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Published in:
American Journal of Surgical Pathology

DOI:
10.1097/PAS.0000000000001449

Clinical, Histologic, and Molecular Characteristics of Anaplastic Lymphoma Kinase-positive Primary Cutaneous Anaplastic Large Cell Lymphoma

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Abstract: Unlike systemic anaplastic large cell lymphoma, the vast majority of primary cutaneous anaplastic large cell lymphomas (C-ALCL) do not carry translocations involving the *ALK* gene and do not express ALK. Expression of ALK protein therefore strongly suggests secondary cutaneous involvement of a systemic anaplastic large cell lymphoma. Recent studies described a small subgroup of ALK-positive C-ALCL, but information on frequency, prognosis, and translocation partners is virtually lacking. A total of 6/309 (2%) C-ALCL patients included in the Dutch registry for cutaneous lymphomas between 1993 and 2019 showed immunohistochemical ALK expression. Clinical and histopathologic characteristics, immunophenotype and disease course were evaluated. Underlying *ALK* translocations were analyzed with anchored multiplex polymerase chain reaction-based targeted next-generation sequencing. Median age at diagnosis was 39 years (range: 16 to 53 y). All patients presented with a solitary lesion. Treatment with radiotherapy (n = 5) or anthracycline-based chemotherapy (n = 1) resulted in complete responses in all 6 patients. Three patients developed a relapse, of whom 2 extracutaneous. After a median follow-up of 41 months, 5 patients were alive without disease and 1 patient died of lymphoma. Immunohistochemically, 3 cases (50%) showed combined nuclear and cytoplasmic ALK expression with underlying *NPM1-ALK* fusions, while 3 cases (50%) showed solely cytoplasmic ALK expression with variant *ALK* fusion partners (*TRAF1*, *ATIC*, *TPM3*). ALK-positive C-ALCL is extremely uncommon, has a comparable favorable prognosis to ALK-negative C-ALCL, and should be treated in the same way with radiotherapy as first-line treatment.

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Key Words: ALK-positive cutaneous anaplastic large cell lymphoma, anaplastic lymphoma kinase, C-ALCL, prognosis, fusion partner, translocation

(*Am J Surg Pathol* 2020;44:776–781)

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) forms a spectrum of CD30-positive lymphoproliferative diseases, together with lymphomatoid papulosis.[1,2] C-ALCL patients mainly present with solitary or few clustered, often ulcerating tumors.[1–3] It is histologically characterized by cohesive fields of CD30-positive anaplastic cells, with a T-cell or null-cell phenotype.[1] First-line treatment consists of radiotherapy (RT) or excision.[4] Approximately 10% of the patients develop the extracutaneous disease during follow-up, mainly limited to regional draining lymph nodes.[1,3,5] Prognosis is excellent with a 10-year disease-specific survival of ~90%.[1,5]

In contrast, systemic anaplastic large cell lymphoma (sALCL) is a more aggressive lymphoma that requires treatment with chemotherapeutic agents.[1,6] sALCL is divided into 2 subgroups depending on the expression of the Anaplastic Lymphoma Kinase protein (ALK) due to an underlying translocation in the *ALK* gene.[6] ALK-positive sALCL has a much better prognosis than ALK-negative sALCL.[6] ALK is a tyrosine kinase that is normally expressed in neural cells and is involved in brain development.[7] In certain cancers, the *ALK* gene is translocated to different fusion partners and thereby consecutively expressed.[8] In sALCL, the nucleophosmin 1 (*NPM1*) gene accounts for the most frequent fusion partner (85%), leading to an t(2;5)(p23;q35), followed by the tropomyosin 3 (*TPM3*) gene in ~10% of the cases.[6,8–10] Remaining rare fusion partners are tropomyosin 4 (*TPM4*), TRK-fused gene (*TFG*), 5′aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (*ATIC*), TNF Receptor Associated Factor 1 (*TRAF1*), and even more are reported.[11,12]

Immunohistochemically, a *NPM1-ALK* translocation shows both nuclear and cytoplasmic ALK expression in

sALCL, while variant translocations only show cytoplasmic ALK expression.[13,14]

