

# Salvage camrelizumab for an intractable NK/T cell lymphoma patient with two instances of intestinal perforation: a case report and literature review

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**Abstract. – BACKGROUND:** The prognosis of natural killer/T cell lymphoma (NKTCL) with multifocal small intestine involvement complicated by intestinal perforation is extremely poor. There is no evidence-based treatment strategy for this intractable condition.

**CASE PRESENTATION:** A 30-year-old male was admitted to our hospital in April 2017 and presented with recurrent fever for three months and multiple painless subcutaneous nodules in the abdominal wall. An excision biopsy of the subcutaneous nodules in the abdominal wall revealed NKTCL. The patient was diagnosed with stage IVB NKTCL with skin and multifocal small intestine involvement according to the imaging results. The first intestinal perforation occurred due to tumor infiltration before the initial treatment. The second intestinal perforation occurred after receiving two cycles of chemotherapy with a modified SMILE regimen. The histone deacetylase inhibitor (HDACi) chidamide was administered as a single-agent therapy after recovery from the second intestinal perforation. Complete remission was achieved. Unfortunately, five months later, the patient was confirmed to have relapsed and received the salvage chemotherapy. The patient suffered from disease progression again after the fourth cycle of chemotherapy. At this point, from May 29, 2018, the patient started to receive injections of the anti-programmed death 1 (PD-1) antibody camrelizumab as a salvage treatment. Two months after the initial anti-PD-1 antibody camrelizumab injection, the response was partial remission. Disease progression was confirmed in March 2021, with a progression-free survival time of 34 months.

**CONCLUSIONS:** NKTCL patients with multifocal small intestine involvement have a high risk of intestinal perforation. The possible etiologies of bowel perforation include tumor infiltration, tumor necrosis in response to therapy, and acute inflammation. The anti-PD-1 antibody camrelizumab may be a new candidate agent for

treating this type of intractable NKTCL. Further observations are necessary to identify the efficacy and safety of new agents in the future.

*Key Words:*

NK/T cell lymphoma, Small intestine, Perforation, Camrelizumab.

## Abbreviations

NKTCL: natural killer/T cell lymphoma, GI: Gastrointestinal, EBV: Epstein-Barr virus, NHL: non-Hodgkin's lymphoma, PET-CT: positron emission tomography-computed tomography, SMILE: dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide, PIDE: pegaspargase, ifosfamide, etoposide, dexamethasone, Aspa-MetDex: pegaspargase, methotrexate, dexamethasone, PR: partial remission, CR: complete remission, PD: progressive disease, PFS: progression free survival, CHOP: cyclophosphamide, adriamycin, vincristine, and prednisolone, L-Asp: L-asparaginase, HDACi: histone deacetylase inhibitor, PD-1: programmed cell death protein 1.

## Introduction

Extranodal natural killer/T cell lymphoma (NKTCL) is a subtype of mature T- and natural killer- cell lymphoma, which typically exhibits an aggressive clinical course and poor prognosis, especially in advanced cases with skin and soft tissue involvement. The incidence rate of NKTCL varies geographically, with lower rates in North America and Europe and higher rates in East Asia and Latin America<sup>1</sup>. Epstein-Barr virus (EBV) may play a vital role in the development of NKTCL.

The gastrointestinal (GI) system is the most common extranodal involved site in patients with non-Hodgkin's lymphoma (NHL). Ding et al<sup>2</sup> reported that extranodal NKTCL was the second most common lymphoma involving the intestinal

tract in China. Bowel perforation and secondary peritonitis are potentially life-threatening complications for lymphoma patients with GI involvement. Several studies<sup>3-5</sup> reported that the prognosis of lymphoma patients with GI involvement became significantly worse when bowel perforation occurred. Jiang's retrospective study<sup>6</sup> revealed that the median survival time of NKTCL patients with GI involvement was only 1.5 months (range 0.3-2.7) when complicated by bowel perforation. Due to the rarity of NKTCL, there is currently no evidence-based treatment strategy for NKTCL with intestinal tract involvement.

