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ALK-positive (2p23 rearranged) anaplastic large cell lymphoma with localization to the skin in a pediatric patient

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Abstract

Anaplastic large cell lymphoma (ALCL) either as primary cutaneous or nodal disease is rare in children and difficult to distinguish, which is important both prognostically and for treatment purposes. We present a case of ALK+ skin-limited ALCL that highlights these challenges and draws attention to pitfalls in assessing ALK status. The patient is an 11-year old girl with a twice recurrent nodule on her right shoulder. Each biopsy revealed a deep infiltrate of atypical lymphocytes that expressed CD3, CD4, CD43, CD45RO and CD30. The initial biopsy was EMA+ with vague cytoplasmic ALK-1 positivity by immunohistochemistry, while the second biopsy was EMA+ and nuclear ALK-1+. Fluorescence in situ hybridization (FISH) analysis for an ALK (2p23) rearrangement of the first specimen was negative, while ALK gene was found in 18% of cells in the second specimen. Therefore, this case was treated as nodal ALCL despite negative bone marrow and radiographic imaging studies. The patient was treated with combination chemotherapy and remains disease-free. Demonstration of nuclear ALK-positivity, ALK (2p23) gene rearrangement is suggestive of systemic ALCL but without evidence of systemic disease, this case raises the possibility of skin-limited ALCL, whose clinical behavior as either cutaneous ALCL systemic ALCL may not be immediately apparent.

Report of a patient

An 11 year-old female with no prior medical history presented with three months of a persistent, tender nodule in the right axilla. The lesion was initially treated with oral antibiotics, including a course of clarithromycin, however, when it failed to resolve, an excisional biopsy was performed. A pathologic diagnosis of anaplastic large cell lymphoma (ALCL) was rendered, and the patient was referred to our institution for care.

Histopathologic review of the biopsy showed a 1 cm wide, ulcerated, deep pan-dermal and subcutaneous diffuse infiltrate of small monomorphic and many large pleomorphic mononuclear cells wreath-like and horseshoe-shaped cells (Figs. 1A and B). Both cell populations extended into the epidermis and obliterated adnexal structures, with focal

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angiocentrism and intravascular involvement.(Fig. 1C). Immunohistochemical stains for CD3, CD4, CD43, CD45RO and CD30 and EMA were strongly and diffusely positive in the neoplastic population. Anaplastic lymphoma kinase (ALK-1) staining showed only a vague cytoplasmic positivity. Fluoresence in situ hybridization (FISH) studies for t(2:5) translocation was negative, despite which the overall findings were suspicious for the possibility of ALCL.

Upon clinical evaluation in our clinic, four weeks after the initial biopsy, a new 0.5 cm, raised, erythematous, non-tender papule was noted on the right shoulder, close to the prior biopsy site. An excisional biopsy was performed. Pathologic evaluation was notable for a superficial and deep multinodular, peri-adnexal and interstitial infiltrate of both small and large atypical cells, with focal involvement of the overlying hyperplastic epidermis (Figure 1D). Immunohistochemical stains for CD3 and CD20 demonstrated a mixture of B and T cells; significantly the large atypical lymphocytes were strongly positive for CD30 (Figure 2,A) and EMA with strong nuclear positivity for ALK-1 (Figure 2,B). FISH analysis of ALK (2p23) in this specimen, performed using the dual color–labeled ALK probe (Vysis, Downers Grove, IL) following the manufacturer's protocol, revealed rearrangements of the ALK gene in 18% of the cells (Figure 3). A bone marrow biopsy was performed and was found to have no morphologic evidence of lymphoma. Lumbar puncture was negative for blasts. Positron emission tomography/computed tomography (PET/CT) scan was negative for extracutaneous disease. Given the size, dense sheet-like arrangement of cells, subcutaneous extension, ulceration of the first lesion, and strong nuclear ALK positivity identified in the second specimen, the findings were felt to be those of a skin-localized lymphoma, specifically, an extracutaneous/nodal ALCL, limited to the skin (stage II ALCL, immunophenotype B, ALK-positive, extramedullary disease: skin). The patient was treated with three cycles of Dexamethasone, Methotrexate, Cyclophosphamide, Cyarabine, Etoposide and Vinblastine, alternated with 3 cycles of Dexamethatsone, methotrexate, Cyclophosphamide, doxorubicine and vinblastine. She tolerated the regimen well, however, post-therapeutic complications included *Clostridium Difficile* colitis. The patient has now been free of disease for 3 years.

