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CASE REPORT

Spitz tumour with ALK rearrangement: A case report and literature review

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Abstract

Spitz tumour with ALK rearrangement is a recently described entity and a rare tumour. The incidence of Spitz tumour was estimated at 3.63 per 100,000 persons in American paediatric population; while there is no data in Asian population. Here we reported a case of an eleven-year-old Asian boy who presented with a left shin nodule of two months' duration. The skin biopsy revealed a Spitz tumour with predominantly spindle cell morphology arranged in fascicles, vertically orientated nests and radial growth pattern. Junctional component, melanin pigment or Kamino bodies were not identified. Immunohistochemical study displayed homogenous cytoplasmic staining for ALK. Fluorescence in-situ hybridisation (FISH) analysis confirmed ALK rearrangement. Review of the literatures demonstrated that positive ALK immunohistochemistry may not correlate with ALK rearrangement. ALK-rearranged Spitz tumour confirmed with FISH analysis favour clinically benign behaviour despite atypical histomorphology or positive sentinel lymph node. Therefore, correlation of histomorphology, immunohistochemical stain and molecular study are important for the definitive diagnosis of this entity.

Keywords: ALK, Spitz, Fluorescence in-situ hybridisation, Rearrangement, Translocation, Skin tumour, Nevus

INTRODUCTION

Spitz tumour is a subgroup of melanocytic neoplasm commonly occurring in children and young adults. This entity was first described in 1948 by Sophie Spitz, based on microscopic features of large cell size, a regular architecture and lack of high-grade atypia. The incidence of Spitz tumour was estimated at 3.63 per 100,000 persons in American paediatric population.[1] However, there is no data on its prevalence in Asian population. Morphologically, most Spitz tumours are classified into Spitz nevus (benign morphology). Occasionally, atypical Spitz tumour (borderline morphology) or spitzoid melanoma (malignant morphology) are diagnosed. However, morphological classification of Spitz tumour may not correlate with clinical behaviour.[2]

Recent reports showed increasing use of molecular techniques for subclassification of Spitz tumour to improve the diagnostic accuracy. The molecular subclassification introduced the diagnostic entities of HRAS-mutant sclerosing Spitz nevi, BAP1-inactivated Spitz tumours, spitzoid melanomas with homozygous deletions of p16, Spitz tumours with BRAF rearrangement (receptor serine-threonine kinase), or Spitz tumours with ALK, ROS1, NTRK1, NTRK3, RET or MET rearrangement (receptor tyrosine kinases).[2,3] It was reported that all this fusion was in mutually exclusive pattern.[2,3] The application of molecular testing enriched the biological knowledge of this tumour. Distinct clinicopathological findings were observed with different genetic alteration.

Herein, we report a case of Spitz tumour with ALK rearrangement in an Asian child, describing the clinical features and pathological findings.

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CASE HISTORY

An eleven-year-old boy with no known comorbidity was referred to a dermatology clinic for a left shin nodule of two months' duration associated with minimal pain. The nodule was not increasing in size. He has no other local symptom. Physical examination revealed a skin nodule measuring six millimetre in maximum diameter. The nodule was firm with a central depression. There was no other similar lesion elsewhere. Clinical impression was dermatofibroma. He underwent an excisional biopsy.

Grossly, the skin excisional biopsy specimen revealed a well circumscribed firm nodule measuring six millimetre in maximum diameter with a whitish cut surface. Microscopic examination showed a polypoidal and symmetrical intradermal lesion with no ulceration (FIG. 1a-d). The lesion was composed of spindle cells arranged in fascicles, vertically orientated nests and radial growth pattern. There were occasional epithelioid cells exhibited round vesicular nuclei, prominent nucleoli and moderate amount of cytoplasm. Mitotic figures were confined to the superficial aspect (one mitosis / one mm2). The deeper portion of the lesion showed evidence of maturation. There were peripheral collarette, occasional multinucleated tumour cells and mild to moderate degree of lymphocytic infiltrates. Junctional component, melanin pigment or Kamino bodies were not seen.

