Successful treatment with anti-programmed-death-1 antibody in a relapsed natural killer/T-cell lymphoma patient with multi-line resistance: a case report

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Abstract

Background: Extranodal natural killer/T-cell lymphoma (NKTCL), nasal type, is an aggressive malignancy with poor prognosis. Currently, there is no recommended standard therapy for relapsed NKTCL.

Case presentation: A 37-year-old woman with lymphadenopathy was diagnosed with NKTCL by biopsy of an enlarged lymph node on the right side of her neck. Enhanced computed tomography revealed no metastasis. For this patient, we performed continuous chemotherapy followed by radiotherapy; however, nodule biopsy showed metastases in her lower limbs 3 months after radiotherapy, which confirmed disease progression. Unfortunately, the patient’s temperature was persistently high and her skin ulcers could not be controlled well using multi-line treatment. Therefore, we attempted treatment with the anti-programmed-death-1 (PD-1) antibody, pembrolizumab. Surprisingly, the patient achieved clinical complete remission (CR) after four cycles of pembrolizumab treatment, despite having persistent detectable Epstein-Barr virus (EBV) DNA. Other molecular monitoring techniques were unavailable for this patient owing to the retrospective nature of the study. The only adverse event was soreness of the upper limb joints and muscles.

Conclusion: This relapsed NKTCL case treated with pembrolizumab showed that multimodal therapy including pembrolizumab would be partially or totally effective for relapsed NKTCL.

Keywords: Salvage treatment, Anti-PD-1 Antibody, Relapsed NKTCL
drugs, impressive clinical responses were observed in diverse types of human cancers [8]. Recent studies of programmed-death-1 (PD-1) blockade in lymphomas have made astounding advances, contributing to the further development of novel immunotherapies for these tumors [9]. However, the effectiveness of anti-PD-1 antibodies in patients with relapsed NKTCL is unknown. In the present case report, we describe a patient with distant relapsed NKTCL who received salvage treatment with an anti-PD-1 antibody.

Case presentation
A 37-year-old female had noticed a mass on her right neck for about 2 weeks before her initial visit to our hospital. A magnetic resonance imaging (MRI) scan of the nasopharynx and neck showed mucosal thickening in the right nasopharynx, together with multiple deep cervical lymph node enlargements. She was diagnosed with extranodal NKTCL by excisions biopsy (nasopharyngeal mass biopsy and cervical mass biopsy) and was transferred to our hospital in October 2014. Immunohistochemical staining demonstrated that the tumor cells expressed surface CD2, cytoplasmic CD3+, TIA-1, and granzyme B, but not CD10, CD15, CD20, CD21, and PAX-5. Bone marrow examination showed no presence of neoplastic cells. She was confirmed as having Ann Arbor stage IIE extranodal NKTCL based on the radiological findings and laboratory tests. She underwent four cycles of interchangeable chemotherapy comprising VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) and AspaMet (pegasparagase and methotrexate), followed by involved-field radiotherapy, and achieved complete remission. In August 2015, cutaneous nodules appeared on her lower limbs, which were proved to be relapsed NKTCL by biopsy, without involvement of the marrow. Immunophenotype showed that the nodules were CD3+, CD20+, CD30+, CD56+, CD5+, TIA-1+, Granzyme B+, Ki-67*: 95%, TCRγ−, and EBERs+. The patient developed a fever, with temperature decreased to normal levels. However, the patient developed soreness of the upper limb joints and muscles, developed tightness of her organs, except the skin of lower limbs; PET-CT was unavailable. She was then treated with pembrolizumab (at a dose of 2 mg/kg every 21 days) from August 17, 2016. The skin ulcers got better after the end of the first cycle (Fig. 1b). Her performance status improved and the lower limbs ulcers had almost healed after four cycles (Fig. 1c). At this time, EBV DNA remained persistently detectable. After another seven cycles of treatment, EBV DNA became undetectable (Fig. 2). Radiological findings and PET-CT images after pembrolizumab therapy were not performed because of the patient’s refusal. The patient developed soreness of the upper limb joints and muscles, as well as a mild increase in uric acid during therapy. These symptoms were controlled well by diet control, and did not reappear after further pembrolizumab therapy. No other treatment-related adverse events were observed.