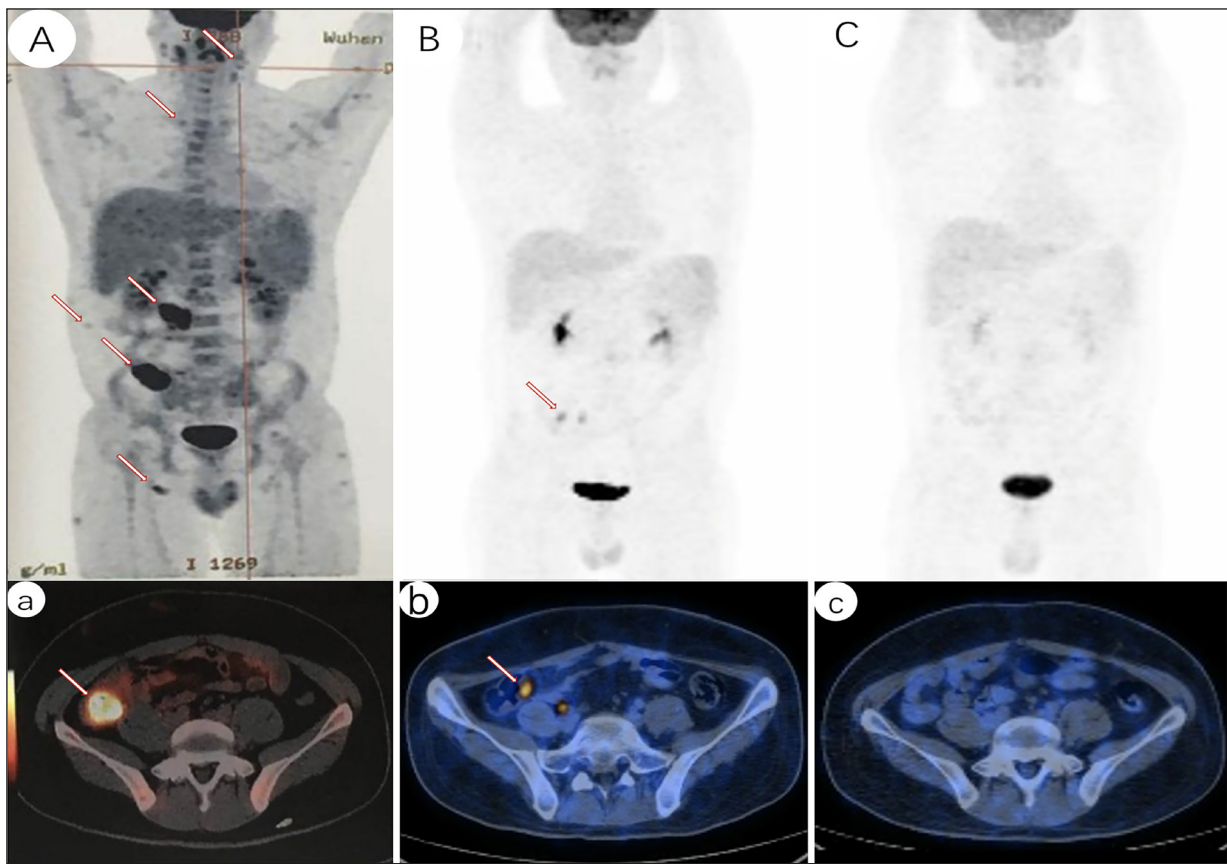
In this report, we describe a case of intractable refractory advanced NKTCL with multifocal small intestine involvement complicated by two instances of bowel perforation in a patient who achieved a long-term progression free survival (PFS) when treated with salvage therapy using the anti-PD-1 antibody camrelizumab.

### Case Presentation

In April 2017, a 30-year-old male was admitted to our hospital, presenting with recurrent fever for 3 months and multiple painless subcutaneous nodules in the abdominal wall. The patient had no personal or family medical history of a malignant neoplasm. An excision biopsy of the subcutaneous nodules in the abdominal wall revealed extranodal NKTCL. Immunohistochemistry showed that the tumor cell population was positive for CD3, CD7, CD30, CD20, GrB, and TIA-1, and negative for CD2, CD4, CD5, CD8, CD43, CD10, CD21, CD23, Bcl-6, Bcl-2, CD79 $\alpha$ , PAX-5, CyclinD1, c-Myc, MUM-1, SOX11, CD56, and ALK. Ki-67 staining was used to determine the proliferation index, which was 80%. The tissue sample was also positive for Epstein-Barr virus-encoded RNA. The load of EBV-DNA was  $6.56 \times 10^4$  copies/mL, which was significantly above the normal range (<400 copies/mL). A further fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan showed multiple FDG-avid enlarged lymph nodes in the bilateral cervical, mediastinal, retroperitoneal, and inguinal regions. The PET-CT also showed pathological FDG uptake in the nasal cavity, subcutaneous nodules of the abdominal wall, and multiple lesions in the intestines, which were considered sites of lymphoma infiltration (Figure 1A, 1a). Bone marrow biopsy was negative for lymphoma. The

