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CASE REPORT

Combination of atezolizumab and chidamide to maintain long-term remission in refractory metastatic extranodal natural killer/T-cell lymphoma: A case report

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Abstract

BACKGROUND

The prognosis of refractory extranodal natural killer/T-cell lymphoma (ENKTL) is poor. Recent data have indicated that immune checkpoint blockade with a programmed cell death protein-1 (PD-1) antibody in combination with administration of histone deacetylase inhibitors represents a potentially effective treatment strategy. Compared with PD-1 antibodies, programmed death-ligand 1 antibodies have fewer side effects. Here, we present a rare case of a patient with refractory metastatic ENKTL who achieved sustained remission of approximately 10 mo with minor adverse effects after combination therapy with atezolizumab, chidamide, and radiotherapy.

CASE SUMMARY

A 56-year-old woman underwent resection of a tumour in her left nasal cavity and was diagnosed with ENKTL (nasal type). Medical examination revealed tumours observed in the bilateral nasal mucosa, the subcutaneous soft tissue of the inner side of the left eye, the soft tissue of the nasopharynx, the bilateral tonsils, and the left preauricular, right hilar, bilateral neck lymph nodes and bone marrow. However, tomography/computed tomography showed increased metabolism of

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the bilateral nasal mucosa and subcutaneous soft tissue of the inner side of the left eye and newly increased metabolism of the left cervical lymph node after chemotherapy. Therefore, combination therapy with chidamide, atezolizumab, and radiotherapy was performed. Fortunately, the patient achieved a complete response following 10 mo of combination therapy.

CONCLUSION
The outcome in this case suggests that the combination of atezolizumab, chidamide, and radiotherapy is a promising regimen for treating refractory metastatic ENKTL following chemotherapy treatment failure.

Key Words: Long-term remission; Refractory metastatic extranodal natural killer/T-cell lymphoma; Histone deacetylase; Programmed death-ligand 1 antibody; Radiotherapy; Case report

Core Tip: extranodal natural killer/T-cell lymphoma (ENKTL) is a subtype of non-Hodgkin lymphoma with poor outcomes because ENKTL cells express high levels of P-glycoprotein that mediate tumour multidrug resistance. Furthermore, the standard treatment modality for chemotherapy-resistant ENKTL remains debated. We have experienced a patient with refractory metastatic ENKTL who was resistant to conventional DDGP chemotherapy. Following systemic therapy with atezolizumab and chidamide in combination with local radiotherapy, the patient achieved sustained remission of approximately 10 mo with minor adverse effects.

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma (ENKTL) is a distinct subtype of mature T-cell and NK-cell lymphoma that is prevalent in regions of East Asia and South America[1-3]. ENKTL progresses rapidly and has a poor prognosis. Although options for therapy continue to evolve, their curative effects remain unsatisfactory. Because ENKTL cells express high levels of P-glycoprotein that mediate tumour multidrug resistance, conventional chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have poor outcomes. Thus, nonanthracycline-based chemotherapy has become the main therapeutic strategy. However, in patients for whom L-asparaginase-based regimens are ineffective, progression-free survival (PFS) after relapse or first progression was only 4.1 mo[4].

Recently, several studies have reported that HDAC inhibitors (HDACis) combined with anti-death protein-1 (PD-1) immunotherapy showed encouraging efficacy, thus representing a new treatment strategy for relapsed/refractory (r/r) ENKTL[5,6]. However, the combination of death-ligand 1 (PD-L1) antibody and HDACi for r/r ENKTL has not yet been investigated. Here, we report the case of a patient with refractory metastatic ENKTL who achieved a durable response following systemic therapy with PD-L1 antibody and chidamide in combination with local radiotherapy.

CASE PRESENTATION

Chief complaints

A 56-year-old woman had been diagnosed with ENKTL (nasal type) for one month.

History of present illness

The patient underwent resection of a tumour in her left nasal cavity and was diagnosed with ENKTL (nasal type). Before being transferred to our hospital, she accepted her first cycle chemotherapy with CHOPE (cyclophosphamide 1000 mg Day 1 + vincristine 2 mg Day 1 + epirubicin 100 mg Day 1 + etoposide 100 mg Days 1-3 + prednisone acetate 100 mg Days 1-5) and developed grade IV myelosuppression.