Discussion and conclusions
The recommended standard protocol for localized NKTCL has evolved greatly over the last decade. Radiotherapy combined with chemotherapy is recommended for those cases with stage I–II nasal disease [10, 11]. However, an optimal treatment modality for relapsed NKTCL remains unclear at present. The choice of salvage treatment is associated with the type of primary regimen and response duration. Currently, the preferred treatment for relapsed NKTCLs is L-asparaginase-containing regimens, such as dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) or L-asparaginase, methotrexate, and dexamethasone (Aspa Met Dex). Kwong et al. [12] defined the efficacy of the SMILE regimen in patients with relapsed NKTL. The Aspa Met Dex regimen was evaluated in a multicenter phase 2 clinical trial [13], where CR rate was 61.1% in 19 relapsed/refractory NKTL patients. Efficacy of L-asparaginase-based regimen is still suboptimal for relapsed/refractory NKTL. Gemcitabine has an impressive effect on L-asparaginase refractory NKTL. Wang et al. [14] reported promising results for the P-GemOx regimen for newly diagnosed advanced stage or relapsed extranodal NKTCL, in which the
overall response rate (ORR) was 80% (28/35) and the CR rate was 51.4% (18/35). With respect to the adverse events, grade 3/4 myelosuppression was observed in 40.0% of patients, with no treatment-related deaths. Results from a multicenter phase II study of chidamide in patients with relapsed/refractory peripheral T-cell lymphoma led to approval of chidamide by the Chinese Food and Drug Administration [15]. However, the efficacy of chidamide-based combination regimens for relapsed NKTCL is uncertain. Zhou et al. [16] found that DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase) is an active regimen for the treatment of relapsed/refractory NKTCLs, with an ORR of 88.2% (15/17). Although promising efficacy was achieved in advanced NKTCL patients treated with a combined regimen comprising pegaspargase, l-asparaginase, and gemcitabine, a part of them still experienced failure and progression.

In the past 10 years, survival of patients has been improved greatly by antibodies targeting immune checkpoints...
in a number of human cancers, such as melanoma, renal cancer, colon cancer, and lung cancer. NKTCL might also be targetable for therapeutic antibodies owing to 67% of NKTCL samples expressing PD-L1 [17]. Lastly, Kwong et al. [18] reported high efficacy of pembrolizumab in relapsed/refractory NKTCL that failed on L-asparaginase. There was a obvious response to skin lesions and EBV DNA level after the first cycle in a case that had biopsy-proven cutaneous relapse. Similar results were observed in our case, which only involved the skin of the lower limbs. EBV DNA became undetectable only after the eleventh cycle. Our patient with only cutaneous relapse has experienced longer progression-free survival (PFS) and fewer side effects compared with those patients who had visceral organ involvement. Our case was meaningful because it proved that an anti-PD-1 antibody could be effective for selected patients with resistance to multi-line treatment.

In conclusion, we encountered a relapsed NKTCL patient with resistance to multi-line treatment, who responded well to the anti-PD-1 antibody pembrolizumab. This preliminary result suggested that pembrolizumab would be partially or totally effective for relapsed NKTCL.

Abbreviations
Aspa Met Dex: L-asparaginase, methotrexate, and dexamethasone; AspaMet: Pegaspargase and methotrexate; CR: Complete remission; DDGP: Cisplatin, dexamethasone, gemcitabine, and pegaspargase; EBV: Epstein–Barr virus; EPOCH: Ifosfamide, cyclophosphamide, vincristine, pirarubicin, and dexamethasone; NKTCL: Natural killer/T-cell lymphoma; ORR: Overall response rate; PD-1: Programmed-death-1; PET-CT: Postron emissiontomography-computed tomography; PFS: Progression-free survival; P-GemOx: Pegaspargase, gemcitabine, and oxaliplatin; SMILE: Dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; VPD: Etoposide, ifosfamide, cisplatin, and dexamethasone

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Availability of data and materials
The datasets used and/or analyzed during the current case report are available from the corresponding author upon reasonable request.

Authors’ contributions
JPL participated in the case collection, drafting, and revising the manuscript. PX participated in drafting and revising the manuscript. XLJ and SZ participated in the case collection. AYL participated in the analysis and interpretation of the data, as well as in drafting and revising all versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Reports describing the case of a single patient are exempt from review by the ethics committee of the Second Affiliated Hospital of Nanchang University. Authors obtained written informed consent and publication consent from the patient.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor of this journal.

Competing interests
The authors declare that they have no competing interests.

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