

ALK-positive Primary Systemic Anaplastic Large Cell Lymphoma with Extensive Cutaneous Manifestation

Kazuha Ando¹, Yasuhiko Tamada¹, Kazuyuki Shimizu², Yoichi Akita¹, Daisuke Watanabe^{1*}, Shigeru Nakamura³, Kazuo Hara⁴ and Yoshinari Matsumoto¹

¹Department of Dermatology and ⁴Division of Pathology, Aichi Medical University, Nagakute, Aichi, 480-1195, ²Department of Hematology, Midori Municipal Hospital and ³Department of Pathology, Nagoya University Graduate School of Medicine, Aichi, Japan. *E-mail: dwatanab@aichi-med-u.ac.jp
Accepted September 9, 2009.

Sir,

Anaplastic large cell lymphoma (ALCL) is a T-cell non-Hodgkin's lymphoma that has a histological appearance consisting of large lymphoid cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped, nuclei. The tumour cells are positive for CD30 on the cell membrane and in the Golgi body. Clinically, ALCL can be divided into three entities containing primary systemic anaplastic large cell lymphoma kinase (ALK)-positive ALCL, primary systemic ALK-negative ALCL, and primary cutaneous ALCL. ALK expression is detectable in approximately 75% of ALCL patients.

Primary systemic ALCL frequently involves both lymph nodes and extranodal sites such as skin, bone, lung and liver. On the other hand, primary cutaneous ALCL is usually ALK-negative and the disease is limited to the skin.

The usual cutaneous manifestations of primary systemic ALCL are red papules or nodules, but ALCL showing macules or plaques are quite rare. We describe here a case of ALK-positive primary systemic ALCL with a long clinical course and extensive cutaneous manifestation like that of cutaneous T-cell lymphoma.

CASE REPORT

A 37-year-old Japanese woman visited our hospital in November 2007 with an extensive cutaneous rash lasting for 3 years. Her medical history was as follows. At the age of 15 years she developed cervical lymph node swelling with fever and nasal bleeding for 2 weeks, then a solitary erosive red tumour 4 cm in diameter appeared on the right forehead (Fig. 1). She visited a local physician. Skin biopsies were performed from both the tumour and the lymph node and she was diagnosed with primary systemic ALCL (data not shown). Weekly CHOP therapy (cyclophosphamide 700 mg, doxorubicin 40 mg, vincristine 1 mg and prednisolone (PSL) 20 mg,) was given for eight cycles, followed by a course of VEMP (vincristine 1 mg, 6-MP 100 mg, cyclophosphamide 100 mg, PSL 5 mg, daily). However, after the 25th cycle of VEMP, red papules appeared on the left thigh and the skin biopsy from the lesion revealed recurrence of ALCL. Chemotherapy with doxorubicin 40 mg, methotrexate 30 mg and procarbazine 100 mg daily was then administered, followed by maintenance chemotherapy using cyclophosphamide 200 mg and PSL 10 mg. However, at the age of 25 years, she had recurring abdominal pain and diarrhoea lasting for one month. Computed tomography (CT) revealed swelling of a small intestinal mesenteric lymph node. The lymph node was removed operatively and histopathologically diagnosed as ALCL (data not shown). At the age of 34 years, the patient had to discontinue cyclophosphamide and PSL treatment due to hemorrhagic cystitis. At the same time, scaly erythema with induration appeared and gradually increased and distributed over the entire body surface.

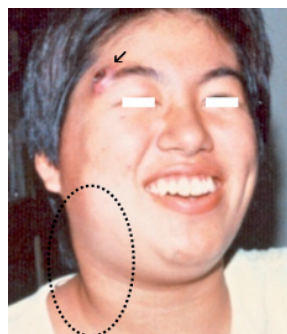


Fig. 1. Clinical features of the patient at the age of 15 years. Swelling of the cervical lymph node (dotted circle) and a solitary erosive red tumour with scaling, 4 cm in diameter, on the right forehead (arrow). The patient has approved the publication of this photo.

