Leukemia & Lymphoma, February 2016; 57(2): 480–482

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2015.1058935

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LETTER TO THE EDITOR

Spontaneous regression of a systemic ALK (+) anaplastic large cell lymphoma carrying ALK gene rearrangement that developed after PPD tuberculin skin test

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Here we report an ALK (+) ALCL carrying *ALK* gene rearrangement that developed after a PPD tuberculin skin test, which spontaneously regressed after an excisional lymph node biopsy and is still in complete remission more than 5 years later without treatment. Written informed consent was obtained from the patient for publication of this manuscript and accompanying images.

A man aged 38 years was admitted to our hematology clinic on receipt of his excisional biopsy pathology report in October 2008. The patient was otherwise healthy and he was asymptomatic. In August 2008, he had noticed aching and swelling in his left armpit 2–3 days after a purified protein derivative (PPD) skin test had been conducted to his left arm. He had also developed high grade fever. The patient's primary care physican first considered it to be an allergic hypersensitivity reaction, and nonsteroidal anti-inflammatory drugs were prescribed. However in the following days the swelling in the left axillary region increased, high grade fever, fatigue, loss of appetite, and weight loss added to his symptoms. A left axillary ultrasound was performed which showed multiple conglomerated lymph nodes, up to 3 × 2.5 cm in diameter. With the exception of the multiple conglomerated left axillary lymph nodes, there was no evidence of disease in any other region, in computerized tomography scans of the neck, chest and abdomen. In his laboratory tests, the white blood cell count was 5300/μL

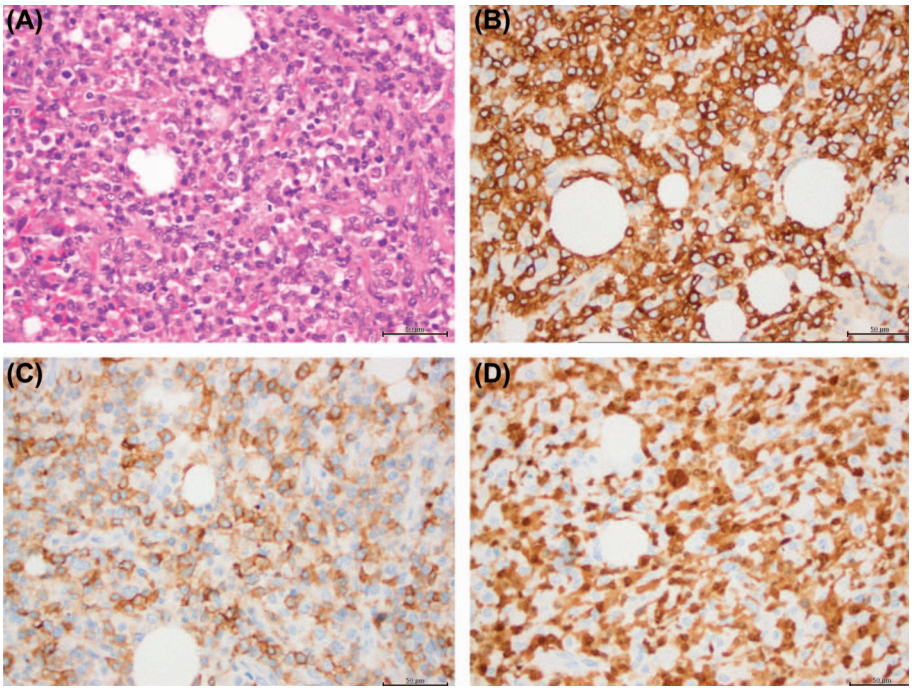

Figure 1. Neoplastic cells are generally medium-sized. Few of them have eccentric kidney-shaped large nuclei ("hallmark" cells). HE × 40 (A); CD30 × 40 (B); EMA × 40 (C); ALK1 × 40 (D).