History of past illness

The patient had a free previous medical history.

Personal and family history

Personal and family history was non-contributory.

Physical examination

The patient's temperature was 36.4 °C, heart rate was 102 beats/min, respiratory rate was 25 breaths/min, and blood pressure was 122/95 mmHg. The clinical examination revealed facial strut and pain.

Laboratory examinations

The tumour cells stained positive for CD3, CD56, TIA-1, and Ki-67 (approximately 40%) but were negative for CD20 (Figure 1). Bone marrow examination was performed. Flow cytometry revealed 0.71% NK cells with the following abnormal immunophenotypes: CD2+, CD7+, CD56+, CD94+, CD161+, CD5-, CD16-, and CD8+/-.

Imaging examinations

Positron emission tomography/computed tomography (PET/CT) was performed for staging, and increased ^{18}F-fluorodeoxyglucose (FDG) uptake was observed in the bilateral nasal mucosa, the subcutaneous soft tissue of the inner side of the left eye, the soft tissue of nasopharynx, the bilateral tonsils, and the left preauricular, right hilar, and bilateral neck lymph nodes. These patterns were consistent with the infiltration of malignant lymphoma (Figure 2).

FINAL DIAGNOSIS

The patient was diagnosed with ENKTL (nasal type). Disease was evaluated as Ann Arbor stage IVE A, the prognostic index for NK/T-cell lymphoma, including Epstein-Barr virus DNA load (PINK-E), was calculated as 3, and disease was classified as high risk.

TREATMENT

Radiotherapy, chidamide, and nivolumab were concurrently administered. The target volume included the partial frontal sinus, the right maxillary sinus, all ethmoid sinuses, the sphenoid sinus, the left orbit and eye contents, the left maxillary sinus, the nasopharynx, the left preauricular lymphoid drainage area, and the bilateral neck level Ib, 2, 3, 4, and 5 Lymphatic drainage areas. The radiation dose was 50 Gy/25 fractions. The patient developed transient rash on the third day after nivolumab treatment and grade 4 thrombocytopenia following the first cycle of combination therapy. Therefore, the PD-1/PD-L1 inhibitor was changed to atezolizumab for subsequent immunotherapy after her haemogram recovered.

OUTCOME AND FOLLOW-UP

After four cycles of chidamide and atezolizumab, PET/CT showed slightly higher metabolism of the nasal cavity. Treatment was continued as planned. Fortunately, PET/CT showed no obvious FDG uptake after 11 cycles of combination therapy with chidamide and atezolizumab (Figure 2). Grade 3 adverse events, including neutropenia and thrombocytopenia, were manageable and resolved during maintenance treatment.

