HHS Public Access

Author manuscript

Int J Dermatol. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Int J Dermatol. 2018 May ; 57(5): 515–520. doi:10.1111/ijd.13804.

ALK-positive primary cutaneous anaplastic large cell lymphoma: a case report and review of the literature

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Abstract

Anaplastic large cell lymphoma (ALCL) limited to the skin is a distinct disease that is designated primary cutaneous ALCL (pcALCL). It has an indolent course with a significantly better prognosis compared to systemic ALCL (sALCL). Anaplastic lymphoma kinase (ALK) expression in lesions of cutaneous ALCL is classically considered to be a marker for skin involvement by sALCL. However recent reports of patients with ALK-positive pcALCL challenge this concept and raise prognostic and therapeutic dilemmas. Herein we report a case of ALK-positive pcALCL in a 45 year-old woman who was treated with local radiotherapy. We review previously reported cases in the literature to better characterize this rare variant. Overall the rates of cutaneous recurrence, systemic dissemination and disease related mortality in ALK-positive pcALCL do not differ from those previously reported in pcALCL. ALK-positive pcALCL is diagnosed at younger age and has a better disease course in children compared to adults with lower incidences of skin recurrence and progression to systemic disease. We conclude that ALK-positivity in cutaneous ALCL does not necessarily imply systemic disease. ALK-positive pcALCL has an excellent prognosis and should be treated by excision and/or radiotherapy. However patients must remain under close long-term follow-up as recurrence and progression to systemic disease may occur.

Introduction

Anaplastic large cell lymphoma (ALCL) is a CD30+ lymphoproliferative disorder that has two distinct forms with different disease courses: primary cutaneous ALCL (pcALCL) which has an excellent prognosis, and systemic ALCL (sALCL), a potentially aggressive

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Conflict of interest disclosures: None.

lymphoma that primarily involves the lymph nodes and carries a less favorable course. sALCL is further divided into ALK-positive and ALK-negative subtypes, depending on the expression of the anaplastic lymphoma kinase (ALK) fusion protein. pcALCL is generally found to be ALK-negative and ALK expression in skin lesions of ALCL evokes high suspicion for secondary skin involvement by sALCL.[1] Recently, ALK-positive pcALCL has been reported in both children and adults[2–18] with heterogenous courses described.

Case Report

A 45 year-old woman presented to our multidisciplinary cutaneous lymphoma clinic with a one-month-history of a rapidly growing ulcerated nodule on her left abdomen. The patient was in otherwise good health without any significant past medical history. Complete review of systems was negative. Physical examination revealed a round 3-cm-in-diameter ulcerated red nodule with surrounding erythema (Figure 1(a–b)). No palpable lymphadenopathy was identified. Histopathological evaluation of lesional biopsies revealed dense dermal infiltrate of large atypical lymphocytes, positive for CD30, ALK-1 and TIA (Figure 1(c)). Complete staging was performed to assess for systemic disease. Laboratory tests were unremarkable. Positron emission tomography–computed tomography (PET-CT) demonstrated a fluoro-deoxyglucose (FDG) avid cutaneous abdominal mass corresponding to the biopsied tumor, hypermetabolic bilateral axillary lymph nodes (2 on 1.1 cm in size), and diffuse heterogeneous uptake by the bone marrow. An ultrasound-guided-biopsy showed reactive follicular hyperplasia of an axillary lymph node with negative ALK staining, and lymph node flow cytometry revealed no abnormal lymphocyte populations. The patient was diagnosed with ALK-positive pcALCL and was treated by local radiation to her left abdominal skin with a complete response. A follow-up PET-CT performed 3.5 months after the initial imaging study revealed resolution of the hypermetabolic lymphadenopathy and the cutaneous mass, and no bone marrow FDG uptake was seen.