Unlike sALCL, the vast majority of C-ALCL do not carry translocations involving the *ALK* gene and do not express ALK. Expression of ALK protein therefore strongly suggest secondary cutaneous involvement of a systemic ALK-positive ALCL.[15–17] However, unusual cases of ALK-positive C-ALCL have been reported, including both cases showing strong nuclear and cytoplasmic ALK staining characteristics of the t(2;5) chromosomal translocation and cases expressing cytoplasmic ALK protein, indicative of a variant translocation.[15,16,18] Many of these cases had an excellent prognosis. However, rapid progression to systemic ALCL has been reported as well.[19,20] It is at present impossible to predict whether such ALK-positive cases presenting with only skin lesions will run an indolent or aggressive clinical course. Moreover, the frequency of these ALK-positive C-ALCL is unknown and *ALK* fusion partners in C-ALCL have not been described. To obtain more insights in ALK-positive C-ALCL, we evaluated clinical characteristics, immunohistochemistry and *ALK* fusion partners of ALK-positive C-ALCL patients included in the Dutch registry for cutaneous lymphomas.

MATERIALS AND METHODS

Patients

Since 1993, ALK1 immunohistochemical staining was routinely performed in patients with C-ALCL. Between January 1993 and July 2019, 309 patients with C-ALCL were included in the Dutch registry for cutaneous lymphomas. This group included 6 patients with an ALK-positive C-ALCL with only skin lesions at presentation. All patients had been diagnosed by an expert panel of the Dutch Cutaneous Lymphoma Group. In all 6 patients staging procedures including blood examination, computed tomography scan and in most patients bone marrow biopsy had excluded extracutaneous disease at the time of diagnosis. Follow-up data were collected from medical records and referring clinicians in case of missing information.

Routinely stained hematoxylin and eosin sections and immunostains with antibodies against CD2, CD3, CD5, CD7, CD4, CD8, CD30, cytotoxic proteins (Granzyme B, TIA-1), ALK1, CD68, CD79a, CD20, and Ki-67 were retrieved from the archives of the participating departments of pathology and subsequently reviewed. This study was evaluated by the Ethics Committee of the Leiden University Medical Center and provided with a waiver of consent.

Molecular Characterization by ArcherDX Panel

Targeted RNA sequencing assay technique (FusionPlex; ArcherDX, Boulder, CO) that simultaneously detects and identifies fusions of ALK translocations by anchored multiplex polymerase chain reaction-based enrichment was performed. Total nucleic acid was isolated from 5 ×10 µm formalin-fixed paraffin-embedded slides using the tissue preparation system (Siemens). After measurement of RNA quantity for formalin-fixed paraffin-embedded material with Qubit fluorometric quantification system (Life Technologies), the target-enriched cDNA library was prepared with the Archer FusionPlex Comprehensive Thyroid and Lung kit as per manufacturer's description.[21] Reverse transcription of RNA was followed by end-repair, adenylation and universal half-functional adapter ligation of double-stranded cDNA fragments. This was followed by 2 rounds of a polymerase chain reaction with universal primers and gene-specific primers, covering 36 target genes that rendered the library fully functional for clonal amplification and sequencing using the S5 system. With the Archer analysis software (version 5.1) the produced libraries were analyzed for the presence of relevant fusions. Sequence quality was assessed by the following criteria: QC score of <30, a minimal total read number of 1.5 million with >40% RNA reads.

Statistical Analysis

The Kaplan-Meier method was used to estimate (5-year) progression-free survival (PFS/PFS5; event defined as development of extracutaneous disease or death by any cause) and overall survival (OS/OS5). Outcomes were compared between groups using the log-rank test. A *P*-value of <0.05 was considered significant. All statistical analyses were performed using SPSS version 23 (IBM Corp.).

RESULTS

Clinical Characteristics

Our study group included 2 males and 4 females and the median age at presentation was 39 years (range: 16 to 53 y) (Table 1). Five cases presented with a solitary (ulcerating) tumor on the arm (n = 3), or trunk (n = 2), and 1 patient with localized lesions on the right lower leg. Lesions ranged in size from 3.0 to 7.0 cm in diameter. One patient (case 4) reported a 1-year history of multiple spontaneously regressing nodules on her leg before persistent tumors developed.