Immunohistochemical studies (IHC) showed that the tumour cells were diffusely positive for S100, Melan A and p16 (FIG. 2a-b). The tumour displayed homogenous cytoplasmic staining for

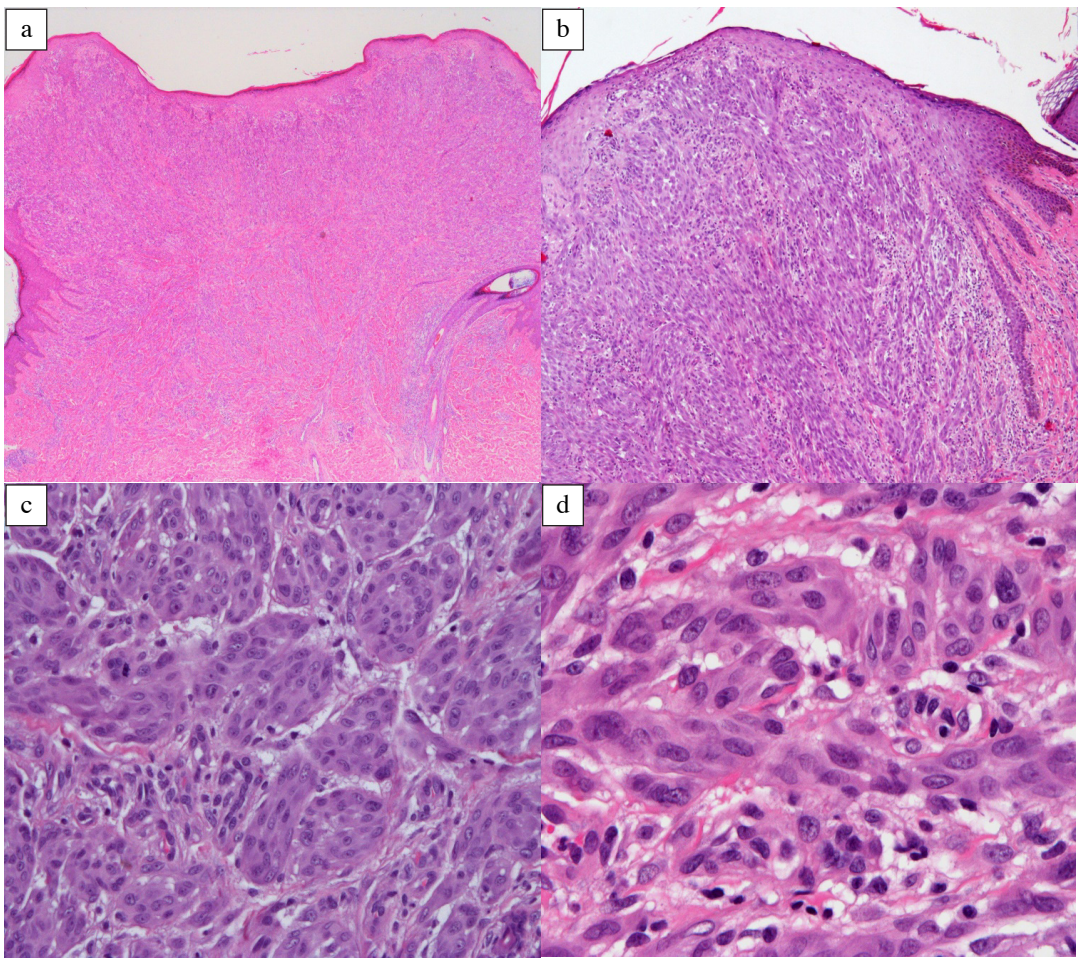

FIG. 1: (a) The skin lesion was a polypoidal and symmetrical intradermal lesion (H&E, ×20). (b) It is composed of predominantly spindle cells arranged in fascicles and vertically orientated nests pattern (H&E, ×40). (c) A mitotic figure was shown (H&E, ×100). (d) There were occasional epithelioid cells exhibited round vesicular nuclei, prominent nucleoli and moderate amount of cytoplasm (H&E ×400).

ALK (clone ALK1, Ventana benchmark XT) (FIG. 2c). Fluorescence in-situ hybridisation (FISH) analysis was performed using the Vysis LSI ALK Break Apart Rearrangement Probe Kit (Abbott Molecular, Des Plaines, IL). The FISH signals were enumerated in 50 non-overlapping intact nuclei. More than 20% of the tumour cells nuclei demonstrated a signal pattern of rearrangement (split of orange and green signals; or single orange signal without a corresponding green signal). ALK rearrangement of the tumour was confirmed (FIG. 2d).

DISCUSSION

Spitz tumour with ALK rearrangement demonstrates distinctive features in histology, IHC and molecular pathology. The prevalence of ALK rearrangement in Spitz tumour was about 10% to 20.6%.[3,4] Wiesner *et al*. reported 8% of Spitz nevi, 5% of atypical Spitz tumours, and 1% of spitzoid melanomas showed ALK rearrangement.[3]

Diagnosis of Spitz tumour with ALK rearrangement needs correlation of morphology, IHC and molecular study. Histologically, Spitz tumour with ALK rearrangement is characterized by large diameter (>nine mm), wedge-shaped, plexiform or fascicular growth pattern, infiltrative edges, adnexa extension, spindle-shaped cells, fibrillary cytoplasm, prominent nucleoli, intercellular clefts or rounded spaces, infrequent melanin and rare Kamino Bodies.[5,6] Our current case demonstrated some of the characteristic histology features of ALK-rearranged Spitz tumour.

