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LETTER TO THE EDITOR

Blastic plasmacytoid dendritic cell neoplasm with response to pralatrexate

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Dear Editor,

We encountered a 75-year-old Japanese male patient with a 1-year history of multiple brown nodules appearing on the abdomen and back. Skin lesion biopsies suggested cutaneous T cell lymphoma (CTCL). Computed tomography scans revealed no evidence of lymphadenopathy, and bone marrow specimens revealed no evidence of lymphoma invasion. The patient was treated with 6 cycles of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy that was administered every 21 days. The nodules initially responded to the CHOP chemotherapy; however, after 3 months, the skin lesions worsened, with multiple, new, larger, brown nodules developing on the back (Fig. 1a). A subsequent skin lesion biopsy of a nodule located on the back revealed recurrent CTCL. Therefore, we attempted a weekly treatment of pralatrexate at a dosage of 30 mg/m^2, intravenously for 3 min, with folate and vitamin B12 supplements. Significant improvement in the tumors was seen after a single course (Fig. 1b). Grade 2 stomatitis and diarrhea side effects began to occur; thus, the pralatrexate dosage was reduced to 20 mg/m^2. Treatment with pralatrexate was continued for 7 cycles over 10 months. However, the skin lesions worsened after 7 cycles of pralatrexate, and at this time, CTCL progressed leukemic phase (Fig. 1c). Bone marrow aspiration smears contained 83% small to medium size blasts. The blasts were characterized as CD3−, CD4+, CD38+, CD56+, and HLA-DR+ by flow cytometry. Upon review of the previous skin biopsy, the diagnosis was changed: instead of CTCL, the patient had blastic plasmacytoid dendritic cell neoplasm (BpDCN) (Fig. 1d–i). Subsequently, the patient was given DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) chemotherapy as a salvage therapy; however, the patient ultimately succumbed and perished.

BpDCN, formerly known as CD4+ CD56+ hematodermic neoplasm or blastic natural killer cell lymphoma, is a rare, clinically aggressive tumor derived from the precursors of plasmacytoid dendritic cells [1]. It represents approximately 0.44% of the hematologic neoplasm cases [2]. The rarity of this disease allows it to be easily misdiagnosed, causing a significant delay between the onset of lesions and the final diagnosis, with a mean time of 6.2 months [3]. Although it is often diagnosed from skin biopsies due to the high frequency of primary cutaneous involvement, the progression of the disease and leukemic dissemination appear to be part of the natural evolution of BpDCN [1]. Chemotherapy regimens used for AML, ALL, non-Hodgkin lymphoma, and myelodysplastic syndrome have all been used to treat BpDCN. Feuillard et al. reported that 12 of 23 BpDCN patients treated with CHOP-like chemotherapy had a complete response (CR) rate of 87%; however, the rate of relapse was very high in those achieving a CR, with a 9-month median time until relapse, and the overall survival rate was quite poor, with a survival rate of 50% at 1 year and 25% at 2 years [4]. Allogeneic transplantation treatments offer a chance at prolonged remission and a possible cure for those who are eligible; unfortunately, relapse rates remain high, ranging from 30 to 40% [3, 5, 6]. In other reports, DeVIC chemotherapy and a methotrexate-asparaginase regimen, which was developed for NK/T cell lymphoma, offer a reasonable alternative to other chemotherapies for BpDCN [7, 8]. NK/T cell lymphoma often has a poor prognosis due to the expression of p-glycoprotein, which mediates multidrug resistance [9]. Although the mechanism by which BpDCN causes drug resistance is not known in detail, p-glycoprotein may also be involved [10]. Although it was temporary, pralatrexate

