

Corresponding anaplastic lymphoma kinase–tropomyosin 3 (*ALK-TPM3*) fusion in a patient with a primary cutaneous anaplastic large-cell lymphoma and a Spitz nevus



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Key words: ALK; anaplastic lymphoma kinase; C-ALCL; CD30; concurrent; corresponding; fusion; primary cutaneous anaplastic large cell lymphoma; rearrangement; Spitz nevus; Spitz tumor; Spitz; TPM3; tropomyosin 3; TPM3-ALK; translocation.

INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is an indolent cutaneous CD30-positive T-cell lymphoma with no signs of extracutaneous localizations at the time of diagnosis. C-ALCL is clinically characterized by single or localized, sometimes ulcerating tumors and histopathologically by diffuse sheets of large anaplastic cells.¹ Spitzoid neoplasms are melanocytic tumors usually occurring in young individuals. They are characterized clinically by pigmented or spherical reddish lesions and histopathologically by spindle-shaped and epithelioid melanocytes.² In a small proportion of patients, both diseases can be driven by or harbor rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene.^{2,3}

CASE REPORT

A 30-year-old man was referred with an ulcerating tumor on his left lower arm since 3 months (Fig 1, A). Microscopic examination of a biopsy specimen revealed a dermal diffuse population of anaplastic large CD30-positive T cells with cytoplasmic ALK expression (Fig 1, B and C). Additional research, including complete blood count, biochemical analysis, positron emission tomography-computed tomography scan, and bone marrow biopsy sample

Abbreviations used:

ALK:	anaplastic lymphoma kinase
C-ALCL:	cutaneous anaplastic large T-cell lymphoma
TPM3:	tropomyosin 3

showed no signs of systemic localizations and led to a diagnosis of an ALK-positive C-ALCL.

The lesion was treated with radiotherapy and showed a complete response. The patient presented 1 year later with a small erythematous papule on his right arm (Fig 2, A). The lesion was excised for histopathologic examination, which revealed a Spitz nevus, with melanocytic nevus cells demonstrating high and aberrant expression of ALK (Fig 2, B and C). The patient's family history reported no cutaneous lymphomas or Spitzoid neoplasms.

Targeted RNA sequencing assay technique (FusionPlex, ArcherDX, Boulder, CO) that simultaneously detects and identifies fusions of *ALK* translocations was performed on both lesions and confirmed *ALK* rearrangements and remarkably revealed tropomyosin 3 (*TPM3*) as an identical fusion partner (Fig 3). Furthermore, the corresponding translocation t(1;2)(q25;p23) of both lesions also shared the same breakpoint on exon 20 (*TPM3*:

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Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

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JAAD Case Reports 2019;5:970-2.
 2352-5126

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<https://doi.org/10.1016/j.jidcr.2019.09.021>

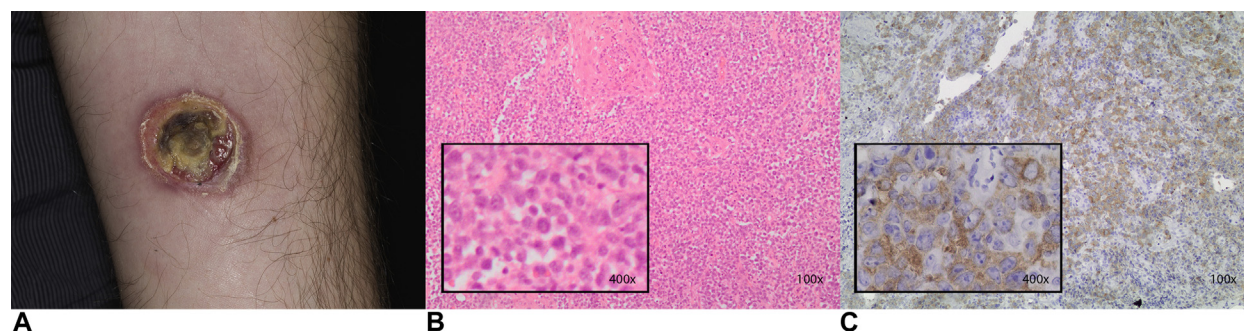


Fig 1. Primary cutaneous anaplastic lymphoma. **A**, Single, ulcerative tumor with a necrotic center on the left forearm. Overview (original magnification: $\times 100$) and detail (original magnification: $\times 400$) shows **(B)** a hematoxylin and eosin staining with a diffuse infiltrate of large anaplastic cells and **(C)** cytoplasmic anaplastic lymphoma kinase expression in the anaplastic cells.

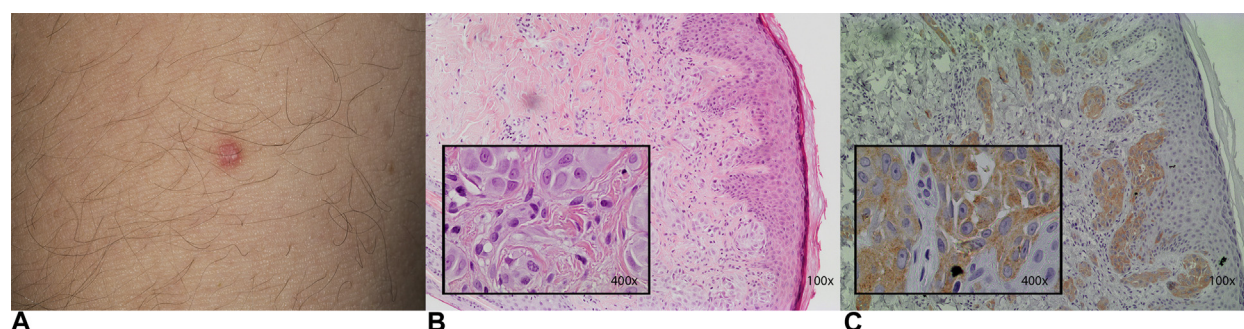


Fig 2. Spitz nevus. **A**, Discrete erythematous papule on right upper arm. Overview (original magnification: $\times 100$) and detail (original magnification: $\times 400$) shows **(B)** a hematoxylin and eosin staining with spindle-shaped melanocytes and **(C)** cytoplasmic anaplastic lymphoma kinase expression in the melanocytes.