Discussion

PcALCL is generally conceptualized as part of the cutaneous CD30+ T-cell lymphoproliferative disorder spectrum. It is most commonly diagnosed in the sixth decade; however it can also occur in childhood or adolescence. The majority of cases present with a rapidly growing solitary ulcerated nodule that can undergo partial or complete spontaneous regression. Overall, pcALCL carries a very favorable prognosis with a 5-year overall survival (OS) of 90%.[19] Cutaneous recurrences are not uncommon and occur in up to 40% of treated patients, however progression to systemic disease is rare, affecting only 12–16%.[1,20,21] Overexpression of the ALK fusion protein has been postulated to have a role in the malignant transformation of sALCL.[22] In sALCL, ALK expression is found mainly in pediatric and young age groups[19] and is of prognostic significance as ALK-positive sALCL has a 5-year OS of 70% compared to an OS of 49% in ALK-negative sALCL.[19] ALK expression can also aid in therapeutic decision making: crizotinib is an ALK tyrosine kinase inhibitor that can be used as a treatment in ALK-positive sALCL.[23]

Following the diagnosis of ALK-positive pcALCL in the presented case, and in a pediatric patient that had been recently reported by our institution,[8] we searched the literature for

ALK-positive pcALCL cases in order to better characterize the course and prognosis of this rare variant. Including our cases, we identified 9 pediatric patients[7,8,13,14,18] and 12 adults[2–6,9–12,15–17] who were diagnosed with ALK-positive pcALCL (Table 1). Complete staging was performed in 15/21 of cases. In one case, no staging procedures were done and a disseminated disease was diagnosed after 1.5 months[17] – we excluded this case from the following analyses as it was most probably sALCL rather than pcALCL.

The median age at diagnosis was 23.5 years (range 5–65) which is noticeably younger than that reported for pcALCL. Overall, the disease course and prognosis in the ALK-positive pcALCL cases reflected the literature on pcALCL[20,21]: 15.8% presented with more than one lesion, skin recurrence occurred in 27.8% and extracutaneous dissemination developed in 16.7%. Two patients (10%) expired due to systemic disease. Differences in disease course could be appreciated between pediatric and adult ALK-positive pcALCL patients. None of the pediatric patients who had complete staging at diagnosis recurred or progressed to systemic disease, whether treated with excision/radiation (6 cases) or with systemic chemotherapy (2 cases). A single pediatric case did progress (11%) and expired due to disease, however he had no staging workup done[14]. Among the adult cases, the rates of cutaneous recurrence and progression to systemic disease were 55.6% and 22.2%, respectively, and one adult died due to disease (11%). The rates of skin recurrence and disease progression and the differences between adult and pediatric cases remained similar when analyzing only the 15 cases that had a complete staging. The median reported follow-up for the reviewed cases was 36 months (10–96 months) for the pediatric cases, and 13 months (9–156 months) for the adults. The relatively short follow-up period (8 months) is a limitation of our case report.

Patients with ALK-positive pcALCL present diagnostic and prognostic challenges and pose questions regarding the ideal treatment and monitoring in such rare cases. It is unclear whether these cases are actually sALCL first manifesting in skin or true pcALCL with ALK overexpression. Summarizing the limited ALK-positive pcALCL reports in the literature, the low rate of systemic dissemination supports the later option. In addition we found that while the prognosis of ALK-positive pcALCL is excellent in pediatric patients, it is heterogenous in adults with an overall similar indolent course and prognosis compared to what had been previously reported in pcALCL.

Reccomendations and conclusions

Complete staging is mandatory in all pcALCL cases and lymphadenopathy per radiology studies alone cannot substitute for a lymph node biopsy if such involvement is suspected, as was demonstrated by the current case. Once the diagnosis of ALK-positive pcALCL is confirmed, it should be treated with skin-directed therapy. Close long-term monitoring is required as extracutaneous dissemination of the skin disease has been reported at 10, 18 and 96 months following the diagnosis of ALK-positive pcALCL .

In conclusion, ALK-positivity in cutaneous ALCL is not an unequivocal indicator of systemic disease. ALK-positive pcALCL has an excellent prognosis particularly in children, and should be treated by excision and/or radiotherapy. Patients must remain under close

long-term follow-up as skin recurrence and progression to systemic disease are possible, mostly in adults.

Acknowledgments

Funding sources: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Shamir Geller is a recipient of a supplemental grant from the American Physicians and Friends For Medicine in Israel (APF).