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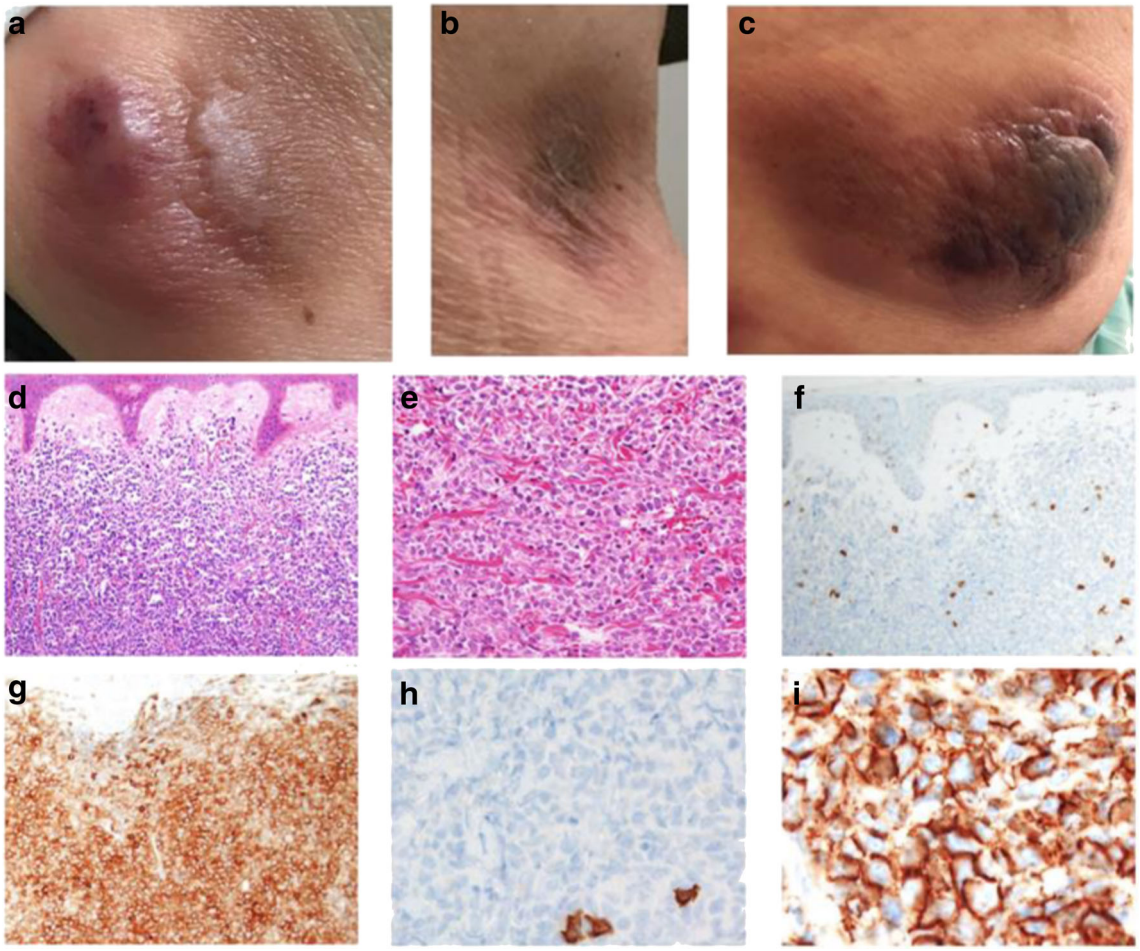

Fig. 1 Skin tumors on his right back before and after pralatrexate therapy, numerous violaceous brown tumor of his back after CHOP chemotherapy (**a**), and regression of skin lesions after 1 cycle of pralatrexate therapy (**b**); however, tumor was worsened 7 cycles of pralatrexate, and this time, BpDCN progressed leukemic phase (**c**). Histological examination of skin biopsy showing dense dermal infiltrate of tumor cells (hematoxylin-eosin, original magnifications × 20) (**d**), × 100 (**e**). Tumor cells diffusely expressed CD4 (**g**) and CD56 (**i**) but negative reactivity for CD3 (**f**), CD8 (**h**), and CD20

was successful in the current reported case; this may be because pralatrexate is not a known substrate for p-glycoprotein [11]. BpDCN responding positively to pralatrexate had been reported only twice before; Justin et al. reported that pralatrexate treatment of BpDCN instigated a sustained response of over 6 months [12], and Christian et al. reported that pralatrexate showed transient response to BpDCN, but after 5 cycles, the patient suffered a leukemic relapse [13].

SL-401, which specifically targets interleukin-3 receptor (IL-3R) protein, is a targeted drug that efficiently kills primary BpDCN cells and may be a promising drug for future BpDCN patients. Since BpDCN overexpress IL-3R and the mechanism of SL-401 cytotoxicity differs from other available therapeutics by inhibiting protein synthesis, the agent is able to target and kill relatively dormant cells. Furthermore, the SL-401 payload, diphtheria toxin, is not a substrate for P-glycoprotein or other drug efflux pumps that are associated with multidrug resistance [10].

The present case demonstrates the possible rescue from BpDCN through pralatrexate therapy; however, further evidence for effective treatment of this rare lymphoma is warranted.

Compliance with ethical standards

Informed consent was obtained from the patient for the treatment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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