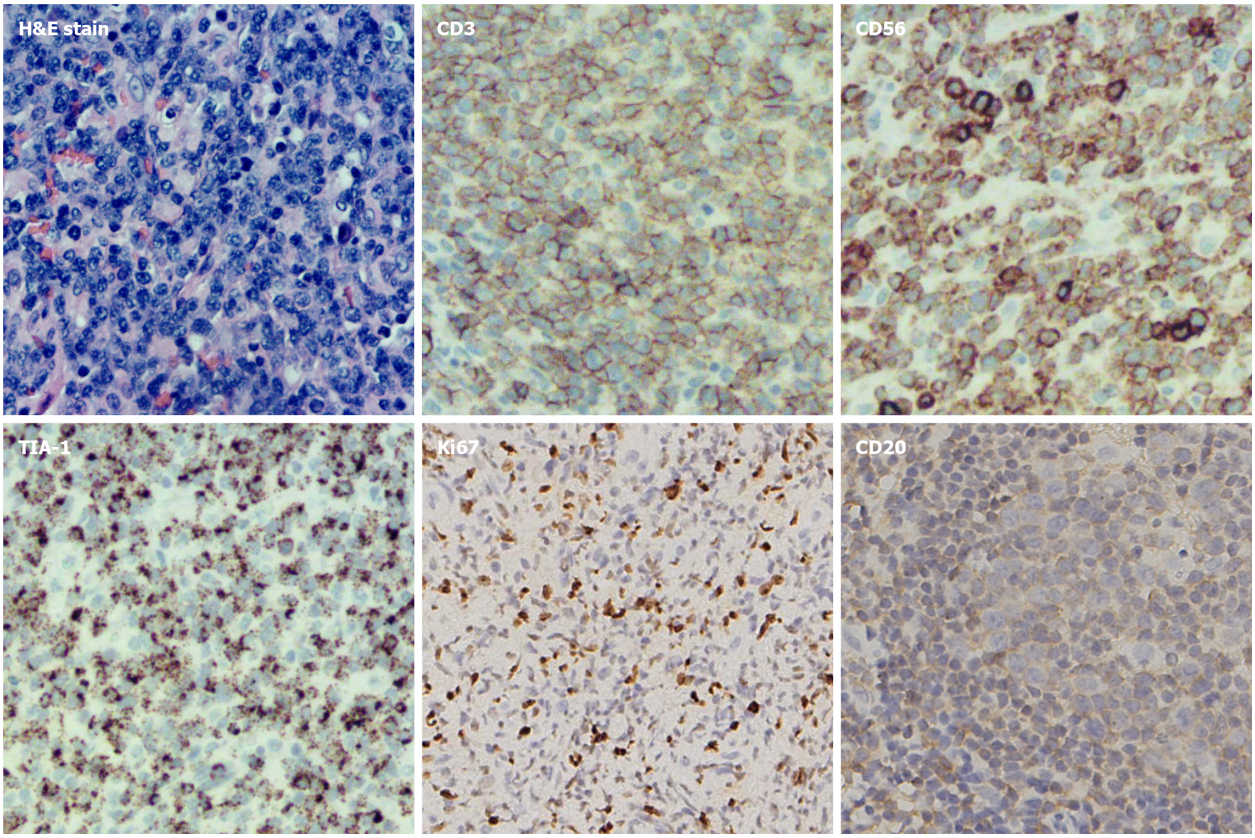

Figure 1 Photomicrographs of the left nasal cavity biopsy demonstrating extranodal natural killer/T-cell lymphoma. Immunohistochemical staining showed that the tissue of the left nasal cavity mass was positive for CD3, TIA-1, Ki67, and CD56 but negative for CD20.

DISCUSSION

ENKTL is a subtype of non-Hodgkin lymphoma with poor outcome. The standard treatment modality for refractory ENKTL is still debated, especially for chemotherapy-resistant tumours[4]. Here, we present the case of a patient with refractory metastatic ENKTL who was resistant to conventional DDGP chemotherapy. Following systemic therapy with a PD-L1 inhibitor and chidamide in combination with local radiotherapy, the patient achieved sustained remission of approximately 10 mo with minor adverse effects.

Previous studies suggested that NKTL was resistant to anthracycline[7]. Thus, pegaspargase, gemcitabine, or other non-anthracycline-based chemotherapy regimens are generally used for the first-line treatment of patients with newly diagnosed refractory NKTL[8,9]. Additionally, as described in previous reports, allogeneic stem cell transplantation (allo-SCT) may be beneficial for patients with ENKTL[10,11]. However, PFS in the subset of patients who maintained remission following allo-SCT was only approximately 10.0 mo. There has been no randomized, prospective study to evaluate the safety and efficacy of allo-SCT in ENKTL[12].

Recently, radiotherapy, PD-1 inhibitors, and HDACis (alone or in combination) have shown promising efficacy in treating r/r ENKTL. Chidamide is a novel benzamide-type HDACi that can selectively block HDAC1, 2, 3, and 10[13]. Recent data demonstrated that chidamide induced growth inhibition and apoptosis in NK/T lymphoma cells[14]. A phase II clinical trial of chidamide for r/r peripheral T-cell lymphoma showed median PFS and overall survival of 2.1 and 21.4 mo, respectively [15]. In this study, 16 ENKTL patients were enrolled and showed lower response rates compared with other studies: one patient achieved a complete response (CR), and two patients achieved partial responses (PRs).

