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Primary cutaneous anaplastic large cell lymphoma successfully treated with local thermotherapy using pocket hand warmers.

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(Title)

Primary cutaneous anaplastic large cell lymphoma successfully treated with local thermotherapy using pocket-hand-warmers.

Running title: ALCL treated with local thermotherapy

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ABSTRACT

Besides for cutaneous deep fungal or mycobacterial infections, thermotherapy has been used for various malignant tumors. We report a case of primary cutaneous anaplastic large cell lymphoma, which responded quite well to topical thermotherapy using chemical pocket-hand-warmers. The treatment resulted in an immediate tumor-regression without recurrence. This method is simple and might be a useful tool against solitary cutaneous lymphoma especially of elderly patients with poor performance status or with various systemic complications.

Key words: ALCL, caspase-3, HSP-90

INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (PCALCL) is one of the indolent lymphomas of the skin. However, frequent local recurrences especially in the elderly patients are occasionally problematic, which may require palliative therapies. We report a case of recurrent PCALCL of elderly Japanese man. We employed topical thermotherapy, which resulted in an immediate regression of PCALCL.

CASE REPORT

An 89-year-old Japanese man showed a 3 cm X 2 cm X 1 cm-sized, dome-shaped, reddish tumor on his chest (Fig. 1A). Despite the resection by a local surgeon, recurrence occurred on the operation scar within 3 months. General examination by CT-scan detected no swollen lymph nodes or other visceral involvements. Blood LDH-, thymidine kinase (TK) - and soluble IL2 receptor (sIL2r) -levels were elevated to 342 IU L^{-1} (normal range; 105-210), 19.0 U L^{-1} (0-5) and 3190.0 U ml^{-1} (220-530), respectively. An excision with 5mm-margin was performed under local anesthesia. Histopathological examination revealed massive infiltration of anaplastic large cells throughout dermis and subcutaneous fat with numerous mitoses and lymphoid cell infiltrates (Figs. 1D). Almost all atypical cells with prominent nucleoli expressed CD30 (Fig. 1E) but not other T- or B-cell markers, such as CD3, CD20 and CD56. Neither ALCL tyrosine kinase (ALK) nor

epithelial membrane antigen (EMA) [1, 2] were expressed on the tumor cells. HSP90 was highly expressed in the cytoplasm of CD30-positive tumor cells (Fig. 1F). Though 70-80 % of large cells variably expressed active caspase-3, no apoptotic cells were detected (Fig. 1G). These results led the diagnosis of PCALCL. Following the excision, however, skin tumor recurred again (Fig. 1B) with increased blood TK level to 28.0 U L^{-1}. Because the patient had suffered from concomitant bacterial and aspiration pneumonia, urinary tract infection, and severe anemia, local thermotherapy using chemical pocket-hand warmers was chosen to control the tumor growth. The tumor was heated for 2 hours daily with disposable pocket-hand-warmers. Two days following the initiation of thermotherapy, erythematous induration was considerably reduced. After 7 treatments, 2 hours thermotherapy was performed every other day. The tumor was almost completely regressed in 10 weeks with blood TK level reduced to 10.0 U L^{-1}. No recurrence of PCALCL on the site of the thermotherapy was detected (Fig. 1C) until the patient died from pneumonia 4 months after starting the thermotherapy. No evidence for systemic involvement was detected at that time.

DISCUSSION

The first line treatment of PCALCL includes moderate dose electron beam therapy and simple excision[3, 4]. Liu et al showed that there are no differences in response

between excision and local radiation therapy for PCALCL.[5] The local thermotherapy using disposable pocket-warmers was employed in our case because of the poor general condition of the patient who showed the tumor-recurrence with increased blood TK levels. This type of disposable pocket-warmer, which has been used for the treatment of deep cutaneous fungal infection or mycobacterial infection,[6, 7] heats chemically with the maximum temperature and average temperature to be around 60 C^o and about 50 C^o, respectively. Although the skin temperature during the thermotherapy was not examined in our case, the temperature of skin surface can reach around 42-43 C^o.[8] The local thermotherapy has also been used for other malignant skin tumor, such as plaque or tumor of mycosis fungoides, squamous cell carcinoma and metastatic tumors[8]. Solitary skin lesion like our case is adequately heated trans-dermally.