complete blood count, lactate dehydrogenase levels, and coagulation function were normal. Subsequently, the patient was diagnosed with stage IVB extranodal NKTCL with skin and multifocal small intestinal involvement. Unfortunately, just as the staging examination of the lymphoma was completed, the patient complained of sudden abdominal pain and was diagnosed with bowel perforation. Emergency exploratory laparotomy and partial enterectomy were performed. There were multiple diffuse lesions distributed in the small intestine and two separate focal perforations in the jejunum and ileum. Histological and immunohistochemical analysis of the lesions in the small intestine revealed NKTCL, which was the same as that of the subcutaneous nodules in the abdominal wall.

Two weeks later, the patient received one cycle of chemotherapy with modified a SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) regimen including one cycle of PIDE (pegaspargase, 2,500 IU/m<sup>2</sup>, day 1; ifosfamide, 1 g/m<sup>2</sup>, days 2-4; etoposide, 100 mg/m<sup>2</sup>, days 2-4; dexamethasone, 40 mg/d, days 1-4, repeated every 6 weeks) and one cycle of AspaMetDex (pegaspargase, 2,500 IU/m<sup>2</sup>, day 1; methotrexate, 3 g/m<sup>2</sup>, day 2; dexamethasone, 40 mg/day, days 1-4, repeated every 6 weeks). The regimens of PIDE and AspaMetDex were administered alternately, and the interval time between the two regimens was three weeks. After 2 cycles of chemotherapy, the subcutaneous nodules of the abdominal wall disappeared. The PET-CT scan confirmed that the response to this treatment was partial remission (PR) with a few residual lesions in the small intestinal tract before receiving the second cycle of PIDE chemotherapy (Figure 1B, 1b). Unexpectedly, the patient complained of sudden pain throughout the whole abdomen and had a fever of 38.7°C on day 3 of the second round of PIDE. The complete blood count showed that the concentration of hemoglobin was 6.4 g/dL (normal values: 12-15 g/dL), which was markedly lower than pre-chemotherapy levels. An intestinal perforation was suspected due to the abdominal tenderness and rebound pain. An abdominal X-ray revealed subdiaphragmatic free air. A second intestinal perforation was confirmed in this patient according to the clinical presentation and imaging results. We immediately stopped chemotherapy and all oral intake, and started antibiotics to prevent secondary peritonitis. Given the poor performance status and the risks associated with a second emergency surgery, conservative

