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CASE REPORT

# Indolent adult T-cell leukaemia-lymphoma successfully treated with bexarotene in an eldery patient

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## Abstract

Adult T-cell leukaemia-lymphoma (ATL) is a mature T-cell malignancy, with more than 50% of cases showing cutaneous involvement. Patients with cutaneous-type ATL (cATL) in the indolent type (i.e., favourable chronic or smouldering type) can usually be managed by watchful waiting and they are primarily treated with skin-directed therapies until the disease progresses to acute crisis, with multiple tumours usually considered intractable. ATL tends to present in older patients, and those with multiple cATL tumours face difficulties in obtaining multiagent chemotherapy used for aggressive types. Although bexarotene is a third-generation novel retinoid X receptor-selective retinoid treatment that is effective for cutaneous T-cell lymphoma, few reports have demonstrated its effectiveness for cATL. We describe an 86-year-old woman with cATL treated safely and successfully with a combination of oral bexarotene and skin-directed therapies, despite renal dysfunction and previous hypothyroidism. After 10 months of treatment, we observed neither new tumours nor disease recurrence, with complete response maintained at 24 months until now while continuing bexarotene. Our experience suggests that oral bexarotene is an effective treatment option, even for elderly patients with cATL.

**KEYWORDS**
adult T-cell leukaemia-lymphoma, bexarotene, retinoids, skin-directed therapy

## INTRODUCTION

Adult T-cell leukaemia-lymphoma (ATL) is a mature peripheral CD4+ T-cell malignancy caused by infection with human T-lymphotropic virus type I (HTLV-1).[1] Over half of affected patients exhibit skin manifestations.[2–4] Although the indolent type (i.e., favourable chronic or smouldering type) is usually managed by watchful waiting until it progresses to acute crisis,[5] patients with indolent cutaneous-type ATL (cATL) primarily require skin-directed therapies, including topical steroids, narrow-band ultraviolet B phototherapy, and local electron beam irradiation. Cutaneous involvement in the indolent type might be an independent risk factor for a poor prognosis.[6–8] Patients with intractable tumours are occasionally treated with multiagent chemotherapy used for aggressive types. However, given a median age of 68 years (interquartile range: 60−75 years) at diagnosis in Japan,[9] many elderly patients with multiple tumours can face difficulty accessing such

aggressive treatment. In the presence of disease that is refractory to skin-directed therapies, these patients typically receive interferon-gamma, oral retinoids, single-agent chemotherapy, and mogamulizumab (anti-CCR4 antibody). Bexarotene is a third-generation novel retinoid X receptor-selective retinoid that has efficacy for treating cutaneous T-cell lymphoma.[10] Despite evidence that all-trans retinoic acid[11] and etretinate[12,13] can reduce skin involvement in cATL (Supporting Information: Table 1), few reports have described the efficacy of oral bexarotene in this setting. We therefore describe an elderly patient with cATL in whom cutaneous lymphoma lesions were successfully treated with oral bexarotene.

## CASE REPORT

An 86-year-old woman was hospitalized with a 1-month history of indurated red tumours on her left cheek, back, and thighs (Figure 1). Investigation confirmed a diagnosis of smouldering type ATL with a modified severity-weighted assessment tool (mSWAT) score of 10.75.

Briefly, skin biopsy from a tumour on her right thigh revealed dense infiltration of atypical lymphocytes in the upper dermis and Pautrier's microabscesses in the epidermis (Figure 2). Immunostaining confirmed that the atypical cells were positive for CD3, CD4, and CD25, and negative for CD20, while Southern blot confirmed the monoclonal integraion of HTLV-1 proviral DNA. Haematological examination revealed no abnormal lymphocytes. Serum testing was positive for anti-HTLV-1 antibody, and the soluble interleukin-2 receptor (sIL-2R) level was 1152 U/mL (reference range: 121−613). Serum lactate dehydrogenase and calcium were normal. Finally, computed tomography showed swollen bilateral inguinal lymph node measuring approximately 1 cm in diameter.

Figure 3 illustrates the clinical course. Her initial treatment comprised a topical steroid, narrow-band ultraviolet B phototherapy to small tumours on her thighs, and local electron beam irradiation (60 Gy) to large tumours on her left cheek and back. Although these caused most tumours to shrink, new nodules appeared on her thighs and the lower abdomen. Based on her age, renal dysfunction, and previous hypothyroidism, we did

