

A magnetic resonance scan revealed a dome-like structure on the dorsum of the left hand with a hyperintense signal on T2-weighted imaging (Fig. 2). The tumour was completely excised, and petrolatum was applied for wound healing. Sentinel lymph node biopsy (SLNB) was not performed.

Microscopic examination revealed spindle-shaped melanocyte-like cells distributed in sheets and bundles with increased deposition of stromal collagen fibres. Some of the tumour cells had a large nucleus with a prominent nucleolus. Mitotic figures were scattered (1/mm^2), and no definite atypical mitotic figures were detected. The presence of spherical spaces or clefts between the cells was noted. These histological features suggested a Spitz tumour with *ALK* fusions. Immunohistochemical studies showed the tumour cells were positive for *ALK* (diffuse) and Melan-A (diffuse), while lacking immunoreactivity for HMB45, indicating the maturation of the melanocytic lesion. The Ki-67 labelling index was approximately 30–40% in the superficial areas, whereas overall index of the lesion was 10%. There was no loss of p16 expression in the tumour cells. Fluorescence *in situ* hybridization revealed 2p23 translocation where the *ALK* gene is located. Based on these findings, the patient was diagnosed with an atypical Spitz tumour with *ALK* fusions (Fig. 3).

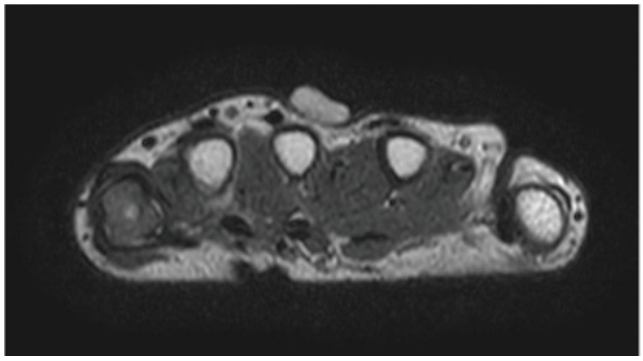

Fig. 2. T2-weighted magnetic resonance imaging shows a dome-like structure on the dorsum of left hand with a hyperintense signal.

The patient is currently undergoing follow-up with periodic imaging examinations. At 1 year postoperatively, there is no evidence of recurrence or lymph node metastasis.

Spitz tumours are melanocytic skin lesions that occur mainly in children and often resemble malignant melanoma on pathological examination. When benign and pathologically distinct from malignant melanoma, these tumours are called Spitz nevi; those with some features of malignant melanoma are called atypical Spitz tumours, and those that are malignant are called malignant Spitz tumours (1).

Recent studies have identified chromosomal abnormalities in Spitz tumours, including mutations in *HRAS* and *MAP2K1* genes, a copy number increase at 11p, and gene fusions involving *ALK*, *ROS*, *NTRK1*, *NTRK2*, *NTRK3*, *MET*, *RET*, *MAP3K8*, and *BRAF* (1, 2).

ALK is located on chromosome 2p and encodes a tyrosine kinase receptor involved in the *PI3K-AKT*, *RAF-MEK1/2-ERK1/2*, and *JAK3-STAT3* pathways. *DCTN1* and *TPM3*

