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An ALK-Positive Epithelioid Fibrous Histiocytoma with Superficial ALK-Rearranged Myxoid Spindle Cell Neoplasms-Like Features and Foamy Histiocyte Infiltration: Report of a Challenging Case

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ABSTRACT

Objective: ALK-related superficial soft tissue tumors represent an emerging category of neoplasms in daily pathology practice. We report the case of a 49-year-old Caucasian woman with an ALK-related neoplasm who presented with a 1,5 cm nodule on her left thigh.

Case Report: The lesion was excised and histopathologically evaluated. Microscopic examination revealed a well-circumscribed nodule composed of epithelioid and oval-to-spindle cells. Although some morphological features were shared with epithelioid fibrous histiocytoma (EFH), there were no epidermal collarettes. In addition, significant storiform architecture and also foamy histocyte groups were detected in the lesions. ALK positivity was observed in both the immunohistochemical and FISH studies. Superficial ALK-rearranged Myxoid Spindle Cell Neoplasms (SAMS) were first considered in the differential diagnosis due to their prominent storiform structures. The lesion shared both EFH and SAMS morphology. Finally, we reported the case as "EFH with SAMS-like features". The patient showed no evidence of recurrence during a 10-month follow-up.

Conclusion: This case presents the diagnostic challenges in ALK-positive neoplasms. Superficial soft tissue tumors associated with ALK include a heterogeneous group of lesions that may share similar morphological features. We believe that a generic term, ALK-Rearranged Superficial Mesenchymal Neoplasms (ARSMN), may serve as a more inclusive diagnostic label for these entities in routine pathology practice.

Keywords: ALK, Epithelioid fibrous histiocytoma, Superficial ALK-rearranged myxoid spindle cell neoplasm

INTRODUCTION

The **a**naplastic **l**ymphoma **k**inase (*ALK*) gene encodes a tyrosine kinase receptor; its fusions and mutations play an important role in human neoplasia. ALK-related skin tumours are a growing group of neoplasms in daily pathology practice. Epithelioid fibrous histiocytoma (EFH), Spitzoid melanocytic neoplasms, melanocytic myxoid spindle cell tumor with ALK rearrangement (MMySTAR), non-neuronal granular cell tumor, ALK (+) histiocytosis, inflammatory myofibroblastic tumors, and superficial ALK-rearranged myxoid spindle cell neoplasms (SAMS) can be included (1-3). Although the morphologic features of EFH are well documented in the literature, we presented a case that shared some morphologic features of SAMS and was secondarily infiltrated by foamy histiocytes.

CASE PRESENTATION

A 49-year-old Caucasian female presented to the hospital with a nodule on her left thigh. The clinical diagnosis was a hemangioma. A soft, grey-red nodule measuring 1.5 cm in diameter was detected macroscopically. Microscopic examination revealed a well-circumscribed nodule composed of epithelioid and oval-spindle cells located in the dermis and subcutis. The cells were generally arranged in sheets. In addition to this pattern, the lesion often had a well-established storiform architecture (whorl-like pattern), usually at its periphery (Figure 1A-C). Additionally, the number of dilated thin-walled vascular structures was increased outside the lesion (Figure 1A). An epidermal collarette was not detected. Around the tumour cells, there was lymphocytic and histiocytic infiltration. There were also foamy histocyte groups (Figure 1D). There was no myxoid stroma, but focal hyaline stroma was also detected (Figure 1E). The immunohistochemical study showed positivity for ALK (D5F3), Factor13a, and focal EMA positivity (Figure 1E, F). Focally, CD68 Kp-1, CD31, Langerin, S-100, and CD1a positivity were seen in histiocytes and dendritic cells, respectively, but not in tumour cells. Additionally, pan-keratin, ERG,