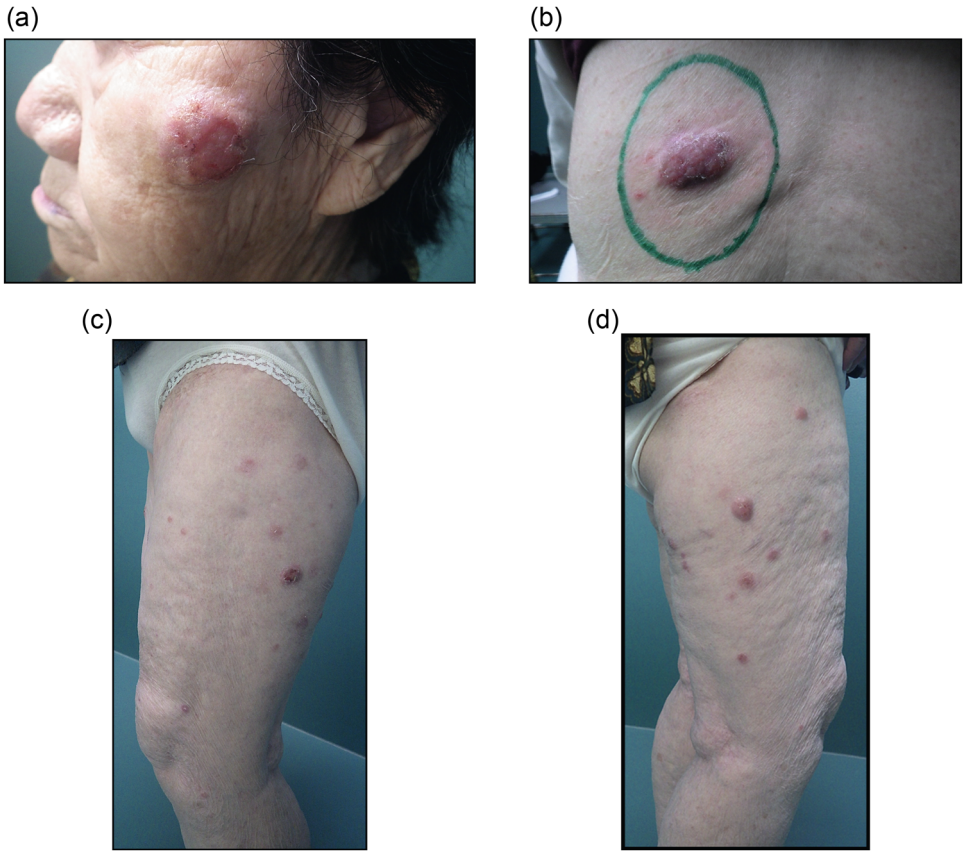


**FIGURE 1** Clinical features at first medical examination. At presentation, the patient had multiple tumours on her left cheek (a), back (b), and both thighs (c, d).

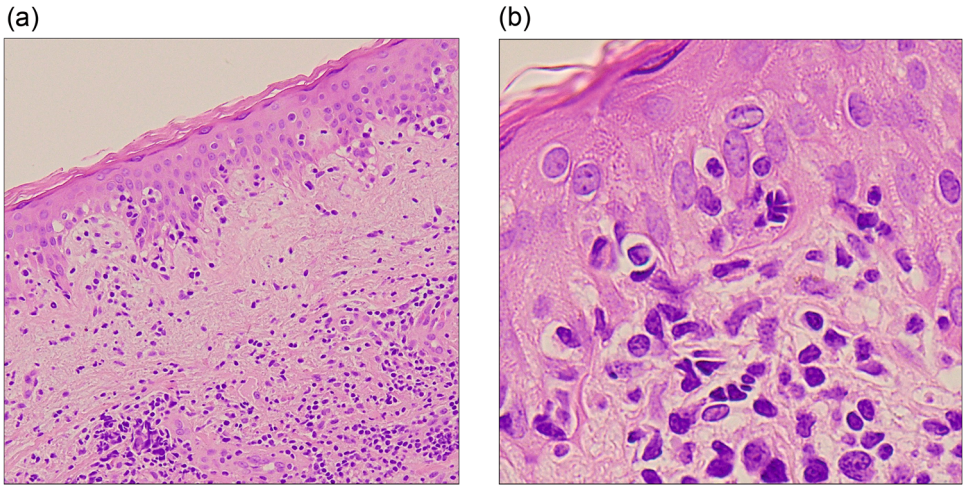


**FIGURE 2** Histopathology of skin biopsy. Hematoxylin-eosin staining of skin biopsy showing dense infiltration of atypical lymphocytes in the upper dermis and Pautrier's microabscesses in the epidermis. Magnifications: (a) ×100; (b) ×400.