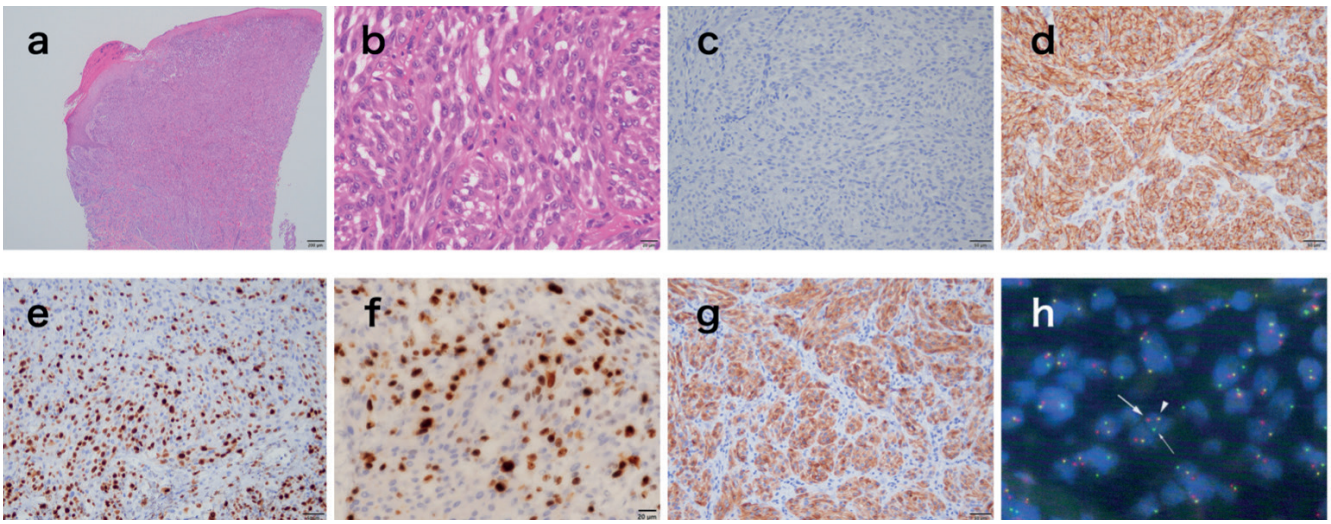

Fig. 3. Pathological examination shows findings typical of atypical Spitz tumour with *ALK* fusion. (a, b) Spindle-shaped, confluent melanocyte-like cells are distributed in sheets and bundles within a stroma with increased collagen fibres. Some of these cells show mitotic figures and some have large nucleus with prominent nucleolus. Small spherical spaces or clefts between the cells. In (b), mitotic figures are observed. The number of mitotic cells is 1/mm^2. (HE stain, Scale bar: a = 200 μm, b = 20 μm) (c) The HMB45 indicates a maturation pattern with dermal descent. (d) Tumour cells show immunoreactivity for *ALK.* (e, f) The Ki-67 labelling rate is 30–40% in the superficial areas and 10% in the deeper parts of the lesion. (c~e: Scale bar = 50 μm, f: Scale bar = 20 μm) (g) Melan-A is positive. (g: Scale bar = 50 μm) (h) Fluorescence in situ hybridization shows *ALK* fusion in 92.5% of cells. The yellow point (triangle) is a pseudo-colour signal, the red point (thick arrow) is the 3′ *ALK* probe, and the green point (thin arrow) is the 5′ *ALK* probe.

are the most common fusion partners for *ALK,* but fusions with *NPM1*, *TPR*, *CLIP1*, *GTF3C2*, *MLPH*, *EEF2*, *MYO5A*, *KANK1*, EHBP1, and *SLC20A1* have also been reported (1, 3–8). *ALK* fusion genes are reported to be present in 10% of all Spitz tumours, approximately 8% of Spitz nevi, 5% of atypical Spitz tumours, and 1% of malignant Spitz tumours (1, 2).

The clinical features of Spitz tumours with the *ALK* fusion gene include a predilection for the extremities in young patients, a large pleomorphic appearance without pigmentation, and a solitary papule or nodule (2). The pathology is characterized by large non-pigmented spindle-shaped melanocytes with pericellular fissures, vesicular nuclei, prominent nucleoli, and plexiform architecture with streak-like growth (2).

Management of atypical Spitz tumours typically involves complete surgical excision with clear margins to ensure removal of all tumour cells. SNLB is generally not considered necessary for atypical Spitz tumours because of their low risk of metastasis. However, careful clinical follow-up with regular physical examination is necessary to monitor for signs of recurrence (9, 10). Cerrato et al. reported no recurrence of atypical Spitz tumour in children at 3 years postoperatively, even without SLNB, when treated with extensive resection alone (10). In a study by Lallas et al., although 39% of patients with atypical Spitz tumour who underwent SLNB in addition to wide excision had positive lymph nodes, only 1% were found to have disease progression beyond the lymph nodes during 5 years of follow-up. Following wide excision, patients in that study also had a high 5-year survival rate (99% with SLNB and 98% without SLNB). Therefore, they concluded that SLNB was not effective in improving the prognosis (9). However, the modest difference in survival rate in that study does not definitively negate the potential advantages of further treatment after a positive SLNB.

The primary treatment of atypical Spitz tumour with the *ALK* fusion gene is biopsy, histological evaluation, and gene retrieval by fluorescence *in situ* hybridization followed by surgical resection with adequate margins (1, 9). The *ALK* fusion gene is a therapeutic target in other carcinomas, and contributes to the increased oncogenicity of Spitz tumours in vitro. Careful long-term postoperative follow-up is warranted (1).

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