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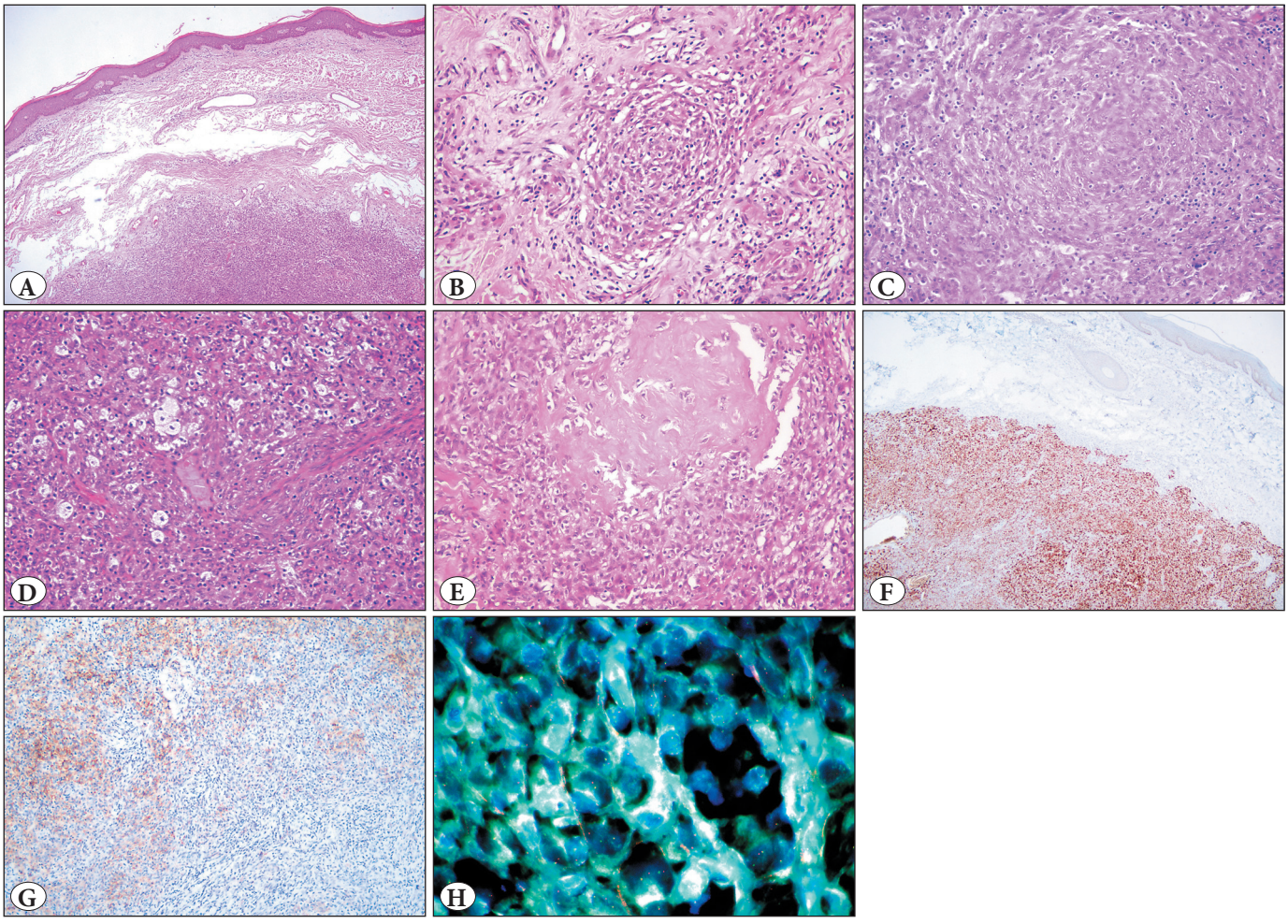

Figure 1: A) A dermal well-circumscribed nodule is seen, dilated thin vessels are remarkable around the tumour (Hematoxylin & eosin, x40). **B)** Spindle cells with the whorled pattern at the periphery of the lesion (Hematoxylin & eosin, x100). **C)** More epithelioid cells also with the whorled pattern are detected in the inner area of the lesion (Hematoxylin & eosin, x200). **D)** Foamy histiocytes are seen around the tumour cells (Hematoxylin & eosin, x200). **E)** Stroma is generally scant, but focal hyalinized stroma is also found (Hematoxylin & eosin, x100). **F,G)** Strong ALK but patchy EMA positivity in the tumour (F: ALK, x40, G: EMA, x100). **H)** ALK FISH positivity, x1000.