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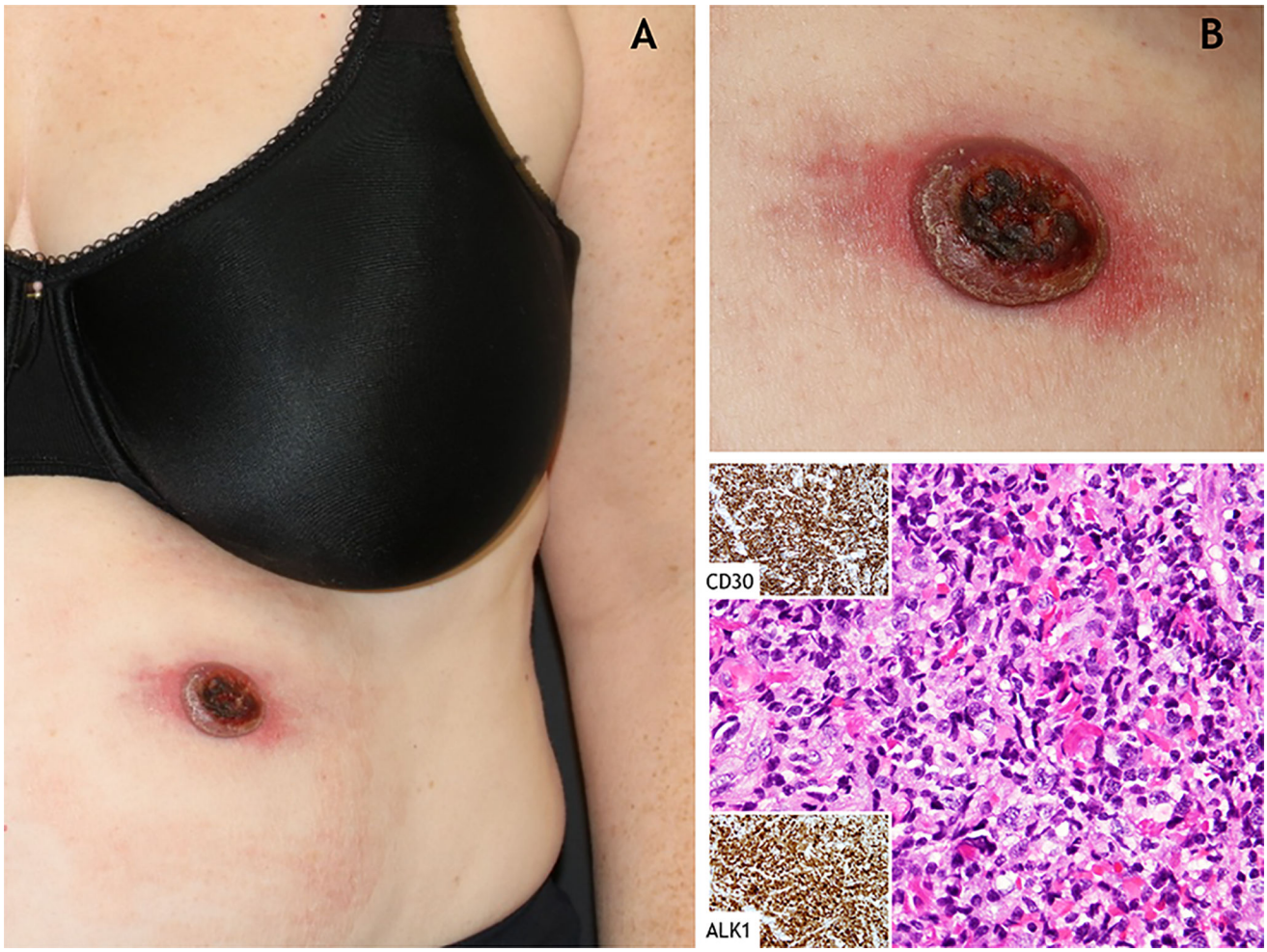

Figure 1.

Clinical and histopathological findings in a 45 year-old woman with ALK-positive primary cutaneous anaplastic large cell lymphoma. (a–b) An ulcerated red nodule with peripheral erythema on the left upper abdomen. (c) Underlying histological features show dense dermal infiltrate of large atypical lymphocytes. The atypical lymphocytes stained positive for CD30 and showed nuclear and cytoplasmic staining for ALK-1 (Hematoxylin and eosin, original magnifications ×40).