Physical examination revealed extensive red-brown macules and plaques, with scaling over the whole body (Fig. 2a–d). A red tumour, 2 × 2 cm in diameter, was also observed on the dorsum of the right foot (Fig. 2e). The clinical appearance resembled tumour stage of mycosis fungoides. She had no fever, night sweats, or weight loss. Laboratory tests revealed normal white blood counts of $8.9 \times 10^3/\text{ml}$, normal liver and renal functions, but serum lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) levels were increased slightly to 273 IU (normal 119–229 IU) and 814 U/ml (normal 145–519 U/ml) each. Anti-HTLV-1 antibody and antinuclear antibody (ANA) were negative. Southern blot analysis from the tumour on the dorsum of the foot confirmed clonal gene rearrangement of the T-cell antigen receptor (TCR) $\text{J}\gamma$ chain. Gallium-67 scintigraphy showed no abnormality. Positron emission tomography (PET)-CT revealed accumulation of fluoro-deoxyglucose (FDG) in the left cervical, bilateral axillary, and bilateral inguinal lymph nodes. No visceral lesions were detected.

Histopathological examination from the tumour on the dorsum of the right foot revealed dense infiltration of large, polymorphic, and atypical lymphoid cells from the epidermis to the deep dermis (Fig. 3a and b). Immunohistochemically, almost all tumour cells were positive for CD30 (Fig. 3b and c), ALK and EMA but, negative for CD3, CD4 CD5, CD20, CD56 and TIA-1 (data not shown). EBV gene encoding RNAs (EBER) were not detected by *in situ* hybridization. Histopathological examination of the left cervical lymph nodes showed atypical cells with large and irregular nuclei, which were CD30- and ALK-positive. With these clinical and pathological findings, the diagnosis of primary systemic ALCL with extensive cutaneous manifestation was made.

Because the patient refused systemic chemotherapy, the cutaneous lesions were treated with intramuscular interferon- γ injection, and oral psoralen plus ultraviolet A (PUVA) therapy. Photodynamic therapy was also applied to the facial lesions. After 80 J of oral PUVA therapy, the erythematous lesions were alleviated, but the skin nodule lesions persisted.

DISCUSSION

ALCL was first described by Stein et al. in 1982 (1) and is either ALK-positive or ALK-negative. ALK expression is related to a non-random t(2; 5)(p23; q35) chromosomal translocation, which fused with the nu-



Fig. 2. Clinical features of the patient at her first visit to the hospital (37 years old). Many erythematous and pigmented macules and plaques with infiltration on: (a) the face; (b) the trunk; and (c and d) the lower extremities. The cutaneous lesions resemble those of mycosis fungoides. (e) Red tumour on the dorsum of the right foot. The patient has approved the publication of these figures.

cleophosmin (NPM) gene, resulting in the expression of p80 chimera proteins, i.e. NPM/ALK transcripts (2). In 1995, Shiota et al. (3) first reported that ALK expression influences the prognosis of systemic ALCL. In 1999, Gascoyne and colleagues (4) reported that the ALK-positive systemic ALCL patients have a better prognosis of 79.8% 5-year survival rate, compared with a rate of 32.9% for other ALK-negative systemic ALCL patients, although the clinical behaviour of individual patients remains unpredictable.

Primary ALK-positive systemic ALCL frequently involves both lymph nodes and extranodal sites. Extranodal lesions commonly include skin (21%), bone (17%), soft tissue (17%), lung (11%) and liver (8%), while central nervous system involvement is rare (5). Cutaneous manifestations of primary systemic ALCL are usually solitary or multiple red papules or nodules (6, 7).