Discussion

ALCL comprises up to 15% of all pediatric non-Hodgkin's lymphoma (1). ALCL is subclassified into 2 groups by the World Health Organization (WHO): (i) primary cutaneous ALCL and (ii) systemic ALCL, which is further categorized into ALK-positive and ALK-negative groups based on the expression of ALK. ALK-positive systemic ALCL has a 5-yr survival rate of 70-100%, whereas ALK-negative systemic ALCL has a 5-yr survival rate of 15-45% (2).

Cutaneous ALCL is a rare form of ALCL, comprising 8-10% of cases (3, 4), and is characterized by an indolent disease course, often resulting in spontaneous remission and a favorable prognosis with 90% 5-yr survival. (5, 6) Cutaneous ALCL often presents in older individual with a median age of 60 years,(7) with 50% of cases presenting as a solitary lesion and 25% presenting with generalized lesions.(4) However, cutaneous ALCL comprises approximately 1/3 of primary cutaneous T-cell lymphoma in children, with a

similar disease course to that in adults. Cutaneous ALCL appears to have a different pathophysiology from systemic ALCL, and often lacks a t(2;5) translocation as described below.(8)

ALK protein expression is associated with a t(2;5) translocation resulting in a fusion protein that joins the N-terminus of nucleophosmin (NPM) to the C-terminus of ALK. This translocation results in the aberrant expression of NPM-ALK, a tyrosine kinase that may trigger malignant transformation through phosphorylation of various intracellular targets. Most ALK-positive tumors are variations of systemic ALCL, which frequently involve extranodal sites such as the skin. In fact, 18-25% of pediatric systemic ALCL cases develop skin involvement, and this is a poor prognostic factor. (9, 10) Published case reports of pediatric cutaneous ALCL have inconsistently explored the expression of ALK in skin lesions, although it is generally considered that cutaneous ALCL is ALK-negative both at the molecular and protein level (11, 12). Recently however, there have been increasing reports of ALK-positive cutaneous ALCL in pediatric patients such as those in the case series by Oschlies et al.(13) The growing numbers of such cases make it more difficult to rely upon ALK expression as a reliable discriminator of systemic ALCL in a pediatric patient.

The distinction between cutaneous ALCL and systemic ALCL, in children, as in adults, is of great importance given that chemotherapy is only indicated for the treatment of patients with cutaneous ALCL who develop extracutaneous disease and is not appropriate for skin-limited cutaneous ALCL. In contrast, systemic ALCL generally requires intensive systemic polychemotherapy. It can be diagnostically difficult to distinguish between skin-lesions of cutaneous ALCL, and secondary systemic ALCL, however. Both may present as localized or multifocal cutaneous disease. Skin-only disease may rarely be considered a manifestation of skin-limited systemic ALCL, such that reliance on imaging to rule out systemic involvement may not be sufficient to capture the potential for nodal behavior. This is where ALK has been helpful in the past. Fortunately, the prognosis of both ALK-positive cutaneous ALCL and ALK-positive systemic ALCL appears to be favorable in children regardless of classification, although it remains controversial whether this is due more to the younger age rather than the ALK status. Therapeutic decision making is therefore the crux of the issue.

Efforts to better distinguish between cutaneous ALCL and systemic ALCL have included examination of key antibody staining patterns. The multiple myeloma oncogene 1 (MUM1), is expressed in 80-100% of systemic ALCL.(4, 14) and similarly in 100% of cutaneous ALCL cases (15). Most cutaneous ALCL cases express the cutaneous lymphocyte antigen (CLA) but lack epithelial membrane antigen (EMA) expression, unlike nodal systemic ALCL (15). It was previously postulated that EMA/MUC1 is preferentially expressed by ALK-positive anaplastic large-cell lymphoma but all such cases were of systemic nodal origin (16). Over the last few years, there have been reports of ALCL with skin-only involvement in younger children, some EMA+, but with ALK status being unknown. Interestingly, in all of these cases, the reported patients had good clinical outcomes regardless of treatment modality and regardless of EMA or clusterin status(17) More recently, Hinshaw et al reported 3 cases of ALK-positive cutaneous ALCL with good outcomes, one with chemotherapy and two with surgery and observation(18) The 6 cases of

skin-limited ALK and EMA-positive pediatric ALCL reported by Oschlies et al.(13) were successfully conservatively treated with local excision and/or radiotherapy. These findings suggest that ALK positivity in children may not have the same significance as in adults with skin-only disease, and that aggressive therapy, as typically given for ALK-positive lymphoma, may not be warranted in such cases.