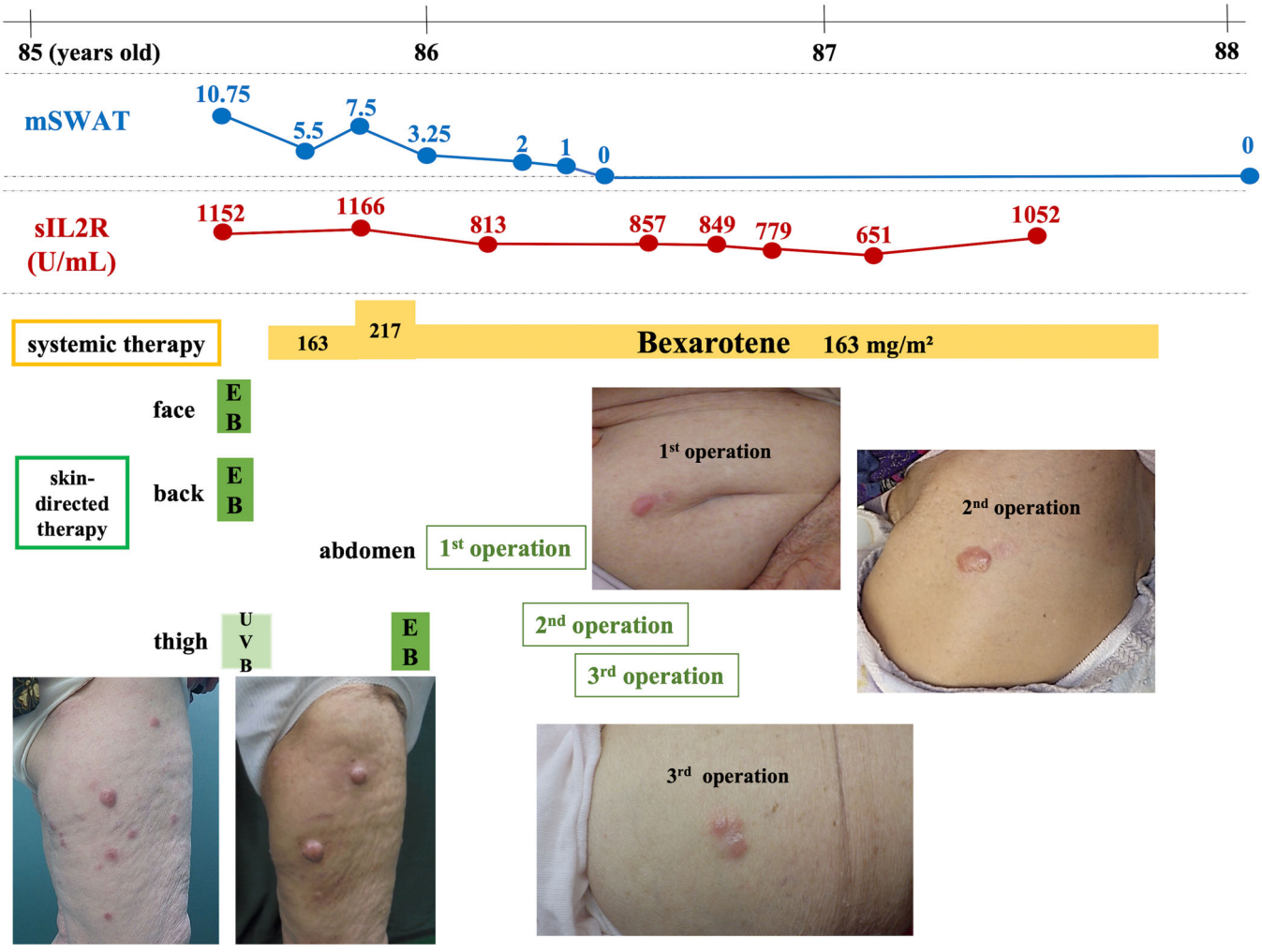


**FIGURE 3** The clinical course of the patient. Tumours were resected surgically from the skin of her abdomen (first operation) and both thighs (second and third operation). The mSWAT score gradually improved with combining oral bexarotene and skin-directed therapies. EB, electron beam; mSWAT, modified severity-weighted assessment tool; UVB, ultraviolet B phototherapy.

not consider aggressive treatment to be suitable and initiated treatment with oral bexarotene at a dosage of 160 mg/m$^2$/day (225 mg/day), complemented with a topical steroid. Thyroid hormone was maintained normally with oral levothyroxine sodium, but 1 week after starting oral bexarotene, asymptomatic but mild hypopituitary hypothyroidism was observed, which improved promptly with an updosing of levothyroxine sodium. Other than above, no adverse events were observed. The nodules on the thighs temporarily disappeared, but new red tumours reappeared in the same location during 10 months after starting treatment, so additional local electron-beam radiation (60 Gy) was administered. After this second electron irradiation, three masses in the nonirradiated areas of the abdomen (first) and thighs (second and third) were surgically resected. Immunostaining of the final operation sample revealed that more than half of the atypical cells were positive for programmed death-1 (PD-1). Thereafter, the patient has continued to take bexarotene, and although serum sIL-2R levels have fluctuated, the skin lesions have remained in a complete remission for 24 months until now and the slightly bilateral swollen inguinal lymph node has remained stable (Figure 4).