To date, ALK immunohistochemical study is probably the best screening method for Spitz tumour with ALK rearrangement because of its

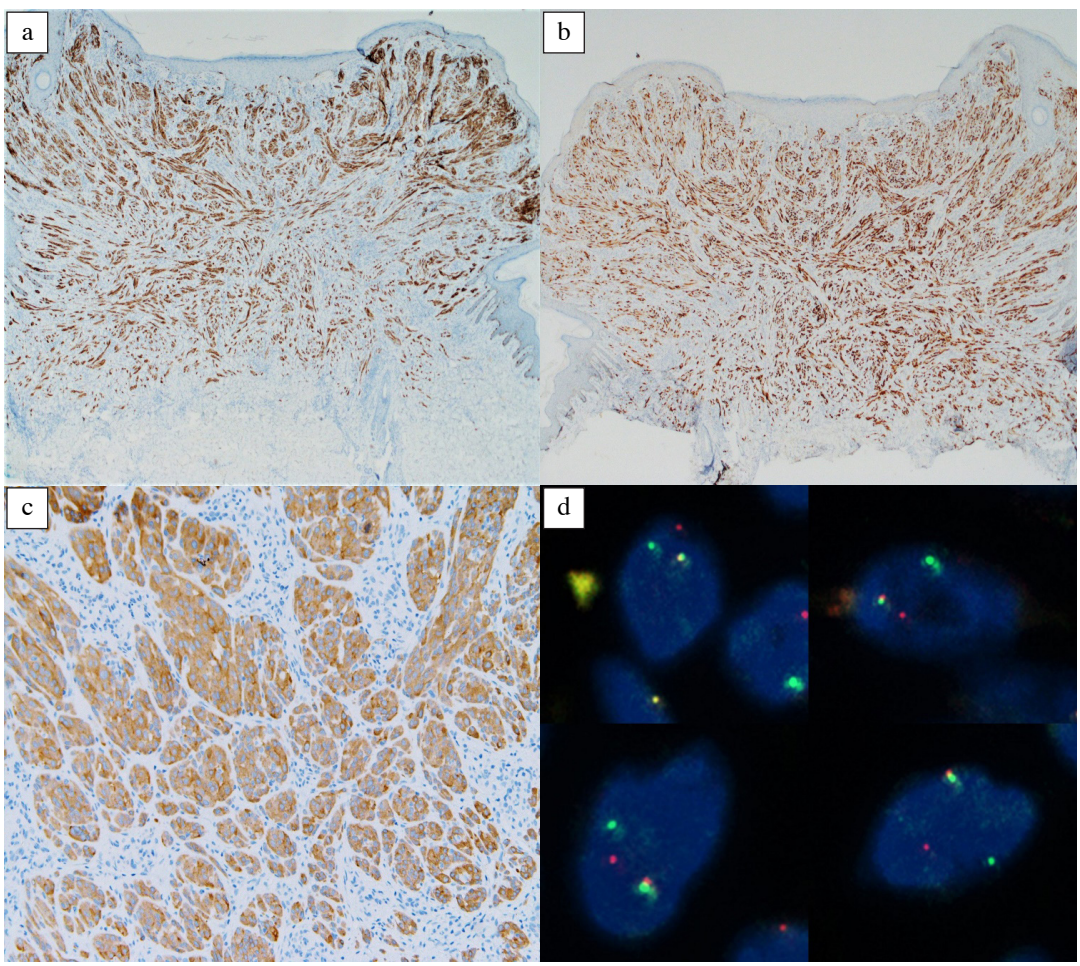

FIG. 2: (a-b) Tumour cells showed positive immunoreactivity for Melan A and p16 (immunohistochemistry ×100, respectively). (c) Immunohistochemistry demonstrated cytoplasmic ALK protein expression (ALK, ×100). (d) FISH demonstrated the ALK split apart signals.

