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Primary cutaneous γ δ -T-cell lymphoma treated with low-dose methotrexate and narrowband ultraviolet B irradiation: Report of a case with testicular involvement

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(Case report)

Primary cutaneous γδ-T cell lymphoma treated with low dose-methotrexate and narrow band-UVB-irradiation: report of a case with testicular involvement

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Running head: Primary cutaneous γδ-T cell lymphoma complicated with testicular involvement

Abstract

Primary cutaneous γδ-T cell lymphoma (CGD-TCL) is a rare entity of cutaneous T cell lymphomas (CTCL) and is characterized by tumoral growth of mature γδ-T cell expressing cytotoxic molecules. The prognosis of CGD-TCL is generally worse than other CTCLs. However, relatively indolent patch/plaque lesions have been described suggesting heterogeneous nature of this entity. Here, we present a case of CGD-TCL with various skin manifestations, such as erythematous plaques/tumors, subcutaneous panniculitis-like lesions. During the follow-up, testicular involvement was detected, which was surgically removed. Histopathology showed mixed features from epidermotropism, dermal infiltration, and subcutaneous panniculitis-like lesions depending on the clinical manifesations. The tumor cells were positive for CD3 and revealed cytotoxic markers, TIA-1 and perforin, but not for CD4, CD8, CD20, CD56, TCRβF1 or EBER. Topical glucocorticoid ointment, narrow band-UVB (NBUVB)-irradiation and low dose-methotrexate (MTX) were effective to control these skin lesions. No visceral involvement was detected thereafter. While CGD-TCL is usually associated with poor prognosis, it seems to be composed of various clinical manifestations, and NB-UVB and low dose MTX could be a choice for indolent patch/plaque and possibly nodular lesions especially for the aged.

Key words: Primary cutaneous γδ-T cell lymphoma (CGD-TCL), testicular involvement, methotrexate, UVB

INTRODUCTION

Primary cutaneous γδ-T cell lymphoma (CGD-TCL) is a rare lymphoproliferative disorder with tumoral proliferation of mature γδ-T cells expressing cytotoxic molecules such as granzyme B, TIA-1, and perforin. Extranodal involvements are common [1] and the prognosis is generally worse than the conventional αβ-T cell counterpart [2]. Here, we report a relatively indolent case of CGD-TCL, in which low dose methotrexate (MTX) and narrow band-UVB (NB-UVB)-irradiation were effective to control the skin lesions.

CASE REPORT

An 81-year-old Japanese man presented with up to 5 cm-sized, bright red erythematous patches/plaques and up to 2 cm-sized ulcerated nodules on his trunk and extremities (Fig. 1a, 1b). The erythematous lesions had been recognized for about 5 years and treated as psoriasis by a local physician without histopathological confirmation. Several months before his first visit to our hospital, ulcerated nodules developed. Histopathology of a plaque on his abdomen showed perivascular granulomatous mixed cell infiltrates including atypical large lymphoid cells with hyperchromatic nuclei, prominent nucleoli and numerous mitotic figures (Fig.1d).

Southern blot analysis for TCRJβ1, Jβ2 and Jγ genes revealed clonal rearrangements. The plaque lesions, which had been followed as psoriasis, also revealed similar cell infiltrates with epidermotropism. Neither atypical lymphocytes in his peripheral blood nor visceral involvements were detected at this point of time. Serum lactate dehydrogenase (LDH), thymidine kinase, and soluble IL-2 receptor (sIL-2R) levels were 202 IU/l (normal: 105-210 IU/l), 4.8 U/l (normal: <5U/l), and 809 U/ml (normal: 145-519 U/ml), respectively. Bone marrow aspiration could not be performed because of his advanced age. These findings suggested cutaneous T-cell lymphoma including mycosis fungoides (MF) with large cell transformation. Although topical glucocorticoid and NB-UVB were slightly effective, ulcerated nodules on the left lower eyelid and groin, and normal skin-colored subcutaneous nodule on the left lower leg (Fig. 1c, 1e) were emerged accompanied by increased sIL-2R level to 1120 U/ml. Asymptomatic enlargement of his right testis was also noted during the course, which was surgically removed (Fig. 1f). Histopathology of repeatedly biopsied skin lesions revealed various features, such as epidermotropism, dermal angiocentric/angioinvasive infiltration of large mononuclear cells and diffuse subcutaneous panniculitis-like cell infltrates depending on the clinical manifestations. Immunohistochemistry disclosed that the tumor cells from both cutaneous and testicular lesions were positive for CD3,

TIA-1, and perforin, but negative for CD4, CD8, CD20, CD56, EBER and TCRβF1 (Fig. 2). Prognostic markers for CTCL, such as p53, Bcl-2 and Foxp3, were also analyzed immunohistologically. Tumor cells highly expressed Bcl-2 but not p53. CD3- and Foxp3-positive cells were less than 5% in the tumor sections (Fig. 2). These findings led to the diagnosis of CGD-TCL with testicular involvement. The addition of MTX (17.5mg/week) in addition to NB-UVB treatment was highly effective for the skin tumors and sIL-2R also decreased to 682 U/ml. No recurrence of testicular lesion has been detected and there have been no visceral involvements for 6 months after the initiation of MTX.