Histologic and Immunohistochemical Examination

The patients showed comparable histologic features and were immunohistochemically characterized by diffuse cohesive fields of CD30-positive anaplastic cells (Table 2). The neoplastic cells showed variable expression of T-cell markers CD2, CD3, CD7, CD4, and CD8 with frequent loss of CD3, CD5 and CD7, and expression of cytotoxic proteins in 5 of 6 cases. The proliferation index (Ki-67) was >50% in most cases. Three patients (cases 1 to 3) showed the typical combined nuclear and cytoplasmic ALK staining pattern, while the other 3 cases only had a cytoplasmic staining pattern (Figs. 1, 2, respectively).

Molecular Findings

All 3 patients with a combined nuclear and cytoplasmic ALK1 staining pattern showed an underlying *NPM1-ALK* translocation (NPM1: NM_002520.6:exon:4; ALK: NM_004304.4:exon:20) (Table 2). The other 3 patients (cases 4

TABLE 1. Clinical Characteristics of 6 ALK-positive C-ALCL Patients

	Case No.					
	1	2	3	4	5	6
Age at onset (y)	34	44	16	50	53	30
Sex	Female	Female	Male	Female	Female	Male
Clinical presentation	Solitary tumor abdomen	Solitary tumor left breast	Solitary tumor left arm	Clustered lesions right lower leg	Solitary tumor right elbow	Solitary tumor left arm
Initial treatment	RT	RT	Anthracycline-based chemotherapy	RT	RT	RT
Response	CR	CR	CR	CR	CR	CR
Relapses (time to relapse)						
Only skin	+ (4 mo)	—	—	—	—	—
Extracutaneous	—	—	—	+ (11 mo)	+ (4 mo)	—
Treatment after relapse	Anthracycline based chemotherapy	—	—	Anthracycline based chemotherapy	Anthracycline based chemotherapy	—
Response	CR			PD	CR	
Follow-up						
Status last follow-up	AWD	AWD	AWD	DOD	AWD	AWD
Duration (mo)	101	65	36	19	46	23

AWD indicates alive without disease; CR, complete remission of 100% disappearance of lesions; DOD, death due to disease; PD, progressive disease.

to 6) with a solely cytoplasmic ALK1 staining pattern contained variant *ALK* fusion partners. Case 4 harbored a *TRAF1-ALK* fusion transcript (TRAF1: NM_005658.4: exon:6; ALK: NM_004304.4:exon:20). Case 5 harbored an *ATIC-ALK* fusion transcript (ATIC: NM_004044.6:exon:7; ALK: NM_004304.4:exon:20). Finally, case 6 contained a *TPM3-ALK* translocation (TPM3: NM_152263:exon:8; ALK: NM_004304.4:exon:20). Remarkably, all 6 patients shared exactly the same breakpoint site of the *ALK* gene on exon 20.

Treatment and Follow-up Data

Five patients were initially treated with local RT and 1 patient (case 4) with anthracycline-based chemotherapy. All patients achieved a complete response. Three patients developed relapses, 1 limited to the skin (case 1) and 2 patients (case 4, 5) developed nodal and visceral extracutaneous localizations (case 4: lymph nodes, pleural fluid, and bone marrow, and case 5: lymph nodes and pulmonary involvement). All 3 patients with relapses were treated with anthracycline-based chemotherapy, 2 of whom (case 1, 5) responded with complete remission, while 1 showed disease progression (case 4). After a median follow-up duration of 41 months (range: 19 to 101 mo), 5 patients were alive without disease and 1 patient (case 4) died due to extensive extracutaneous disease 19 months after diagnosis (Table 1).