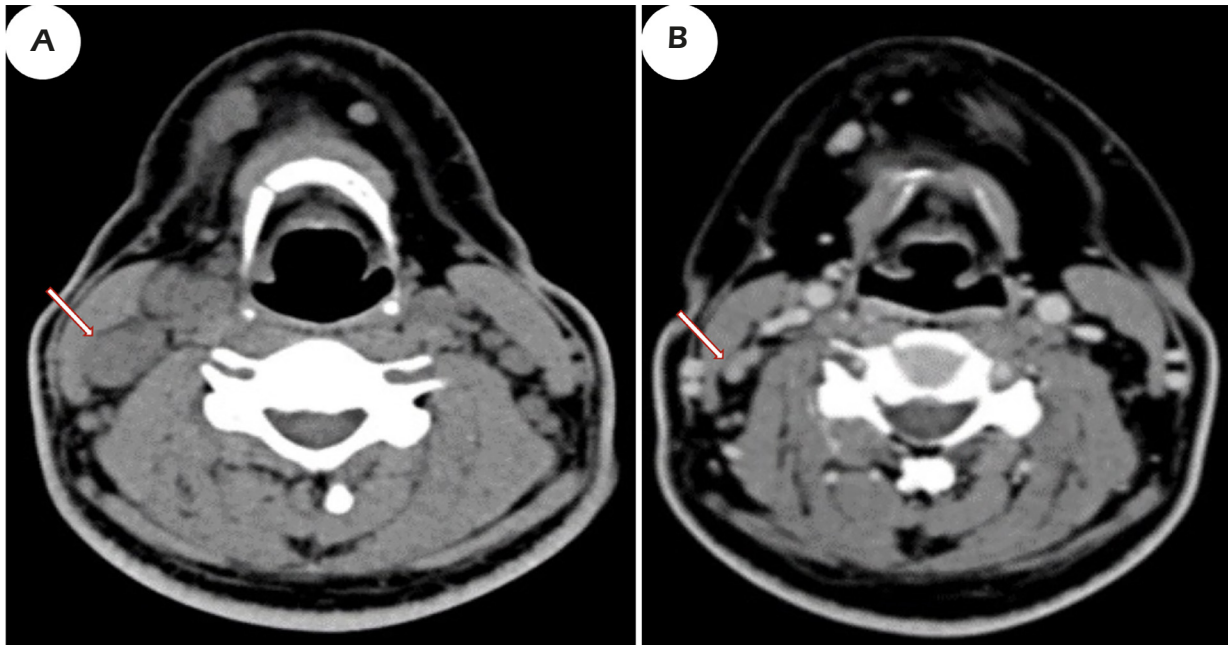


**Figure 1.** A, At the time of initial diagnosis, the PET-CT scan showed multiple FDG-avid enlarged lymph nodes in the bilateral cervical, mediastinal, retroperitoneal, and inguinal regions, and pathological FDG uptake in subcutaneous nodules of the abdominal wall and multifocal regions of the intestinal tract (a) (indicated by the arrows). B, After two cycles of chemotherapy, the PET-CT scan revealed only a few residual lesions in the intestinal tract (b) (indicated by the arrows). C, the PET-CT scan confirmed that all FDG-avid lesions had disappeared and no residual lesions in the intestinal tract (c) after receiving treatment with the HDACi chidamide.

medical management strategies were administered, including anti-infection agents, hemostasis therapy, fluid replacement therapy, total parenteral nutrition therapy, etc. Fortunately, the abdominal pain and fever subsided 10 days later. Upon re-examination using an abdominal X-ray, the subdiaphragmatic free air was confirmed to have disappeared.

The patient was very weak and could not tolerate further chemotherapy after experiencing the second bowel perforation. Therefore, the new agent chidamide (30 mg, po, biw) was administered. Considering the limitations of the CT scan that had been performed upon discovering the lesions in the small intestine, another PET-CT scan was performed three weeks later and showed that all lesions that initially exhibited high FDG uptake had disappeared (Figure 1C, 1c). The response was evaluated as complete remission (CR). However, the patient refused the recommended autologous stem cell transplantation as consolidation treatment and

continued with oral chidamide as a maintenance treatment. Five months later, he returned, presenting with recurrent fever for two weeks. A CT scan showed multiple enlarged lymph nodes in the bilateral cervical regions (Figure 2A), which were confirmed to be lymphoma by fine needle aspiration cytology. Considering the efficacy of PIDE in the first-line treatment, we continued the PIDE regimen of chemotherapy as the second-line salvage treatment, repeated every three weeks. The patient's response after 2 cycles of PIDE was PR (Figure 2B). Unfortunately, the patient suffered from disease progression after the fourth cycle of chemotherapy with enlarged lymph nodes in the bilateral cervical and retroperitoneal regions (Figure 3A). At this point, with his consent, the patient started to receive injections of the anti-programmed death 1 (PD-1) antibody camrelizumab (200 mg, every two weeks), commencing on May 29, 2018. Two months after initial treatment with



**Figure 2.** A, The CT scan showed enlarged lymph nodes in the cervical regions (indicated by the arrow). B, After receiving two cycles of the salvage chemotherapy, the CT scan revealed that the enlarged lymph nodes in the cervical region were shrinking (indicated by the arrow).