## DISCUSSION

This report describes an 86-year-old woman with cATL. Despite her advanced age, renal dysfunction, and previous hypothyroidism, we safely treated cutaneous lesions with oral bexarotene and skin-directed therapies. Although the administration of mogamulizumab was also considered in this case, ADCC activity, which is responsible for the therapeutic effect of mogamulizumab, decreases with age.[14] In some cases, mogamulizumab can cause severe drug eruptions that may further worsen the quality of life. Therefore, we should use mogamulizumab with adequate attention to adverse events as other therapies. Furthermore, not mogamulizumab and bexarotene was volume-adjustable treatment according to adverse events. For these reasons, bexarotene was chosen in this case. Unfortunately, immunostaining revealed PD-1, a quantitative marker that predicts an unfavourable overall survival in patients with cATL.[15] This case formed rapidly from erythema lesions to masses, and then the masses increased rapidly. Although bexarotene monotherapy may not completely suppress the rapid progression of multiple tumours in such cases, the treatment response in this report demonstrates the

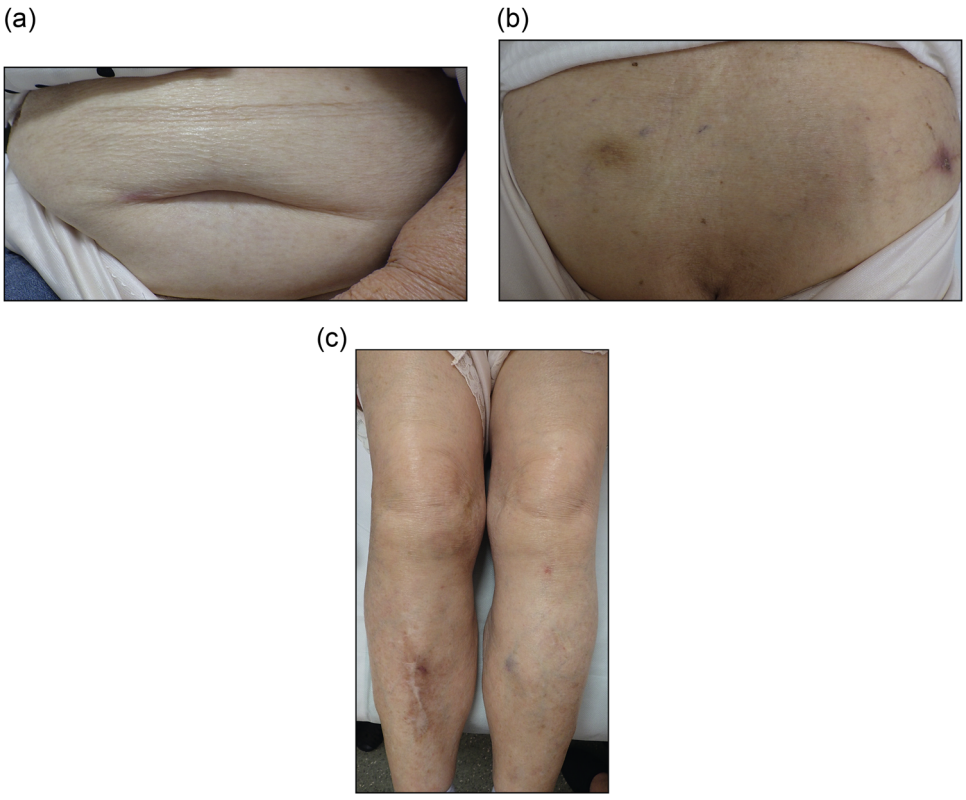


**FIGURE 4** Clinical features after the final tumour resection. After the final surgical resection, we observed neither recurrence of the skin lesions nor the development of new tumours. Complete response was maintained for 24 months until now while continuing bexarotene. We show clinical features of the area (a, abdomen; b, c, both thighs) where multiple tumours had previously appeared.

therapeutic benefit of combining oral bexarotene and skin-directed therapies. Indeed, our experience suggests that oral bexarotene could be an effective treatment option for elderly patients with cATL. However, further research is needed to validate these findings.

## AUTHOR CONTRIBUTIONS

Maho Nakashima and Moti Takenaka saw the patient. Maho Nakashima wrote the manuscript. Motoi Takenaka and Hiroyuki Murota edited the manuscript. All have approved the final version of the manuscript.

## CONFLICTS OF INTEREST STATEMENT

M. N. has received speaker's fees from Minophagen Pharmaceutical Co., LTD. H. M. has received fees to chair a sponsored seminar from Minophagen Pharmaceutical Co., LTD. The remaining authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## ETHICS STATEMENT

This study was approved by Nagasaki University Hospital Clinical Research Ethics Committee (22051623). All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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