Table 1

Clinical features, treatment and outcome in ALK-positive primary cutaneous anaplastic large cell lymphoma (pcALCL) cases

Reference	Age	Gender	Localization	Staging tests performed	Initial treatment	Local/distant Skin recurrence (time to recurrence, months)	Systemic dissemination (time to dissemination, months)	Treatment of recurrence / dissemination	Outcome	Follow up period (months)
Pediatric cases (< 18 years old)										
Tokuyama et al[13]	5	F	Single (arm)	CT, PET-CT, US, LNB, OMB, LP	Dexamethasone, cyclophosphamide, methotrexate, ifosfamide, cytarabine, etoposide and doxorubicin	No	No	N/A	DF	28
Fauconneau et al[18]	17	F	NR	CT, PET-CT, OMB	Radiotherapy	No	No	N/A	DF	48
Pulitzer et al.[8]	11	F	Multifocal (trunk)	PET-CT, OMB, LP	Methotrexate, cyclophosphamide, cytarabine, etoposide and vinblastine, doxorubicine	No	No	N/A	DF	36
Oschlies et al.[7]	9.1	NR	Single (leg)	CT, OMB, LP, bone scan	Excision	No	No	N/A	DF	96
	7.5	NR	Single (neck)	CT, OMB, LP, bone scan	Excision	No	No	N/A	DF	28
	10	NR	Single (leg)	CT, OMB, LP, bone scan	Excision	No	No	N/A	DF	96
	11.9	NR	Single (leg)	CT, OMB, LP, bone scan	Radiation	No	No	N/A	DF	62
	13.8	NR	Single (leg)	CT, OMB, bone scan	Excision, radiation	No	No	N/A	DF	12
Rannan-Eliya et al[14]	14	F	Single (trunk)	NR	Excision	No	Yes (10m)	dexamethasone, cyclophosphamide, methotrexate, ifosfamide, cytarabine, etoposide and doxorubicin	DOD	10
Adult cases (> 18 years old)										
Xue et al[10]	21	F	Single (groin)	CT, OMB	Excision, CHOP	No	No	N/A	DF	12
Paolina et al.[9]	62	M	Single (trunk)	CT, OMB	Excision	Local (0.5m)	No	Excision, radiation	DF	12

Reference	Age	Gender	Localization	Staging tests performed	Initial treatment	Local/distant Skin recurrence (time to recurrence, months)	Systemic dissemination (time to dissemination, months)	Treatment of recurrence / dissemination	Outcome	Follow up period (months)
Quintanilla-Martinez[15]	27	M	Single (NR)	NR	Excision	No	No	N/A	DF	12
Kumaran et al.[12]	65	M	Single (Trunk)	CT, OMB	NR	NR	NR	NR	NR	NR
Chan et al.[2]	33	M	Multifocal (head, trunk, leg)	CT, OMB	CHOP	Distant (4m, 16m)	Yes (18m)	Excision, ifosfamide, carboplatin, and etoposide, autologous stem cell transplantation	DF	31
Chao-Lo et al.[11]	47	F	Multiple (arm)	CT	CHOP	Recurrence type not defined (12m)	No	Radiation	DF	18
Kadin et al.[6]	57	M	Single (leg)	NR	Excision	Distant (16m, 60m, 92m, 105m)	No	Excision, radiation	DF	156
Campo et al[16]	26	M	Single (leg)	NR	NR	No	No	N/A	DF	9
Sasaki et al[5] and Hosoi et al.[3]	54	F	Single (head)	NR	Spontaneous regression	Distant (1m, 30m)	Yes (96m)	Excision, radiation for recurrences, CHOP for first dissemination, ESHAP for 2nd dissemination	DOD	71
Aoki et al[17]*	22	F	Single (arm)	NR	Cisplatin, etoposide	Local and distant (18m)	Yes (1.5m)	Cisplatin, etoposide	DF	84
Su et al.[4]	57	F	Multifocal (trunk)	CT, OMB	CHOP	No	No	N/A	DF	13
Current case	45	F	Single (trunk)	PET-CT, LNB	Radiotherapy	No	No	N/A	DF	8

*Most probably sALCL.

M male; *F* female; *CT:* computerized tomography; *PET-CT:* positron emission tomography CT;US: ultrasound; *OMB:* osteomedulary biopsy; *LP:* lumbar puncture; *LNB:* lymph node biopsy; *DF* disease free; *NR:* not reported; *CHOP* cyclophosphamide, adriamycin, vincristine, prednisone; *N/A* not applicable; *DOD* death of disease

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