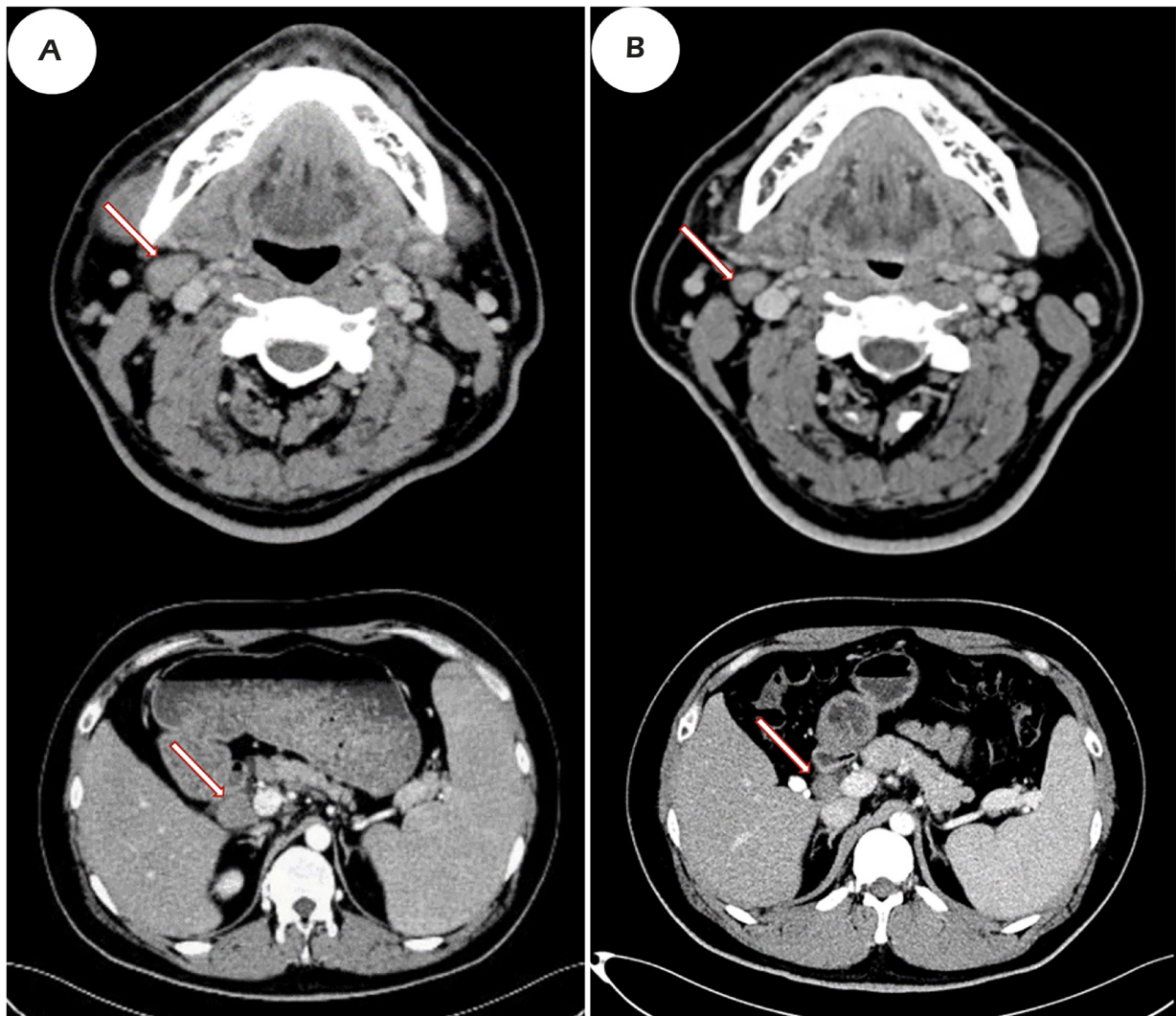
camrelizumab, a PET-CT scan confirmed that the response was PR (Figure 3B). During the period of receiving camrelizumab injections, the patient experienced a good quality of life without severe adverse effects. However, in March 2021, disease progression was again confirmed, combined with lymphoma-associated hemophagocytic syndrome (LHPS), resulting in a progression free survival (PFS) of 34 months. The patient died due to LHPS in April, 2021, with the overall survival time of 47 months. The timeline is shown in Figure 4.