TABLE 1: Previously reported Spitz tumour with ALK rearrangement

First author, year	No. of cases	Morphological classification	ALK IHC	ALK rearrangement (ISH)	Fusion partner	Treatment	Lymph node dissection	Clinical follow up
Busam 2014[11]	17	SN (5 cases), AST (12 cases)	Positive	Positive	TPM3, DCTN1	Excision (17 cases)	SLN positive (2 cases performed and both were positive)	SN and AST (17 cases, NED 2 months-4 years)
Yeh 2015[5]	15	SN (4 cases), AST (9 cases), SM (2 cases)	Positive	Positive	ND	Excision (2 cases), re-excision (10 cases), ND (3 cases)	SLN negative (1 case)	SN (3 cases, NED 3-9 months), AST (4 cases, NED 9-12 months), SM (2 cases, NED 16-40 months), ND (6 cases)
Wu 2016[2]	1	SM	Positive	Positive	TPM3	Excision	SLN negative	NED 6 months
Rand 2017[12]*	1	SM	Positive	Positive	ND	Excision, SLN biopsy and interferon therapy	SLN positive	NED 20 months
Fujimoto 2018[8]	1	AST	Positive	Positive	MLPH	Re-excision, regional lymph node dissection and chemotherapy (dacarbazine, nimustine, vincristine)	SLN positive	NED 9 years
Saraggi 2018[7]†	9	SN (6 cases), AST (3 cases)	Positive	Positive	TPM3, DCTN1	ND	SLN negative (2 cases performed)	SN (5 cases, NED 17-137 months), AST (3 cases, NED 32-91 months), ND (1 case)
Melchers 2019[14]	1	SN	Positive	Positive	TPM3	Excision	ND	NED 23 months
Kastnerova 2020[13]	17	SN (5 cases), AST (12 cases)	Positive	Positive	TPM3, DCTN1, MLPH, EEF2, MYO5A	Excision (15 cases), re-excision (2 cases).	SLN negative (16 cases performed)	SN (5 cases, NED 6-88 months), AST (11 cases, NED 6-45 months), ND (1 case)
Present case	1	SN	Positive	Positive	ND	Excision	Not performed	NED 10 months

Abbreaviations: AST: Atypical Spitz tumour; IHC: immunohistochemistry; ISH: in-situ hybridization; ND: no data; NED: No evidence of disease; SLN: sentinel lymph node; SM: spitzoid melanoma; SN: Spitz nevus.

* One case reported homozygous deletion of 9p21.

† One case reported presence of BRAF V600E mutation.

simplicity and shorter turnaround time. It is useful as a surrogate marker prior to a confirmatory molecular study. ALK rearrangement and its fusion partner can be identified using molecular studies, such as fluorescence in-situ hybridisation (FISH), reverse transcription polymerase chain reaction (RT-PCR) or sequencing.[3,7] Nevertheless, discrepancy of ALK IHC and molecular study was reported.[8,9] Fujimoto *et al*. reported a case of ALK-rearranged Spitz tumour stained negative for ALK1 antibody clone, while positive for 5A4 antibody clone. The reason for discrepancy was due to the different type of primary antibody clone, detection method or fusion partner.[8] On the contrary, ALK IHC expression without ALK rearrangement has also been reported.[9] The ALK IHC expression could be due to ALK amplification or a mutated ALK isoform.[5,7,10] Therefore, molecular testing for ALK rearrangement is essential to make a distinction between them. Other helpful features are mutated ALK isoform melanomas usually display a non-spitzoid morphology and the ALK IHC staining intensity is often variable in cases without ALK rearrangement.[10]

The reported fusion partners for ALK rearrangement are TPM3, DCTN1, MLPH, EEF2, MYO5A.[2,7,8,11-13] Histologically, lesion with DCTN1-ALK fusion showed higher proportion of large epithelioid melanocytes and more nuclear pleomorphism.[11] In terms of IHC, Fujimoto *et al*. proposed that different type of fusion partners may showed different level of ALK expression, which might affect the ALK IHC sensitivity.[8] Despite this, the clinical significance of identifying ALK fusion partner is yet to be determined.

Spitz tumour with ALK rearrangement is a recently described entity and few reports are available in the English-language literature. The reported cases of ALK-rearranged Spitz tumour reviewed were listed in Table 1; after excluding cases without ALK IHC study, ALK rearrangement molecular testing or clinical follow-up data. Among the 63 cases of ALK-rearranged Spitz tumour, 4 are morphologically classified as spitzoid melanoma, 37 cases as atypical spitzoid tumour and 22 cases as Spitz nevus. All the patient diagnosed with atypical spitzoid tumour is disease free up to 91 months of follow-up.

Total of 24 cases underwent sentinel lymph node biopsy and tumour cells were identified in 4 cases. All the patient with positive sentinel lymph node were alive and none has evidence of recurrence with clinical follow-up data up to nine years. This information further supports that Spitz tumour with ALK rearrangement has a clinically benign behaviour despite its atypical morphology or positive sentinel lymph node.[7]

In conclusion, Spitz tumour with ALK rearrangement is a recently described entity with characteristic morphology, IHC profile and molecular findings. ALK immunohistochemical study is a useful surrogate marker, but molecular study is needed for confirmation of the diagnosis. ALK-rearranged Spitz tumour favours a benign clinical behaviour as there is no recurrence or mortality reported.

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