In cutaneous ALCL cases, ALK localization is either cytoplasmic or cytoplasmic and nuclear. Recent reports have demonstrated that ALK protein expression in ALCL may occasionally be the result of ALK rearrangements other than NPM-ALK. Estimates of the frequency of these other rearrangements can be deduced from the number of reported ALK-positive cases without t(2;5) or on the number of cases without nuclear staining. Cases without nuclear staining are unlikely to be associated with the *NPM-ALK* rearrangement since this results in both cytoplasmic and nuclear staining of the neoplastic cells attributable to dimerization of NPM-ALK fusion protein with wild-type NPM, which carries nuclear localization motifs.(19) 10-20% of ALK-positive cases have been reported to carry ALK rearrangements other than NPM-ALK. (20) Cases of cutaneous ALCL with cytoplasmic ALK have been previously described (21-23). Sasaki et al(22) reported a 54-year-old Japanese woman presenting with an ulcerated nodule comprised of an inflammatory infiltrate that was CD3-negative but positive for CD30, CD4, and CD25, with a monoclonal T-cell receptor [beta] gene rearrangement. This case showed cytoplasmic expression of ALK, suggesting a variant other than the t(2;5) transcript was responsible for the ALK positivity. A second patient had cutaneous ALCL manifested as skin nodules that showed a cytoplasmic ALK staining pattern, without evidence for expression of the NPM-ALK fusion transcript by reverse transcription-polymerase chain reaction analysis. Both Kadin et al.(24) and Aoki et al(23) each reported a patient with cutaneous ALCL staining for cytoplasmic ALK.

Of the cutaneous ALCL cases reported by Oschlies et al,(13) 5 of 6 reported to be ALK-positive by immunohistochemistry (both nuclear and cytoplasmic) showed no evidence of systemic involvement, and all were treated by complete excision (along with adjunctive radiation in one case). The dual localization of the labeling pattern suggests the possibility of a role for the NPM-ALK transcripts in these 5 cases while one case, with only cytoplasmic staining, might have been an unknown and different ALK rearrangement. In our case, we saw strong nuclear staining in the absence of any cytoplasmic staining, which is in agreement with previously reported nuclear ALK localization in cases with NPM-ALK transcripts, the majority of which are systemic ALCL(17).

In children, CD30-positive lymphoproliferative disorders are rare. Within the English literature, approximately 100 cases of these lymphoproliferative disorders in children have been reported, the majority of which are comprised by cases of lymphomatoid papulosis and for which there is a lack of agreement about clinical course and management. There have been no case reports of ALK-positive lymphomatoid papulosis but a negative ALK status in addition to a CD30+ lymphocytic infiltrate does not confirm the diagnosis of lymphomatoid papulosis. The diagnosis relies on 3 parameters: typical papulonectrotic or papulonodular lesions, supportive histopathologic features and a clinical course that is marked by spontaneous disappearance and recurrence (waxing and waning). In the skin, distinguishing

ALCL from lymphomatoid papulosis is most important for prognosis (95% vs 100% survival in 5 years) and therapy (surgery/radiation therapy vs. none), so the true clinical significance may be small. In our case, we considered the diagnosis of lymphomatoid papulosis, but in the context of clear ALK expression and translocation, the findings altogether were best regarded as skin-limited systemic ALCL. We note however, that the surgical and chemotherapeutic treatment of the disease made it impossible to know what the natural course of disease might have been.

In the present case, the initial ALK immunohistochemistry was suboptimal, perhaps because poor tissue fixation precluded good hybridization of both the antibodies and the FISH probes. Therefore, another consideration when ALK is cytoplasmic and not nuclear, is that one may need better preserved tissue, as well as that other ALK rearrangements may be present. This is particularly important because cytoplasmic ALK alone in skin-only disease may bias the diagnosis towards cutaneous ALCL. In fact, it may well be that many or all of the ALK-positive cutaneous ALCL cases reported are actually skin-limited systemic ALCL. One of the skin-only pediatric cases reported in the series by Oshilies et al.(13) was positive for minimal disseminated disease, confirmed by PCR-detected NPM-ALK transcripts in bone marrow and blood despite staging work-up with imaging and bone marrow biopsy being negative for ALCL. This was the only patient in the series treated with chemotherapy and was reported to do well with no recurrence. Our patient was similarly treated with chemotherapy given the concern for systemic disease despite skin-limited presentation.