DISCUSSION

The aim of the present study was to collect information on the frequency, translocation partners and

TABLE 2. Immunophenotypic and Genetic Features of 6 ALK-positive C-ALCL Patients

	Case No.					
	1	2	3	4	5	6
Immunophenotype						
CD30	+	+	+	+	+	+
CD2	−	−	−	+	+	+
CD3	−	+	−	−	−	−
CD5	−	−	−	−	−	−
CD7	ND	−	ND	−	−	+
CD4	+	−	+	+	+	−
CD8	−	+	−	−	−	−
Granzyme B						
TIA-1	+	+	ND	+	+	+
Ki-67	+	+	ND	−	−	+
ALK1	ND	> 80%	ND	50%	> 60%	> 75%
Nuclear	+	+	+	−	−	−
Cytoplasmic	+	+	+	+	+	+
Genetics						
Translocation	*NPM1-ALK*	*NPM1-ALK*	*NPM1-ALK*	*TRAF1-ALK*	*ATIC-ALK*	*TPM3-ALK*
Exon	4:20	4:20	4:20	6:20	7:20	7:20

ND indicates not done; +, positive staining in at least 30% of the cells; −, negative staining or positive in < 30%.

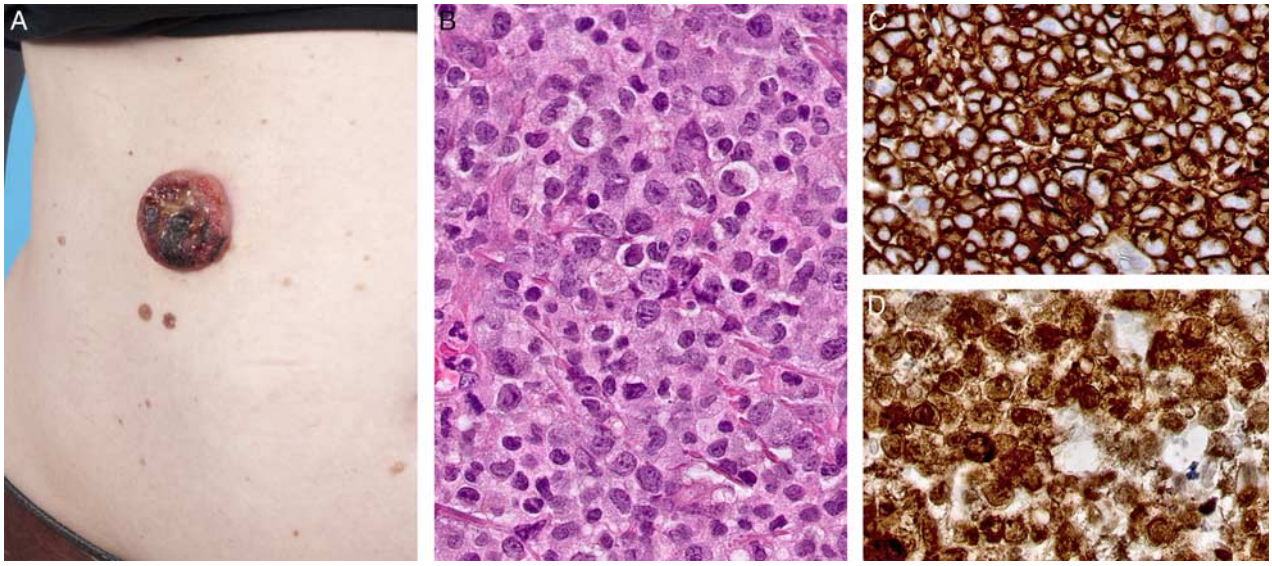

FIGURE 1. Clinical and histologic features of ALK-positive C-ALCL with a combined nuclear and cytoplasmic staining pattern. Case 1: single ulcerated tumor of 5×4 cm on the abdomen (A) with histologically a hematoxylin and eosin staining with a typical diffuse nonepidermotropic infiltrate (B) consisting of cohesive fields of large $CD30^+$ cells with anaplastic morphology (C) and both nuclear and cytoplasmic ALK-expression (D).

clinical behavior and prognosis of patients with an ALK-positive C-ALCL. ALK-positive C-ALCL is indeed rare and thus far only 21 cases have been reported (see a review of Geller et al[15]). In the present study, ALK expression was found in 6 of 309 (2%) C-ALCL patients included in the Dutch registry of cutaneous lymphomas between January 1993 and July 2019.