ALK-expression is observed in some cases of systemic ALCL with more favorite prognosis, while PCALCL is negative for ALK. It has also been reported that heat-shock-proteins (HSP) are essential for thermo-tolerance, and the expression of ALK depends on HSP-70 and 90.[9, 10] Gerrgakis et al[11] showed that HSP90 was expressed in 90% of ALK-positive ALCL and in 58% of ALK-negative ALCL. In addition, the expression of HSP family including HSP-90 is inversely correlated with prognosis of myelodysplastic syndrome patients[12] and the inhibition of HSP-90 increases the susceptibility to other

anti-tumor therapies.[13] These results suggest that HSP-90 expression might be inversely correlated with thermosensitivity of the tumor. In our patient, however, HSP90 was highly expressed in the tumor cells. It has also been known that thermosensitivity of tumor cells depends on hypoxic condition. Rapid tumor growth with necrotic center suggested hypoxic condition in our case. Actually, active caspase-3 was partially positive in the tumor suggesting hypoxia-induced pre-apoptotic condition. This might be a factor for satisfactory response of the thermotherapy.

In our case, the local thermotherapy was quite effective for the control of the tumor-regrowth. This simple method might be useful for PCALCL especially of elderly people, possibly in combination with other therapies, such as electron beam-irradiation and low-dose chemotherapy. Although more experiences should be collected, clinical appearance of necrosis with caspase 3-activation might be a favorable factor for the efficacy of topical thermotherapy against the cutaneous lymphomas.

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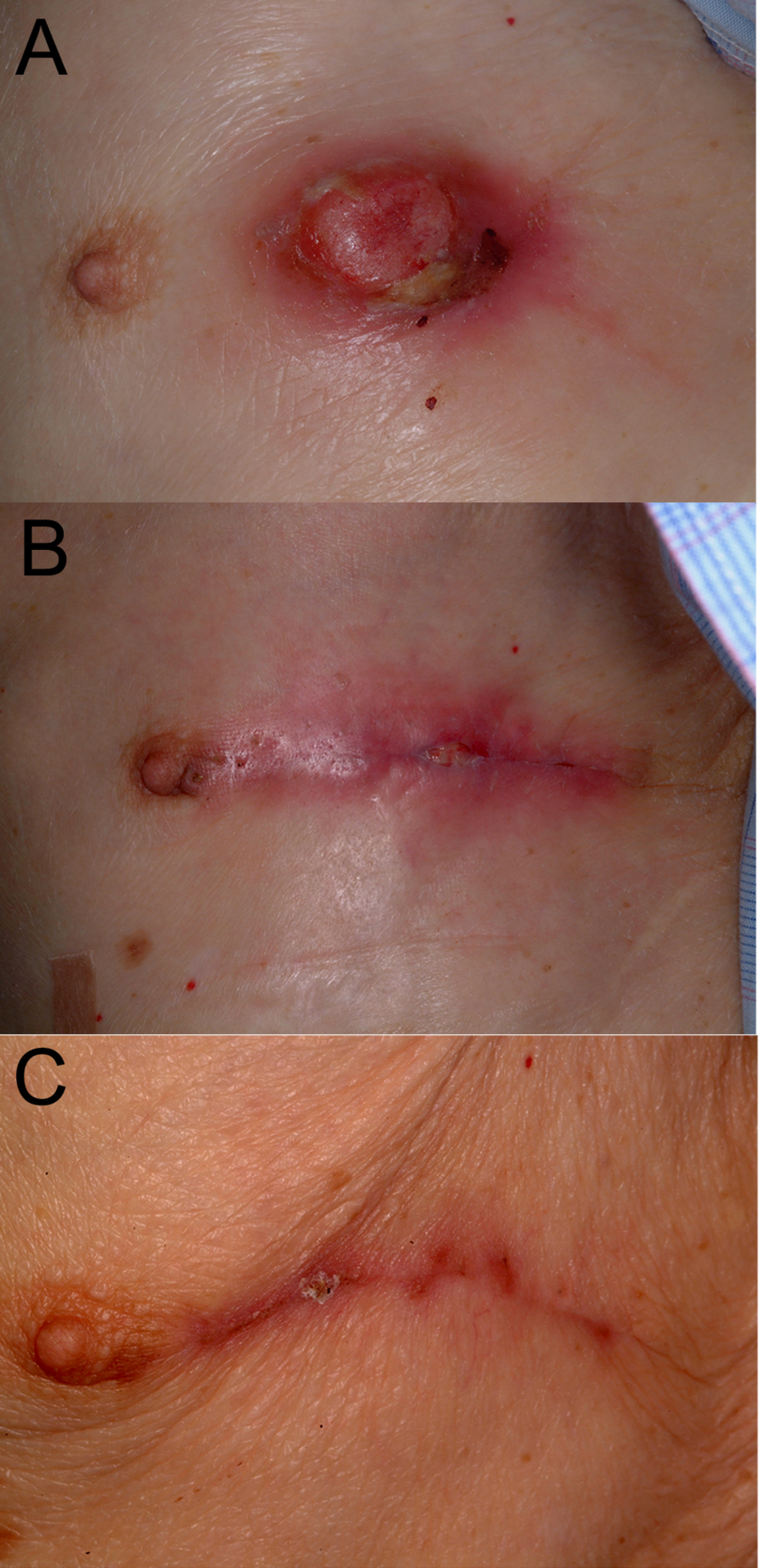
FIGURE LEGENDS