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Received 16 February 2015; revised 14 April 2015; accepted 31 May 2015

hemoglobin was 12.5 g/dl, platelet count was 248000/mcL, LDH was 423 U/L (N:135–225), erythrocyte sedimentation rate was 26 mm/hour and β2-microglobulin was 2.2 mg/L (N: 0.7–1.8). Tests for HBV, HCV and HIV were negative. Tuberculosis lymphadenitis was then suspected and an excisional biopsy was performed. The patient reported that, his fever had resolved immediately after the biopsy. The result of the biopsy was consistent with ALK(+) anaplastic large cell lymphoma. Fluorescent *in situ* hybridization using a break apart probe was positive for *ALK* gene rearrangement. Immunohistochemical staining with ALK showed strong nuclear and cytoplasmic staining, which was consistent with t(2;5)(p23;q35) (Figure 1). At the time of admission the patient had no peripheral lymphadenopathy, splenomegaly or hepatomegaly. The patient's LDH and β2-microglobulin levels both normalized (LDH:188 U/L, β2-microglobulin: 1.6 mg/L). A PET/CT was performed which showed no evidence of disease. In conclusion there was no sign of residual disease after excisional biopsy. Due to the fact that this lesion had developed after a PPD test, and the symptoms had completely resolved immediately after the lymph node excision, with no further evidence of disease present, we decided to follow-up the patient without treatment. In the follow-up we saw no signs of disease progression. The patient is still in complete remission as of January 2015 without having received any kind of treatment.

Anaplastic large cell lymphomas (ALCLs) are a subtype of peripheral T cell lymphomas that express CD30. They account for less than 5% of all cases of non-Hodgkin lymphomas (NHLs). The World Health Organization (WHO) classification currently recognizes three entities: systemic anaplastic lymphoma kinase (ALK)-positive ALCLs, systemic ALK-negative ALCLs, and primary cutaneous ALCLs (pcALCLs). In addition, primary breast ALCL, which is exclusively associated with breast implantation, is another entity with favorable prognosis and is ALK (-). Cells in ALK(+) ALCL express an ALK fusion protein derived from an ALK rearrangement, and also express CD30. The best described and most frequent translocation, t(2;5)(p23;q35), causes the nucleophosmin (NPM) gene (5q35), to fuse with the ALK portion on chromosome 2p23. The translocation product, NPM-ALK, acts as an active tyrosine kinase, which triggers malignant transformation, and activates antiapoptotic pathways. This translocation can be seen in 70–75% of ALK (+) ALCLs [1–4].

Systemic ALCL is an agressive type of NHL which is lethal if left untreated. Although, it is known that primary cutaneous ALCLs may spontaneously regress, spontaneous regression of a systemic ALCL is very rare. However primary cutaneous ALCLs are classically ALK (-), which are generally confined to the skin and categorized as a different entity. ALK positivity, younger age, normal LDH level, good performance status, early stage, absence of extranodal involvement and low IPI score are reported as favorable prognostic factors for systemic ALCL [5–6].

In the literature, only four cases of spontaneously regressing systemic ALCL have been reported. None of them had skin infiltration. Of these cases, three progressed in follow-up and required treatment. Only one case remained in remission

Table I. Reported cases of spontaneously regressed systemic ALCLs.

Age (years)	Sex	Accompanying condition	Skin lesion	B symptom	Stage	IPI	ALK	t(2;5)	Relapse after spontaneous regression	Clinical course	Treatment
12	F	Sjogren Syndrome	(−)	(+)	IB (at diagnosis) IB (at relapse)	Low	(+)	(+)	(+)	Diagnosed in 1987. Relapsed in 1995. Treated in relapse.	Vincristine, methotrexate, bleomycin, cyclophosphamide, adriamycin, dexamethasone induction chemotherapy.
44	M	Not any condition reported	(−)	(+)	IVB	High	(+)	NA	(+)	Relapsed 2 months after discharge.	CHOP regimen.
77	M	Left soft palate mass occured just after buccal anesthesia injection.	(−)	(−)	IIA (at diagnosis) IIA (at relapse)	Low	NA, but tumor was positive for pan-B cell and CD30 positive.	NA	(+)	Remained in remission 12 months after spontaneous regression.	Remission achieved with 6 cycles of CHOP regimen.
35	F	No condition reported.	(−)	(+)	IB	Low	(+)	(+)	(−)	Still in remission without treatment.	Did not require treatment.
38	M	Left axillary mass occured just after PPD skin test.	(−)	(+)	IB	Low	(+)	IHC and BAP FISH for ALK gene rearrangement were positive. for t(2;5).	(−)	Still in remission without treatment.	Did not require treatment.