In our patient, cervical lymph node enlargement and a cutaneous tumour first appeared when she was 15 years old, and approximately 10 years later ALCL lesion recurred in the mesenteric lymph node. Although our patient was treated with multiple chemotherapies, extensive skin lesions, clinically and histopathologically resembling mycosis fungoides, appeared when she was

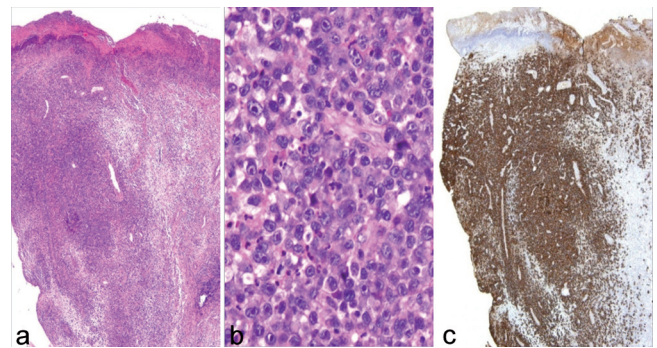


Fig. 3. Histopathological findings for the red tumour. (a) Sheet-like proliferation of atypical lymphocytes is seen from the epidermis to the subcutaneous fat tissue (haematoxylin-eosin stain $\times 40$). (b) At higher magnification, infiltrated cells are composed of large, polymorphic, and atypical lymphoid cell (haematoxylin-eosin stain $\times 200$). (c) Immunohistochemical staining for CD30.

34 years of age. To our knowledge, this is the first case report of such cutaneous manifestations of systemic ALCL. It is possible that the mycosis fungoides-like skin lesions arose as secondary lymphoma. However, although we could no longer confirm the clonality, we believe that the two lymphomas are identical because of the same positive staining pattern of CD30, ALK and EMA in the atypical cells.

Recently, systemic ALCL has been treated using multidrug chemotherapy including doxorubicin (8–10), with a complete response rate of 95%. However, recurrence has been reported in more than 40% of patients (9–11). Although a favourable prognosis is expected with ALK-positive ALCL and the extranodal lesion is currently limited to the skin, close follow-up will be needed for our patient.

The authors declare no conflict of interest.

REFERENCES

- Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, et al. The expression of the Hodgkin disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985; 66: 848–858.
- Stein H, Foss HD, Dürkop H, Marafioti T, Delsol G, Pulford K, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood* 2000; 96: 3681–3695.
- Shiota M, Nakamura S, Ichinohasama R, Abe M, Akagi T, Takeshita M, et al. Anaplastic large cell lymphomas expressing the chimeric protein p80 NPM/ALK: a distinct clinicopathologic entity. *Blood* 1995; 86: 1954–1960.
- Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. *Blood* 1999; 93: 3913–3921.
- Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; 105: 3768–3785.
- Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F,

- Geerts ML, van Vloten WA, 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.
7. Mencia-Gutiérrez E, Gutiérrez-Díaz E, Salamanca J, Martínez-González MA. Cutaneous presentation on the eyelid of primary, systemic, CD30+, anaplastic lymphoma kinase(ALK)-negative, anaplastic large cell lymphoma(ALCL). *Int J Derm* 2006; 45: 766–769.
 8. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peters C, et al. ALK+ lymphoma: clinico-pathological findings and outcome. *Blood* 1999; 93: 2697–2706.
 9. Brugières L, Deley MC, Pacquement H, Meguerian-Bedoyan Z, Terrier-Lacombe MJ, Robert A, et al. CD30+ Anaplastic large-cell lymphoma in children: analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. *Blood* 1998; 92: 3591–3598.
 10. Amin HM, Lai R. Pathobiology of ALK+ anaplastic large-cell lymphoma. *Blood* 2007; 110: 2259–2267.
 11. Brugières L, Quartier P, Le Deley MC, Pacquement H, Perel Y, Bergeron C, et al. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children – a report from the French Society of Pediatric Oncology. *Ann Oncol* 2000; 11: 53–58.