Clinically, most patients were of relatively young age (below < 50 y) and presented with a solitary tumor, which went into complete remission following RT in 5 cases, and anthracycline-based chemotherapy in 1 patient. A cutaneous relapse was observed in 1 patient, progression to systemic disease in 2 patients, while 1 patient died of lymphoma (Table 1). When our 6 cases and the 21 cases reviewed by Geller et al[15] are combined, a skin relapse is observed in 7 of 27 patients (26%), development of extracutaneous disease in 6 of 27 patients (22%), and death of lymphoma in 3 of 27 patients (11%) (Table 3). These results are very similar to those reported in ALK-negative C-ALCL. In a previous study of our group on

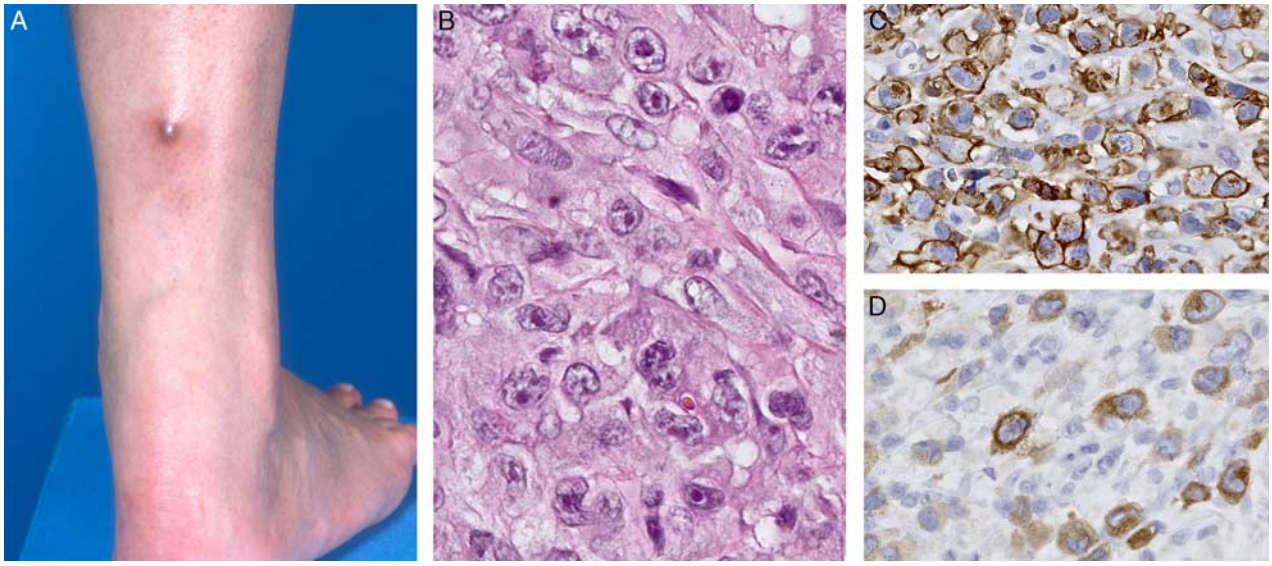

FIGURE 2. Clinical and histologic features of ALK-positive C-ALCL with a solely cytoplasmic staining pattern. Case 4: Single nodule on the lower right leg (A) with histologically a hematoxylin and eosin staining with a typical diffuse nonepidermotropic infiltrate (B) consisting of cohesive fields of large $CD30^+$ cells with anaplastic morphology (C) and solely cytoplasmic ALK-expression (D).

TABLE 3. Clinical and Molecular Characteristics of 27 ALK-positive C-ALCL Patients (%)*

Sex (male:female)	8:14
Age at diagnosis, median (range) (y)	27 (5-65)
Extent	
Solitary/localized	23 (85)
Multifocal	3 (11)
Not reported	1 (4)
ALK1 staining pattern	
Nuclear+cytoplasmic	10 (37)
Cytoplasmic	7 (26)
Not reported	10 (37)
Treatment	
Excision	7 (26)
RT	9 (33)
Anthracycline-based chemotherapy	8 (30)
Spontaneous regression	1 (4)
Not reported	2 (7)
Relapses	
No relapse	16 (59)
Cutaneous relapse	4 (15)
Systemic (+cutaneous) relapse	6 (22)
Not reported	1 (4)
Status last follow-up	
AWD	23 (85)
DOD	3 (11)
Not reported	1 (4)
Follow-up duration, median (range) (mo)	29.5 (8-156)

*Including 6 patients of the current study and 21 patients reviewed by Geller et al.[15]

AWD indicates alive without disease; DOD, death due to disease.