PD-1/PD-L1 inhibitors are additional new agents for the treatment of r/r ENKTL. In previous reports (Table 1), combining PD-1 antibody with chemotherapy or chidamide obtained satisfactory results, and most of the cases achieved complete response and sustained curative effects[16-21]. The anti-PD-1 antibody (sintilimab) plus chidamide regimen was evaluated in a phase 1b/II clinical trial[22], where the CR rate was 44.4% in 41 r/r-NKTCL patients. A previous study demonstrated that anti-

Table 1 Reports regarding the application of death protein-1/death-ligand 1 inhibitors in refractory or relapsed extranodal natural killer/T-cell lymphoma

Ref.	Number of cases	Age mean year (range)	Gender	Treatment	Stage	Response	OS or PFS
McGehee *et al* [16] 2021	1	72	1 M	Pembrolizumab plus RT	IV	CR	33 mo, alive
Du *et al*[17] 2020	3	52 (51-54)	3 M	PD-1 antibody, plus Chidamide, etoposide, and thalidomide	1 (33.3%) IV; 1 (33.3%) III; 1 (33.3%) II	2 (66.7%) CR; 1 (33.3%) PD	-
Kwong *et al* [18] 2017	7	49 (31-68)	7 M	Pembrolizumab	5 (71.4%) IV; 2 (28.6%) IE	5 (71.4%) C; 2 (28.6%) PR	-
Li *et al*[19] 2018	7	47 (17-61)	4 M; 3 F	Pembrolizumab	2 (28.6%) IV; 3 (42.9%) II; 1 (14.3%) IIIE; 1 (14.3%) IE	2 (28.6%) CR; 2 (28.6%) PR	5 mo OS; 4.8 mo PFS
Diab *et al*[20] 2021	1	82	M	Pembrolizumab	IV	CR	21 mo, alive
Lai *et al*[21] 2017	1	37	F	Pembrolizumab	IV	CR	-
Gao *et al*[22] 2020	41	48 (20-72)	27 M; 14 F	Sintilimab plus chidamide	26 (70.3%) IV; 15 (29.7%) Non-IV	16 (44.4%) CR; 5 (13.9%) PR	-
Kim *et al*[24] 2020	21	≤ 60 16; > 60 5	13 M; 8F	Avelumab	-	5 (23.8%) CR; 3 (14.3%) PR	-

OS: Overall survival; PFS: Progression-free survival; M: Male; F: Female; Non-IV: Non-stage IV patients; RT: Radiotherapy.

PD-L1 antibodies have better efficacy and fewer adverse effects[23]. In particular, an open-label phase 2 study demonstrated that a PD-L1 antibody as a single agent induced tumour remission in a subset of patients. CRs were observed in 24% of patients, and the overall response rate was 38%; the study was terminated because of a lower than expected response rate[24]. Five responders in this study continued to show sustained responses, and the only adverse events observed were grades 1 or 2. However, to our knowledge, there have been no case reports evaluating the effects of PD-L1 antibody for r/r-ENKTL patients who could not tolerate previous treatment with PD-1 antibody.

Recently, multiple lines of evidence have demonstrated that HDACis could enhance the therapeutic effects of PD-1 antibodies[25,26]. Epigenetic modification could regulate T cell trafficking and reactivation, thus enhancing the efficacy of the PD-1 antibody. A few case reports suggested that the combination of PD-1 antibodies and HDACis might be effective in patients with refractory ENKTL[5,6]. However, the antitumour effect of combination therapy with PD-L1 antibody and chidamide has not been demonstrated for refractory ENKTL. The patient described here was successfully treated with local radiotherapy and systemic therapy with chidamide and PD-L1 antibodies. Evaluation 10 mofollowing the end of radiation therapy showed a sustained CR. We presume that the sustained therapeutic efficacy observed in this patient may result from synergistic effects of PD-L1 antibody, chidamide, and local radiotherapy. Studies with larger numbers of patients are needed to evaluate the efficacy and safety of this combination therapy regimen for refractory ENKTL.

CONCLUSION

We present a rare case of a patient with refractory ENKTL who was successfully treated with a combination of radiotherapy, chidamide, and PD-L1 antibody. Additional evidence is needed to evaluate the potential activity and safety of this regimen.

