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(Citation)
The Journal of Dermatology,50(7):e210-e212

(Issue Date)
2023-07

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100482872

CD4/CD8 double-negative T-cell lymphoma successfully treated with the combination of bexarotene and total skin electron beam therapy

RUNNING HEAD: CD4/CD8 double-negative T-cell lymphoma treated with bexarotene and TSEBT

Ayano Tanigawa[1], Takeshi Fukumoto[1] *, Shinya Imamura[1], Korefumi Nakanura[1], Tomonori Tanaka[2], Tomoo Ito[2], Eiji Nakano[1], Chikako Nishigori[1], and Akiharu Kubo[1]

[1]*Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 6500017, Japan*

[2]*Division of Pathology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 6500017, Japan*

CORRESPONDING AUTHOR: Takeshi Fukumoto, M.D., Ph.D.
Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
Tel.: +81-78-382-6134
Fax: +81-78-382-6149
E-mail: fuku@med.kobe-u.ac.jp

FUNDING STATEMENT: None.

CONFLICTS OF INTEREST: None.

INFORMED CONSENT: We obtained the written informed consent of the patient.

KEYWORDS: CD4/CD8 double-negative, T-cell lymphoma, bexarotene, total skin electron beam therapy

AUTHORS' CONTRIBUTIONS: A.T., T.F., K.N., and C.N. designed the study. A.T., T.F., S.I., E.N., T.T., T.I., C.N., and A.K. drafted the manuscript. A.T., T.F., S.I., K.N., E.N., T.T., T.I., C.N., and A.K. contributed to data collection and interpretation of the results. All authors have read and approved the final manuscript.

WORD COUNT: 496/500 words

REFERENCES: 5

FIGURE: 1

SUPPLEMENTARY FIGURE: 2

Dear Editor

CD4/CD8 double-negative T-cell lymphoma (CD4/8-DN TCL) is rare, which is not included in the revised fourth edition of the World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues.[1,2] CD4/8-DN TCL would be categorized in the "primary cutaneous peripheral T-cell lymphoma, NOS (not otherwise specified)" in the WHO classification. The treatment of CD4/8-DN TCL has not been established.[1,2] Here, we present a case of CD4/8-DN TCL that responded to combination therapy of bexarotene and total skin electron beam therapy (TSEBT).

A 41-year-old man represented skin lesions that had spread throughout his body within a few months. Numerous patches, plaques, and nodules, measuring up to 10 cm, were observed (Figure 1a–c). Positron emission tomography-computed tomography did not show other extracutaneous lesions (Figure 1d). A skin biopsy from the left arm showed dense infiltration of atypical lymphocytes into the dermis (Figure 1e–f). Biopsy of axillary lymph node, bone marrow, and tonsil showed no infiltration. On immunohistochemical examination, the atypical lymphocytes in the dermis were positive for CD3, CD5, CD7, granzyme B, and TIA1, but negative for CD4, CD8, CD20, CD25, CD30, EBER, and CD56 (Figure 1g–r). T-cell receptor-β (TCRβ)-chain gene rearrangement was positive by Southern blotting. The atypical lymphocytes were positive

for TCRβ-chain and negative for TCRδ-chain by immunohistochemical examination (Supplementary Figure 1). Flow cytometry of the skin biopsy specimen showed the expression of CD3, CD5, and CD7 with minimal expression of CD4 and CD8 (Supplementary Figure 2). The diagnosis of mycosis fungoides is not likely because of the lack of epidermotropism and the positive stain of CD7. The patient was diagnosed with CD4/8-DN TCL.

Psoralen plus ultraviolet radiation A photochemotherapy (300–400 mJ/cm^2/time, once per week, four times in total) and steroid ointment had been performed during one month for TSEBT preparation, which was ineffective. Next, the patient was treated with bexarotene (675 mg/day) and TSEBT (1 Gy/time, a total of 30 Gy during eight weeks) in combination. After the combined therapy, the nodules distributed throughout the body regressed. However, after the combined therapy, the treatment of bexarotene was switched to etretinate due to the patient's financial constraints. The regression continued for 19 months by keeping etretinate (Figure 1s-u).

CD4/8-DN TCL remains challenging to diagnose because it is not classified in the current TCL classification.[1,2] CD4/8-DN TCL has been reported in various forms, including variants of mycosis fungoides or primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL.[1,2] Future accumulation and evaluation of patients are

necessary to evaluate the independence of the CD4/8-DN TCL.

Bexarotene is an agonist of the retinoid X receptor and is used for refractory-advanced cutaneous TCL (CTCL).[3,4] The response rate and progression-free survival of patients with CTCL improved with the combination of bexarotene and TSEBT compared to TSEBT monotherapy.[5] However, this is the first case that showed the effectiveness of the combined use of bexarotene and TSEBT to treat CD4/8-DN TCL. Other case series are needed to evaluate the efficacy of the bexarotene and TSEBT combination therapy for CD4/8-DN TCL.

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FIGURE LEGEND

Figure 1. Clinical manifestations before and after treatment with the histopathological findings. (a–c) Asymptomatic patches, plaques, and nodules, measuring up to 10 cm, throughout the patient's body. (d) Positron emission tomography-computed tomography imaging showing multiple areas of fluorodeoxyglucose accumulation on the skin. (e, f) Hematoxylin-eosin staining of the skin biopsy specimen from the left arm revealed diffuse infiltration of atypical lymphocyte-like cells within the dermis. (e: ×20, bar=500 μm, f: ×400, bar=20 μm). Immunohistochemical staining showing the atypical lymphocytes positive for (g) CD3, (h) CD5, (i) CD7, (j) granzyme B, and (k) TIA-1 and negative for (l) CD4, (m) CD8, (n) CD20, (o) CD25, (p) CD30, (q) EBER, and (r) CD56 (g–r: ×400, bar=20 μm). (s–u) Improvement of the nodules throughout the patient's body after treatment with bexarotene and TSEBT.

Supplementary Figure 1. The results of T-cell receptor-β (TCRβ)-chain and TCRδ-chain by immunohistochemical examination. (a) The atypical lymphocytes were positive for TCRβ-chain. (b) The atypical lymphocytes were negative for TCRδ-chain. (a, b ×400, bar=20 μm).

Supplementary Figure 2. The results of flow cytometry analysis by using skin biopsy specimen.

Figure1, Tanigawa et al.