135 ALK-negative C-ALCL, 53 of 135 patients (39%) had a relapse limited to the skin, 20 of 135 patients (15%) developed the extracutaneous disease, while 12 of 135 patients (9%) died of lymphoma.[22] Statistical analysis did not show significant differences between the 27 ALK-positive and 135 ALK-negative C-ALCL patients in PFS5 (75% vs. 75%, respectively; $P = 0.96$) and OS5 (90% vs. 82%, respectively; $P = 0.79$).

Factors associated with disease progression in this rare group of patients are unknown. We wondered whether there could be a relationship between the type of translocation and clinical behavior. Using the Archer DX panel, it was found that 3 cases with both nuclear and cytoplasmic ALK staining had the corresponding *NPM-ALK* translocation, while the other 3 cases with a solely cytoplasmic ALK staining pattern harbored variant translocations (*TRAF1-ALK*, *ATIC-ALK*, and *TPM3-ALK*). This is the first time these variants are described in C-ALCL patients but are already known in the systemic variant in low frequencies.[19,23–30] However, due to the few events, lack of information on the ALK staining pattern and type of translocation in most previous studies, conclusions on a potential relationship between the type of translocation and clinical behavior or prognosis cannot be drawn. Also, in sALCL, no differences in prognosis were found between tumors with the classic *NPM1-ALK* translocation and tumors with variant translocations.[25,31–34]

In conclusion, current evidence suggests that ALK-positive ALCL presenting with only skin lesions in most cases have an excellent prognosis and should be treated in the same way as ALK-negative C-ALCL with RT as first-line treatment.[4,35]

ACKNOWLEDGMENTS

The authors thank P.G. Leenheer, medical photographer, for his valuable contribution regarding the clinical images and figure preparation. Furthermore, they would also like to thank D. de Jong for retrieving slides from the Department of Pathology, Vrije University Medical Center, Amsterdam, The Netherlands.

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;95:3653–3661.
2. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133:1703–1714.
3. Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol*. 2003;49:1049–1058.
4. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood*. 2011;118:4024–4035.
5. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768–3785.
6. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;111:5496–5504.
7. Iwahara T, Fujimoto J, Wen D, et al. Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system. *Oncogene*. 1997;14:439–449.
8. Cao Z, Gao Q, Fu M, et al. Anaplastic lymphoma kinase fusions: roles in cancer and therapeutic perspectives. *Oncol Lett*. 2019;17:2020–2030.
9. Bohling SD, Jenson SD, Crockett DK, et al. Analysis of gene expression profile of TPM3-ALK positive anaplastic large cell lymphoma reveals overlapping and unique patterns with that of NPM-ALK positive anaplastic large cell lymphoma. *Leuk Res*. 2008;32:383–393.
10. Giuriato S, Foisseau M, Dejean E, et al. Conditional TPM3-ALK and NPM-ALK transgenic mice develop reversible ALK-positive early B-cell lymphoma/leukemia. *Blood*. 2010;115:4061–4070.
11. Liang X, Meech SJ, Odom LF, et al. Assessment of t(2;5)(p23;q35) translocation and variants in pediatric ALK+ anaplastic large cell lymphoma. *Am J Clin Pathol*. 2004;121:496–506.
12. Li C, Takino H, Eimoto T, et al. Prognostic significance of NPM-ALK fusion transcript overexpression in ALK-positive anaplastic large-cell lymphoma. *Mod Pathol*. 2007;20:648–655.
13. Montes-Mojarro IA, Steinhilber J, Bonzheim I, et al. The pathological spectrum of systemic anaplastic large cell lymphoma (ALCL). *Cancers (Basel)*. 2018;10:E107.
14. Benharroch D, Meguerian-Bedoyan Z, Lamant L, et al. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. *Blood*. 1998;91:2076–2084.
15. Geller S, Canavan TN, Pulitzer M, et al. ALK-positive primary cutaneous anaplastic large cell lymphoma: a case report and review of the literature. *Int J Dermatol*. 2018;57:515–520.
16. Oschlies I, Lisfeld J, Lamant L, et al. ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. *Haematologica*. 2013;98:50–56.