In summary, we present a rare case of skin-limited t(2:5) translocated ALCL in a pediatric patient with a thus far indolent disease course, in the context of an evolving literature on this disease. We feel that the presence of the translocation, ALK- and EMA-positivity in the absence of any clinical evidence of systemic involvement suggest a diagnosis of skin-limited variant of systemic ALCL. The decision to treat the patient with chemotherapy was made prior to the publication of the few ALK-poisitive cutaneous ALCL cases. It may well be that this case reflects a rare variant of cutaneous ALCL, but given the age of the patient, the unusual cytogenetics and the paucity of ALK-positive cutaneous ALCL cases in literature, a decision to treat this case as skin-limited form of SALCL was made. This case highlights the careful considerations by the clinician, pathologist and patient that have to be made in each individual case given how very little is known about long-term outcomes. Further studies assessing for unusual translocation partners in skin limited ALCL in pediatric populations will likely yield more information about this disease. Such cases should be evaluated on an individual basis with adequate staging, and aggressive pursuit of adequate tissue samples for molecular and immunohistochemical work-up.

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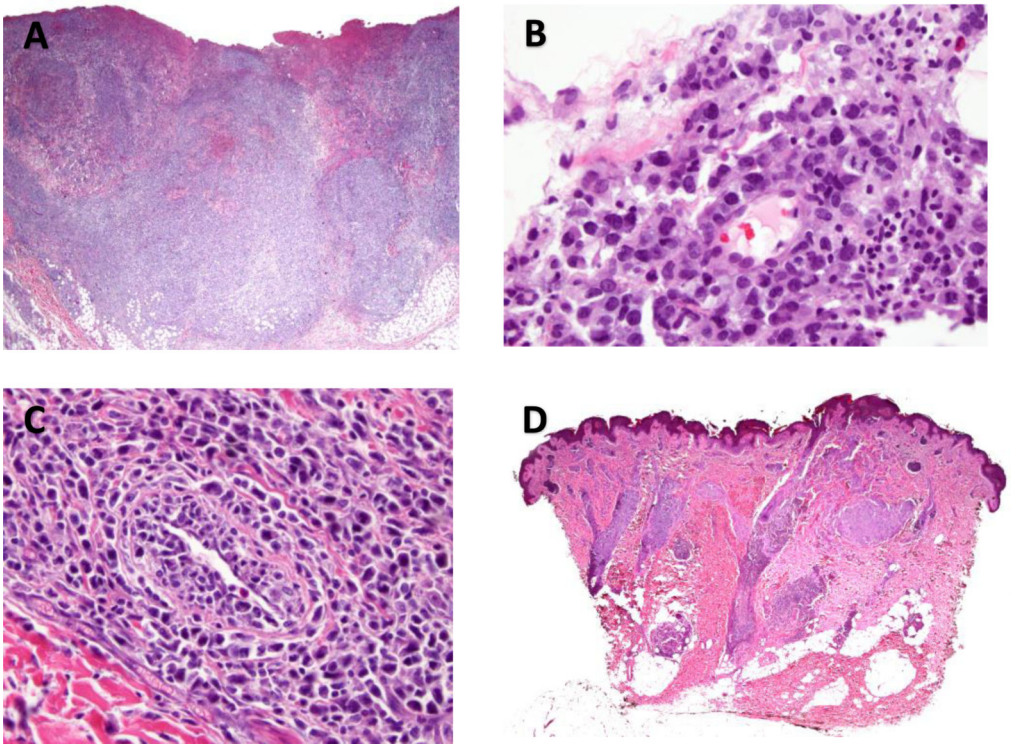

Fig. 1.

A) Skin biopsy specimen shows a pan-dermal infiltrate of monomorphic atypical lymphocytes from the first nodule, ×40, hematoxylin and eosin. B) Atypical lymphocytes from the first nodule are depicted, ×100, hematoxylin and eosin. C) There is a perivascular and intravascular infiltrate of atypical lymphocytes in the second nodule, ×40, hematoxylin and eosin. D) Skin biopsy specimen demonstrates a superficial and deep periadnexal infiltrate of leomorphic lymphocytes in the second nodule, ×40, hematoxylin and eosin.