CD34, S100, HMB45, HHV-8, SMA, Desmin, CD4, CD45, CD10, CD34 and TFE3 were all negative in tumour cells. Ki-67 proliferation index was very low (~1%), and no significant mitotic activity was seen. The FISH study showed *ALK* translocations in the tumour (Figure 1G). Despite the absence of adnexal collarette, significant foamy histiocyte infiltration, and well-established storiform architecture, we diagnosed the case as an EFH with atypical morphologic features. The lesion had clear surgical margins; therefore, no additional surgery was performed. The patient showed no evidence of recurrence during a 10-month follow-up. We would like to discuss here the morphological features of EFH and differential diagnosis due to the morphological overlap with other ALK (+) diagnoses, primarily SAMS.

Conventional EFH is a well-circumscribed cutaneous neoplasm composed of epithelioid cells often with an adnexal collarette in the extremities of young to middle-aged adults (4). However, EFHs consisting of spindle cells have also been described, despite the name (5). Interestingly, in addition to the spindle cell pattern, similar to our case, well-formed storiform or whirling architectural patterns have also been described in the literature, as seen in SAMS (6-8). Spindle cell EFHs generally show significantly different morphology from the classical morphology of EFH. According to the literature, an adnexal collarette may not be seen in this group and may share some morphological features with conventional dermatofibroma (5, 6). Furthermore, the storiform and whorled architecture of spindle cells as seen in SAMS was observed in spindle cell EFHs (6). However, this pattern was also described in epithelioid-dominant EFH as seen in our case (8). Immunohistochemistry may be helpful for differential diagnosis. Although ALK positivity is observed in

both tumors, SAMS may be positive for CD34 and S100 (1, 9). In our case, we detected focal EMA and ALK positivity but no CD34 and S100 positivity. EMA positivity has not been reported in SAMS in the early literature (1). However, DeSimone MS. et al., Hegazy S., and Naous R. recently presented SAMS cases with EMA positivity (9, 10). In our case, we have also detected a significant number of foamy histiocytes, like some subtypes of cutaneous fibrous histiocytoma (dermatofibroma). This finding has not been reported in EFH and SAMS in the literature before. However, a recent report described Touton-like giant cells in EFH (11). A new report from Agaimy et al. demonstrated three ALK-rearranged mesenchymal neoplasms with prominent foamy/pseudo-lipogenic cell morphology. However, only one of their cases was from the skin and it showed no morphological similarities to EFH or SAMS (12).

DeSimone MS et al. recently presented a novel observation about EFH and SAMS. They showed that 11 of 35 SAMS tumours were characterised by hybrid morphologic properties between EFH and SAMS, and 9 of them (82%) presented cytomorphology typical of EFH but with whorled growth, myxoid stroma, and/or areas of spindle cell morphology (9). Furthermore, they also demonstrated that two hybrid tumours displayed sharp transitions between a region typical of EFH and a region typical of SAMS, with a coexisting sharp transition in EMA, CD34, and S-100 expression by IHC (9). In their series, the authors also identified several ALK fusion partner genes that have been previously described in EFH. In addition, they pointed out that SAMS should be considered a histologic variant of EFH (9).