17. Lamant L, Pileri S, Sabattini E, et al. Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases. *Haematologica*. 2010;95:449–455.
18. Kadin ME, Pinkus JL, Pinkus GS, et al. Primary cutaneous ALCL with phosphorylated/activated cytoplasmic ALK and novel phenotype: EMA/MUC1+, cutaneous lymphocyte antigen negative. *Am J Surg Pathol*. 2008;32:1421–1426.
19. Wehkamp U, Oschlies I, Nagel I, et al. ALK-positive primary cutaneous T-cell-lymphoma (CTCL) with unusual clinical presentation and aggressive course. *J Cutan Pathol*. 2015;42:870–877.
20. Hosoi M, Ichikawa M, Imai Y, et al. A case of anaplastic large cell lymphoma, ALK positive, primary presented in the skin and relapsed with systemic involvement and leukocytosis after years of follow-up period. *Int J Hematol*. 2010;92:667–668.
21. Lam SW, Cleton-Jansen AM, Cleven AHG, et al. Molecular analysis of gene fusions in bone and soft tissue tumors by anchored multiplex PCR-based targeted next-generation sequencing. *J Mol Diagn*. 2018;20:653–663.
22. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. *Arch Dermatol*. 2009;145:1399–1404.
23. Lim MS. Unraveling ALK signaling through phosphoproteomics. *Blood*. 2009;113:2615–2616.
24. Trinei M, Lanfrancone L, Campo E, et al. A new variant anaplastic lymphoma kinase (ALK)-fusion protein (ATIC-ALK) in a case of ALK-positive anaplastic large cell lymphoma. *Cancer Res*. 2000;60:793–798.
25. van der Krogt JA, Bempt MV, Ferreiro JF, et al. Anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with the variant RNF213-, ATIC- and TPM3-ALK fusions is characterized by copy number gain of the rearranged ALK gene. *Haematologica*. 2017;102:1605–1616.
26. Colleoni GW, Bridge JA, Garicochea B, et al. ATIC-ALK: a novel variant ALK gene fusion in anaplastic large cell lymphoma resulting from the recurrent cryptic chromosomal inversion, inv(2)(p23q35). *Am J Pathol*. 2000;156:781–789.
27. Meech SJ, McGavran L, Odom LF, et al. Unusual childhood extramedullary hematologic malignancy with natural killer cell properties that contains tropomyosin 4—anaplastic lymphoma kinase gene fusion. *Blood*. 2001;98:1209–1216.
28. Lawrence K, Berry B, Handshoe J, et al. Detection of a TRAF1-ALK fusion in an anaplastic large cell lymphoma patient with chemotherapy and ALK inhibitor-resistant disease. *BMC Res Notes*. 2015;8:308.
29. Abate F, Todaro M, van der Krogt JA, et al. A novel patient-derived tumorgraft model with TRAF1-ALK anaplastic large-cell lymphoma translocation. *Leukemia*. 2015;29:1390–1401.
30. Lee SY, Choi Y. TRAF1 and its biological functions. *Adv Exp Med Biol*. 2007;597:25–31.
31. Falini B, Pulford K, Pucciarini A, et al. Lymphomas expressing ALK fusion protein(s) other than NPM-ALK. *Blood*. 1999;94:3509–3515.
32. Yu R, Chen G, Zhou C, et al. Extra copies of ALK gene locus is a recurrent genetic aberration and favorable prognostic factor in both ALK-positive and ALK-negative anaplastic large cell lymphomas. *Leuk Res*. 2012;36:1141–1146.
33. Hoshino A, Nomura K, Hamashima T, et al. Aggressive transformation of anaplastic large cell lymphoma with increased number of ALK-translocated chromosomes. *Int J Hematol*. 2015;101:198–202.
34. Armstrong F, Lamant L, Hieblot C, et al. TPM3-ALK expression induces changes in cytoskeleton organisation and confers higher metastatic capacities than other ALK fusion proteins. *Eur J Cancer*. 2007;43:640–646.
35. Willemze R, Hodak E, Zinzani PL, et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;24:vi149–vi154.