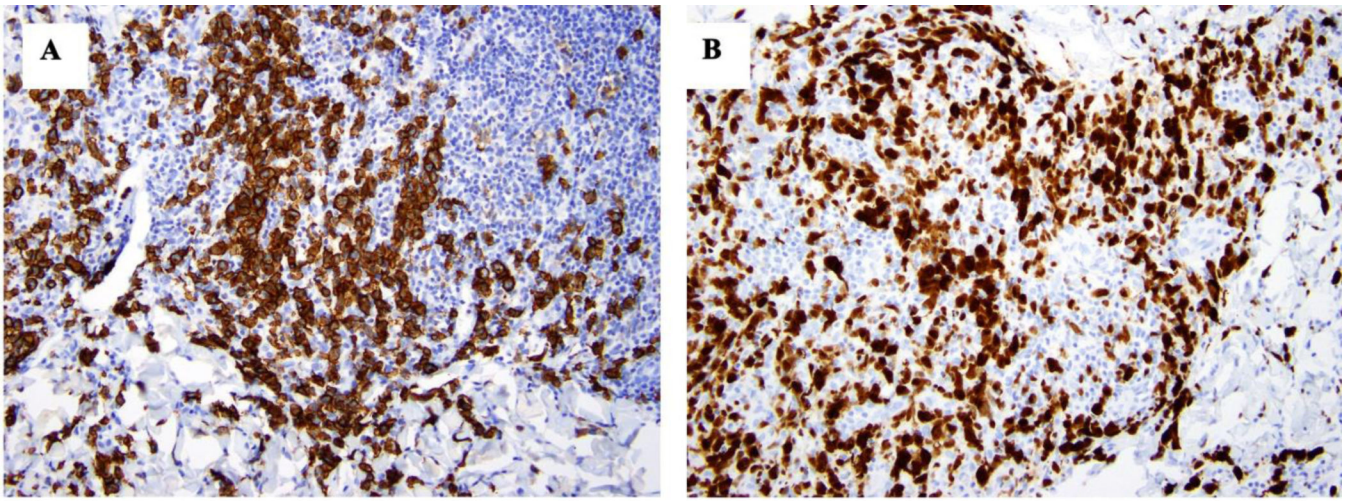

Fig. 2.

Immunohistochemical stains from the second nodule are depicted: CD30 (A), anaplastic lymphoma kinase (ALK) (B), ×40.

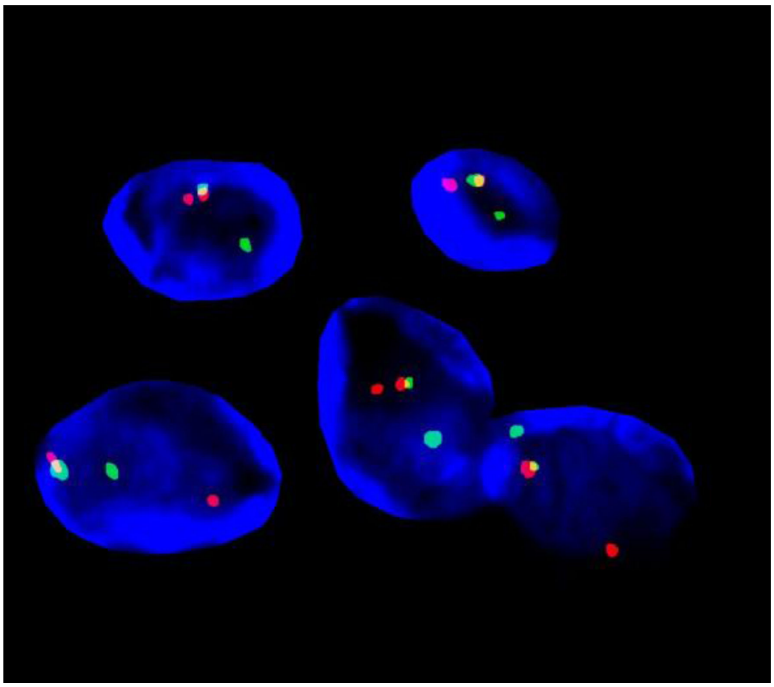

Fig. 3.

Fluorescence *in situ* hybridization (FISH) using a dual-color 2p23 LSI anaplastic lymphoma kinase (ALK) locus-specific probe on a paraffin-embedded section from the skin biopsy of the second nodule demonstrates separation of the red and green signals, thus indicating rearrangement in the 2p23 anaplastic lymphoma kinase gene locus.