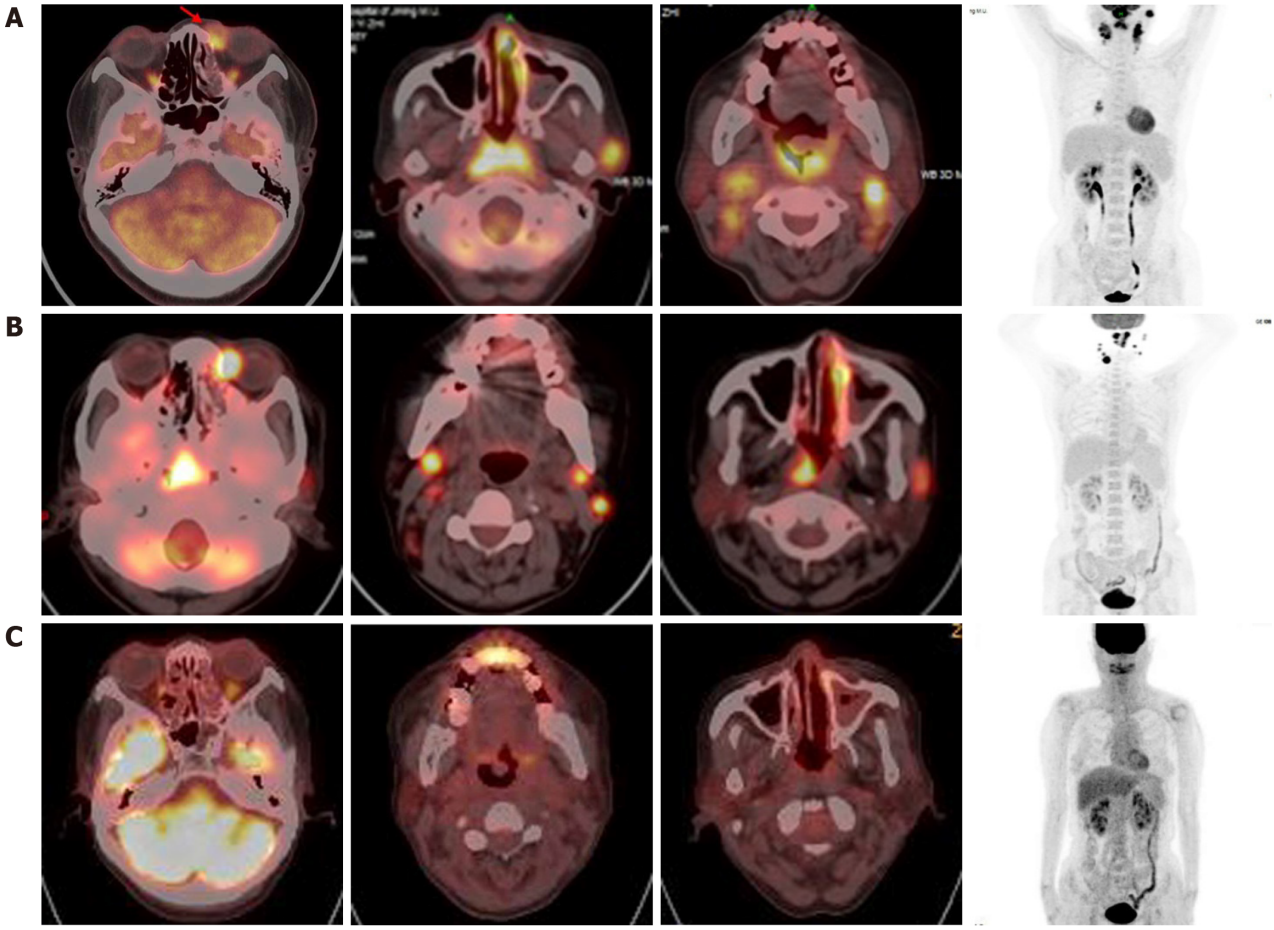

Figure 2 Imaging at diagnosis, after four cycles of chemotherapy with DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase), and 10 mo posttreatment withdeath-ligand 1antibody and chidamide. A: Positron emission tomography showing hypermetabolism in the bilateral nasal mucosa, the subcutaneous soft tissue of the inner side of the left eye, the soft tissue of the nasopharynx, the bilateral tonsil, and the left preauricular, bilateral neck, and right hilar lymph nodes; B: After four cycles of DDGP chemotherapy, increased metabolism of the lesions was observed except in the right hilar lymph nodes; C: Patient achieved sustained remission for approximately 10 mo.

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