## Discussion

The majority of NKTCLs occur in the midline facial structures such as the nasal cavity and its adjacent sites. Other extranodal tissues that are commonly involved include the skin, GI tract, lungs, liver, and testes, especially in advanced cases. The GI tract is one of the most common extranodal sites of NKTCL. Among GI-NKTCL patients, the incidence rate of intestinal involvement is higher than that of gastric involvement. It has been reported<sup>7</sup> that the most commonly involved GI sites are intestinal, especially the ileum and jejunum. Meanwhile, other studies<sup>8</sup> report that the large intestine is the most common site. The most common appearance of GI-NKTCL under

endoscopy features focal, multifocal, or diffuse irregular ulcers. Bowel perforation is relatively common among GI-NKTCL patients; a retrospective study by Vaidya et al<sup>9</sup> estimated that the incidence rate of bowel perforation in lymphoma patients with GI involvement is 9% (92/1062). A separate study by Kim et al<sup>10</sup> reported a higher incidence rate of 15% (12/81). The German Study Group on intestinal NHL reported<sup>11</sup> a similarly higher incidence of bowel perforation in intestinal T-cell lymphoma compared to the equivalent B-cell lymphoma. Bowel perforation can occur at diagnosis as the initial manifestation of lymphoma or during the period of treatment. The most common site of bowel perforation among patients with lymphoma with GI involvement is the small intestine, and the most common symptoms are abdominal pain, fever, and gastrointestinal hemorrhage<sup>9</sup>. The possible etiologies of bowel perforation in lymphoma patients with GI involvement included tumor infiltration, tumor necrosis in response to therapy, acute inflammation, and so on. The occurrence of bowel perforation may result in increased morbidity from severe peritonitis, intestinal hemorrhage, and delay in treatment for lymphoma<sup>3,5</sup>.

Systemic intensive chemotherapy is an important treatment for advanced NKTCL patients. L-asparaginase (L-Asp)-based chemotherapy

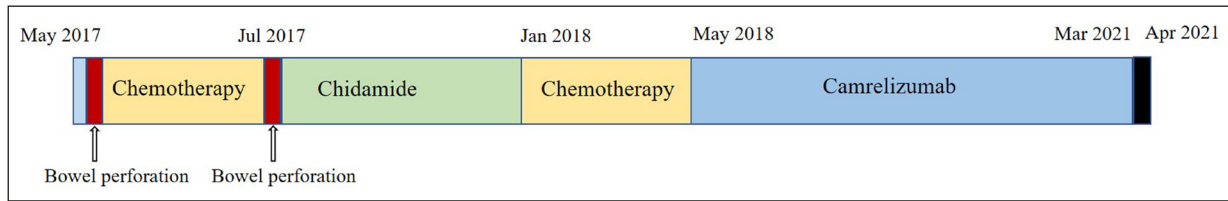


**Figure 3.** A, The CT scan showed enlarged lymph nodes in the cervical and retroperitoneal regions (indicated by the arrows). B, Two months after initial camrelizumab treatment, re-examination by CT scan revealed that the enlarged lymph nodes in the cervical and retroperitoneal regions were shrinking (indicated by the arrows).

regimens have shown<sup>12</sup> to be more effective in the treatment of both localized and systemic NKTCL compared to anthracycline-based chemotherapy. AspaMetDex and SMILE chemotherapy regimens are recommended by the National Comprehensive Cancer Network (NCCN) practice guideline (available at: <https://www.nccn.org>) for T-cell lymphoma. Although the SMILE chemotherapy regimen has shown excellent efficacy in advanced NKTCL, chemotherapy-related severe bone marrow suppression and infection have also been reported<sup>13</sup>. A study by Kim et al<sup>10</sup> revealed that the prognosis following L-Asp-based chemotherapy, such as SMILE, was not superior to that of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) or CHOP-like chemotherapy due

to the high incidence rate of treatment-related mortality in NKTCL patients with GI tract involvement. Chemotherapy-related adverse events including neutropenia, thrombocytopenia, and coagulation disorders may hinder the appropriate and optimal surgical intervention if bowel perforation occurs during chemotherapy in GI-NKTCL patients. Therefore, some studies<sup>5,6</sup> report that patients with GI-NKTCL typically have an aggressive clinical course with a poor prognosis and short survival time when complicated by primary or secondary bowel perforation.