IPI, International prognostic index; ALK, Anaplastic lymphoma kinase; IHC, Immunohistochemistry, BAP, Break apart probe; FISH, Fluorescent *in situ* hybridization

without treatment. Consistent with these cases reported in the literature, our patient also showed B symptoms, was at a relatively young age, in an early stage of the disease, had ALK positivity and lower IPI score, which are favorable prognostic features for systemic ALCL. Interestingly, the shortest remission period (2 months) among these cases was observed in a patient aged 44 years who had advanced stage disease and a high IPI score. In a 77-year-old patient with left soft palate mass CD30 and pan-B-cell markers were positive which may indicate the patient was CD30 (+) B cell lymphoma instead of ALCL. The ALK status was also unknown in this case (Table I) [7–10].

Systemic ALK (+) ALCL frequently presents with extranodal involvement. Skin involvement has been reported in approximately 20–30% of all cases. The diagnosis of primary systemic ALK (+) ALCL displaying cutaneous involvement is difficult. It may be frequently misdiagnosed as an inflammatory disease in cases in which there is a clinical history of an inciting event like the application of PPD test in our case. In these cases, the investigation of the ALK status and verification of the accompanying t(2;5)(p23;q35) mutation/translocation leads to accurate diagnosis. In our case we used both to confirm our diagnosis.

Factors that render clinical decision making problematic in asymptomatic patients with ALCL include the aggressive nature of the disease and the difficulties in correct diagnosis. Once the correct diagnosis is made, treatment with systemic chemotherapy has a high success rate. However our case shows that treatment may not be always necessary in younger patients with early stage disease (especially stage I disease) and low IPI score in systemic ALK(+) ALCL. Complete resection of the involved lymph node may be an important factor in such cases. A recent study published by Attarbashci *et al.* supports this theory. In their study, all six patients with complete resection neither experienced relapse nor died following treatment of three cycles of chemotherapy, whereas relapse was observed in patients without full resection. This study was performed in a pediatric population [11].

The allergic hypersensitivity reaction after the PPD test was the first clinical presentation of primary systemic ALK(+) ALCL in our case. This phenomenon can be explained either as a coincidence or the patient may have had an occult disease of primary systemic ALK(+) ALCL when the PPD test was performed. It is also possible that cytokines induced by the PPD test stimulated the neoplastic cells to the site of inflammation via chemotaxis. Or tuberculin test antigens may result in an influx of T-lymphocytes, some of which may bear the t(2;5) translocation that results in the expression of the oncogenic nucleophosmin-ALK fusion protein, consequently resulting in uncontrolled proliferation. Similarly, we considered that there is a possibility that the tuberculin test antigens may have triggered this case of primary systemic ALK(+) ALCL. To our knowledge, this phenomenon has not previously been reported.

In conclusion, we report a case of primary systemic, ALK positive ALCL, carrying *ALK* gene rearrangement that developed after a tuberculin skin test which spontaneously regressed without any therapy. We emphasize the importance of showing ALK positivity for such cases and highlight that treatment may not always be required in patients who have good prognostic factors.

Acknowledgements

The authors of this letter thank Professor Ahmet Dogan, MD, PhD for performing break apart probe FISH to show the ALK gene rearrangement in this case report.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal

References

[1] Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. Adv Anat Pathol 2015;22:29–49.
[2] Pletneva MA, Smith LB. Anaplastic large cell lymphoma: features presenting diagnostic challenges. Arch Pathol Lab Med 2014;138(10):1290–1294.
[3] Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124–4130.
[4] Lazzeri D, Agostini T, Bocci G, et al. ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. Clin Breast Cancer 2011;11:283–296.
[5] 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.
[6] Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913–3921.
[7] Inaba H, Kawasaki H, Nakamura S, et al. Anaplastic large cell lymphoma associated with Sjögren's syndrome. Leuk Lymphoma 1998;32:183–188.
[8] Kashiwabara K, Nakamura H, Kusama H, et al. Ki-1 (CD30)-positive anaplastic large cell lymphoma, sarcomatoid variant accompanied by spontaneously regressing lymphadenopathy. Intern Med 1999;38:49–53.
[9] Savarrio L, Gibson J, Dunlop DJ, et al. Spontaneous regression of an anaplastic large cell lymphoma in the oral cavity: first reported case and review of the literature. Oral Oncol 1999;35:609–613.
[10] Patel P, Godwin J, Velankar M, et al. Nodal ALK positive anaplastic large cell lymphoma of the axilla with spontaneous regression. Leuk Lymphoma 2007;48:1250–1252.
[11] Attarbaschi A, Mann G, Rosolen A, et al. Limited stage I disease is not necessarily indicative of an excellent prognosis in childhood anaplastic large cell lymphoma. Blood 2011;117:5616–5619.