Significant morphological and immunohistochemical overlap between EFH and SAMS in the literature and the novel study of DeSimone MS. et al. might show that EFH and SAMS are in a spectrum of the same tumour group (Table I). However, the differential diagnosis may be more confusing. Significant foamy histiocytes, as in our case, should

Table I: Comparison of Epithelioid Fibrous Histiocytoma and Superficial ALK-rearranged Myxoid Spindle Cell Neoplasms (SAMS)

	Epithelioid Fibrous Histiocytoma	**Superficial ALK-rearranged Myxoid Spindle Cell Neoplasms (SAMS)**
Clinical presentation (1, 9, 14, 16)	• Young, middle-aged adults. • Upper extremity, lower extremities, trunk, head, and neck. • Exophytic tan/red-coloured papule, nodule, sometimes flat.	• Adults, but rare paediatric cases. • Lower extremities, upper extremities, trunk, head, and neck. • Erythematous, violaceous papule or nodule.
Histopathology (1, 7, 14, 17, 18)	• Collarette (+/-) • Plump epithelioid cells with amphophilic cytoplasm with vesicular nuclei and small nucleoli. • Epithelioid, mixed epithelioid and spindled cells, spindled cell pattern. • Sheets of cells, whorled pattern (-/+) • No pleomorphisms • Rare Mitosis • Generally scant, collagenous, fibrous focal myxoid. • Rare pericellular calcifications, • Lymphocytes, neutrophils in the stroma.	• Collarette (-) • Spindled, oval-shaped cells with fine chromatin, scant to moderate eosinophilic cytoplasm, and indistinct cell borders • Whorled pattern (+) • Rare pleomorphism • Rare Mitosis • Myxoid, hyalinized stroma. • Lymphocytes in the stroma.
Immunohistochemistry (1, 16, 17)	• ALK (+), EMA (+/-), SMA (-), CD68 (-/+)	• ALK (+), CD34 (+), S100 (+/-), EMA (-/+)
ALK-Fusion partners (1, 7, 14-16, 18-20)	• *AP3D1, CARS, CLTC,* ***DCTN1,*** COL***1A2,*** ***EML4****, ETV6, LRRFIP2, MLPH, MPRIP, PPFIBP1, PRKAR1A, PRKAR2A,* ***SPECC1L,*** *SP100,* ***SQSTM1****, TMP3,* ***VCL****.*	• * ***COL1A2*** ǂ, ***DCTN1*** ¥, ***EML4*** ǂ , *FLNA, FMR1,* ***FXR1*** *, HMBOX1, KLC1, LIP1, MMP2, MYH10, PLEKHH2,* ***PRKAR1A*** ¥***,*** *PRRC2B,* ***SPECC1L*** ¥ , ***SQSTM1*** ¥*, STRN,* ***MPRIP*** ¥***,*** *TKT, TLN2* ***,*** *TIMP3,* ***VCL*** ¥ *.*

*Included only superficial ALK rearranged neoplasms; some of the cases did not qualify as SAMS. ¥ Described in DeSimone MS et al. series. ǂ Described in the literature in SAMS and/or EFH in literature other than DeSimone MS et al.

be included in the differential diagnosis of ALK-positive histiocytosis with skin involvement due to ALK positivity, shared fusion partners, and CD68-positive histiocytes (13). SAMS are described in the literature as superficially located neoplasms. However, ALK-related deep or visceral tumors, a group of spindle or epithelioid neoplasms, have also been reported in the literature, with some shared morphological, immunohistochemical, and molecular data (14, 15).

As in our case, Dermawan et al. (three patients under follow-up) and DeSimone et al. (eleven patients under follow-up) did not observe recurrence (1,9). Despite its hypercellular and spindle cell morphology, this tumor demonstrated benign behavior consistent with other EFHs (5).

CONCLUSIONS

ALK-related soft tissue neoplasms are complex neoplasms that are not easily classified. Hence, until there is sufficient knowledge in the literature, we believe that **A**LK **R**earranged **S**uperficial **M**esenchymal **N**eoplasms (ARSMN) as a generic diagnosis is better used for this group of mesenchymal neoplasms in daily practice.

Conflict of Interest
The authors declare no conflict of interest.

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Ethics Approval
Not applicable, anonymity of the patients' and their confidentiality was preserved.

Authorship Contributions
Concept: **AA, EA, OB,** Design: **OB,** Data collection or processing: **AA, EA,** Analysis or Interpretation: **AA, EA, OB,** Literature search: **AA, EA, OB,** Writing: **OB,** Approval: **All of authors.**

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