DISCUSSION

CGD-TCL belongs to a subtype of primary cutaneous peripheral T-cell lymphoma, unspecified (PTCL/U) [2]. This case was diagnosed as CGD-TCL, because the tumor cells were positive for CD3, TIA-1 and perforin, but negative for CD56, EBER, and specifically TCRβF1. CGD-TCL usually shows aggressive course with poor prognosis with median disease-free survival time of approximately 15 months [2]. Cases with long term survival, however, have also been reported sporadically [3], and our case also showed indolent course after emergence of the skin lesions, which

apparently had been treated as psoriasis for a considerable time.

The international prognostic index (IPI) and the prognostic index for peripheral T-cell lymphoma (PIT) have been proposed [4, 5], where the extranodal involvements are the significant factor. Because IPI and PIT values were both 3 in our case, careful observation is required especially for the detection of the bone marrow invasion. Besides the skin lesions, our case showed testicular involvement during the follow-up , which is uncommon in the conventional primary cutaneous peripheral T-cell lymphomas [6, 7]. T/NK cell lymphoma, which expresses CD56 having affinity to testicular Leydig cells, may show testicular involvement [6, 8], our case, however, showed no CD56-positivity. So far, several prognostic molecular markers associated with apoptosis, cell proliferation and immunoregulation have been proposed in MF and other CTCLs. p53, Bcl-2 and Foxp3, which were analyzed in our case, are among the prognostic markers. Cases with double positivity of both p53 and Bcl-2 are strongly associated with poor prognosis than cases with negative p53 [9]. High expression of Foxp3, a marker for regulatory T cells, is associated with indolent course [10]. Immunohistological analysis of prognostic markers in our case shows high expression of Bcl-2 but low expression of p53 and Foxp3. These results could not explain the indolent course of our case suggesting a heterogenous nature of this entity.

There is no established treatment for CGD-TCL with disappointing results by standard chemotherapies such as CHOP therapy [2,11]. Histone deacetylase (HDAC) inhibitor and mTOR (mammalian target of rapamycin) inhibitor, which appear to be effective for other peripheral T cell lymphomas [12], might be a candidate for the treatment of CGD-TCL. No case report using these agents for CGD-TCL has been published.

Although CGD-TCL usually shows progressive course with poor prognosis, previous reports revealed that PUVA or NB-UVB could be effective for patch/plaque lesions [13,14]. At least 4 cases of CGD-TCL with favorable clinical course have been described[14-17]. Notably 3 of them presented with patch or plaque lesions fairly responded to UV-irradiation and/or glucocorticoid ointment [15-17]. In our case, NB-UVB combined with low dose-MTX was chosen, which succeeded in controlling patch/plaque lesions as well as tumor lesions. MTX has been favorably applied for multifocal primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis and is recommended in a guideline for the treatment of cutaneous CD30+ lymphoproliferation. It and has been also recognized as one of the treatment options of cutaneous T cell lymphoma [18, 19, 20]. Besides the testicular involvement, no other visceral involvement has been detected during the follow up. These findings are

consistent with the heterogeneous nature of CGD-TCL, and mild, moderate therapy including NB-UVB plus relatively low dose of MTX could be a useful treatment of some patch/plaque and possibly tumor lesions, especially in the aged.

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FIGURE LEGENDS

Figure 1

Clinical manifestations (a-c) and histopathology of these lesions (d-e)

a) Erythematous plaques on the chest

b) An ulcerated tumor on the right groin

c) An indurated subcutaneous lesion on the lower leg

d) Histopathology of an infiltrated plaque (HE). Atypical large lymphoid cell infiltrates are observed from epidermis to deep dermis.

e) Histopathology of a subcutaneous lesion (HE). Massive infiltration of tumor cells is recognized in the subcutaneous tissue. Angiocentric infiltrarion of tumor cells are also seen.

f) Histopathology of the testicular lesion(HE). Massive testicular infiltration of tumor cells is observed with destruction of deferent duct.

Scale bars in (d), (e), and (f) indicate 100, 50, and 50μm, respectively.

Figure 2. The expression of tumor markers (a-c) and prognostic markers (d-f). Scale bars indicate 50μm.

Immunohistochemistry for CD3 (a), TIA-1 (b), TCR-βF1 (c), bcl-2 (d), p53 (e), and Foxp3 (f) are shown. The results are summarized in (g) and (h). Scoring of these markers was performed by counting the numbers of positive cells in three independent areas (100μmX100μm). The result was defined as negative (positive cells<10%) or positive (positive scells=or> 10%) as previously reported [15].