NM_152263:exon:8:*ALK*: NM_004304.4:exon:20). After a follow-up of 23 months, the patient was alive without disease.

DISCUSSION

ALK-positive C-ALCL and ALK-positive Spitz are uncommon, and a combination in the same patient with a similar gene rearrangement is unique. ALK is normally expressed in neural cells and is involved in brain development.⁴ In cancer, the ALK tyrosine kinase is translocated to a fusion partner and thereby consecutively expressed.⁴ ALK rearrangements are found in a minority of C-ALCL and Spitz lesions.^{2,3} In the current patient, however, both diseases harbored the identical fusion partner *TPM3*.⁵

TPM3 is an actin-binding protein involved in providing stability to actin filaments. These tumors developed from cell types derived from different embryonic germ layers, with lymphocytes originating from the mesoderm and melanocytes from the neural crest. This makes genetic mosaicism as a causative mechanism; that is, a translocation that

occurred during embryogenesis in a common precursor cell highly unlikely. Moreover, ALK expression was not observed in surrounding areas of the biopsy samples from the C-ALCL and Spitz lesion and neither in subsequent skin biopsy samples of hyperpigmented macular lesions on the trunk (revealing nonspecific dermatitis).

We assume therefore that the *ALK-TPM3* translocations have occurred independently in cells of the lymphoid and melanocytic compartment. The coincidence might be explained by a fragile site. A fragile site is a specific genomic region that is unstable and susceptible to form double strand breaks. It is however remarkable that both disease translocations share the same fusion partner. Possibly, the 2 genes resemble, are in close proximity, or are both fragile sites/hotspots in this patient.

To our knowledge, this is the first report describing *ALK-TPM3* fusions in 2 distinct tumors. To date, this phenomenon has only been described in malignancies with a common precursor.⁶ We presume a putative fragile site/sequence similarity

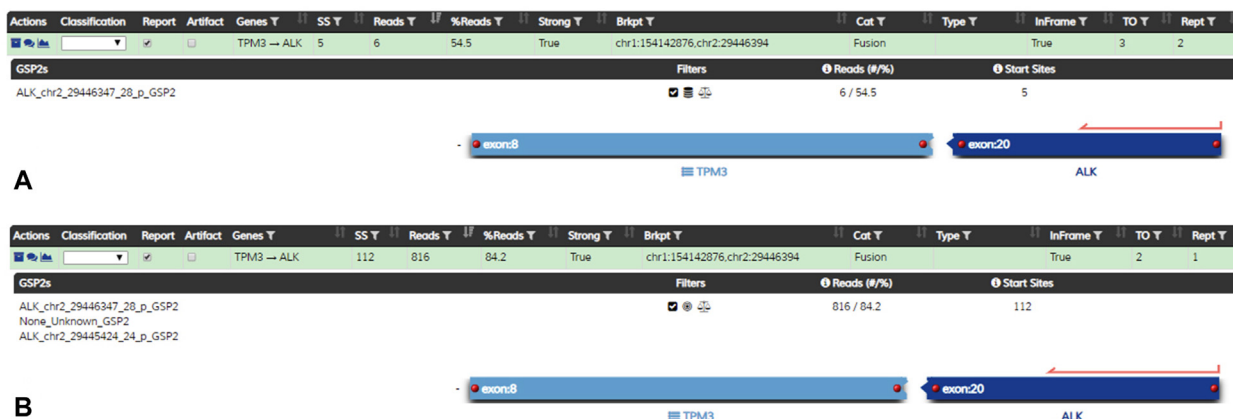


Fig 3. Mutation profiles of the translocation t(1;2)(q25;p23) of (A) a cutaneous anaplastic large T-cell lymphoma and (B) Spitz lesion in the same patient, illustrating an identical breakpoint on exon 20 (tropomyosin 3 [*TPM3*]: NM_152263:exon:8; anaplastic lymphoma kinase [*ALK*]: NM_004304.4:exon:20). GSP2s, Gene-specific primers 2.

predisposing to translocation events. Patients with *ALK-TPM3* fusions, either Spitz or C-ALCL, appear to be at increased risk of developing multiple tumors driven by this oncogenic translocation. On the basis of the current case, however, this fusion seems to be associated with a favorable disease course.

We thank P.G. Leenheer for his contribution in the figure preparation.

REFERENCES

1. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000;95(12):3653-3661.
2. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. *Nat Commun*. 2014;5:3116.
3. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714.
4. Cao Z, Gao Q, Fu M, Ni N, Pei Y, Ou WB. Anaplastic lymphoma kinase fusions: roles in cancer and therapeutic perspectives. *Oncol Lett*. 2019;17(2):2020-2030.
5. Lamant L, Dastugue N, Pulford K, Delsol G, Mariame B. A new fusion gene *TPM3-ALK* in anaplastic large cell lymphoma created by a (1;2)(q25;p23) translocation. *Blood*. 1999;93(9):3088-3095.
6. Chang K, Liu JH, Yu SC, Lin CW. *FGFR1* translocation with concurrent myeloproliferative neoplasm, systemic mastocytosis, and lymphoblastic lymphoma: a case report. *Hum Pathol*. 2018;74:114-121.