Fig 1. (A) A tumor on the left chest. (B) Tumor recurrence on the operation scar. (C) Operation site on the chest 10 weeks after starting topical thermotherapy. (D) Dense infiltration of atypical large cells and lymphocytes between dermal collagen bundles. Inlet: Atypical large cells with prominent nucleoli and mitotic figures. (E) Immunohistochamistry for CD30. (F) Immunohistochemistry for HSP90. (G) Immunohistochemistry for active caspase-3. Scale bar in D and E-G show 100 μm and 50 μm respectively.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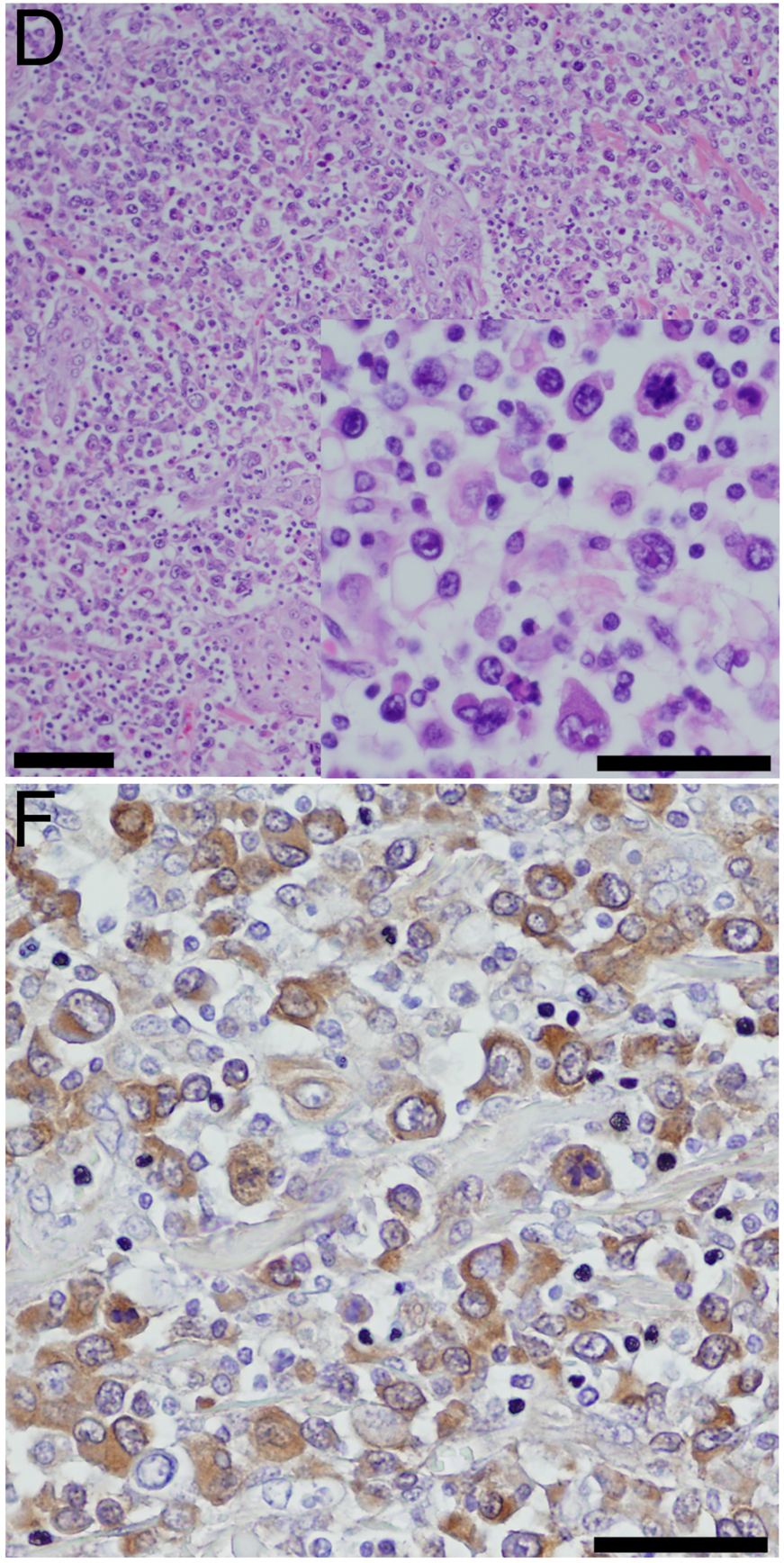
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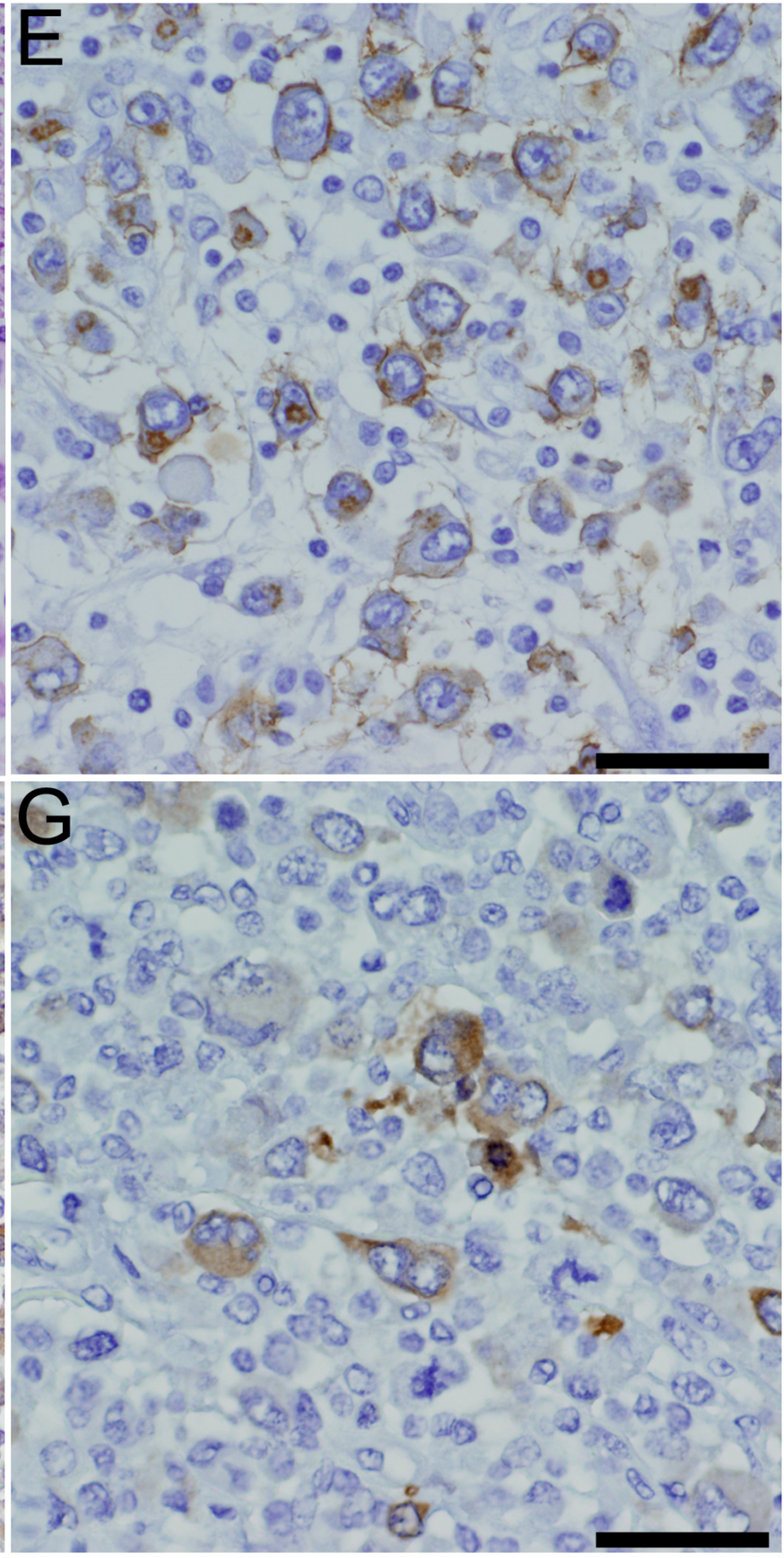
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