There is still no established treatment strategy for NKTCL involving the GI tract. The treatment of GI-NKTCL complicated by bowel perforation is intractable. In the present case, we designed



**Figure 4.** Timeline. The clinical course of the treatment for this intractable NK/T cell lymphoma patient with two occurrences of intestinal perforation. The patient was diagnosed with NK/T cell lymphoma and suffered from the first intestinal perforation in May 2017. The second intestinal perforation occurred after receiving two cycles of chemotherapy in Jul 2017. The HDACi chidamide was administered as a single-agent therapy from Jul 2017 after the patient recovered from the second intestinal perforation. Relapse was confirmed in Jan 2018 and the patient received 4 cycles of chemotherapy. The response was PR after two cycles of chemotherapy, but disease progression was confirmed after the fourth cycle of chemotherapy. The patient started to receive injections of the anti-PD-1 antibody camrelizumab from May 29, 2018 and disease progression was confirmed in March, 2021. The patient died in April, 2021.

a new modified SMILE chemotherapy regimen including PIDE and AspaMetDex considering the patient's tolerance to chemotherapy and the risk of bowel perforation. This regimen was expected to reduce the toxicity of chemotherapy and the risk of a second bowel perforation through decreasing the intensity of chemotherapy and prolonging the administration time. The etiology of the first bowel perforation was tumor infiltration and destruction of the intestinal wall, which was confirmed by a timely emergency exploratory laparotomy. The cause of the second bowel perforation during the period of chemotherapy remains uncertain. We speculate that acute inflammation or tumor necrosis as a response to chemotherapy may have contributed to the later bowel perforation. Unfortunately, as expected, the two instances of bowel perforation resulted in a delay in systemic chemotherapy and a reduction of the patient's tolerance to further intensive systemic chemotherapy.

In many cases, GI-NKTCL patients who suffer from bowel perforation do not receive any further treatment for NKTCL due to their poor health conditions. A potential salvage therapy in this case may be chidamide, a novel orally bioavailable histone deacetylase inhibitor (HDACi), which has inhibitory activity against HDAC1, HDAC2, HDAC3, and HDAC10<sup>14</sup>. Chidamide has shown activity against several types of tumors *in vitro* and *in vivo*<sup>15,16</sup>. In the context of NKTCL, chidamide showed antitumor effects *in vitro* by inhibiting the protein kinase B/mammalian target of rapamycin (AKT/mTOR) and mitogen-activated protein kinase (MAPK) signaling pathways and activating the ATM-Chk2-p53-p21 signaling pathway<sup>17</sup>. In the clinic<sup>18</sup>, chidamide demonstrated preferential efficacy and good tolerance in 79 patients with refractory or relapsed peripheral T-cell lymphoma, including 16 patients with refractory

or relapsed NK/T cell lymphoma, achieving an overall response rate of 28%. Most responses were observed within the first 6 weeks of oral chidamide administration, and the median duration of response was 9.9 months (range: 1.1 to 40.8). The overall response rate was 19% (3/16) in patients with refractory or relapsed NKTCL, including one patient with complete remission and two patients with partial remission. Based on this study, chidamide was approved for the treatment of relapsed or refractory peripheral T-cell lymphoma patients by the China Food and Drug Administration in December 2014. In the current report, the patient could not tolerate the intensive combination chemotherapy due to his poor health condition. Therefore, chidamide was administered with close attention to the adverse effects. Fortunately, this new agent was effective and tolerated well in this patient. Despite a poor performance status, the patient gained 5 months of progression-free survival time with chidamide, which allowed him to recover and receive further treatment with good tolerance. Autologous stem cell transplantation had been recommended as a consolidation therapy for patients with relapsed/refractory NKTCL responding to primary therapy, according to the 2017 National Comprehensive Cancer Network practice guideline (<https://www.nccn.org>) of T-cell lymphoma. However, the patient in this report refused the recommended autologous stem cell transplantation as consolidation treatment and continued with oral intake chidamide as a maintenance treatment.

Unfortunately, relapse was confirmed five months later. The prognosis for relapsed/refractory NKTCL patients is extremely poor, in part due to the lack of an established standard treatment strategy for these patients. All refractory/relapsed NKTCL patients are potential candidates for

clinical trials of new agents. Recent studies<sup>19,20</sup> suggested that immune checkpoint blockade with antibodies against programmed cell death protein 1 (PD-1) is a potential strategy for relapsed/refractory NKTCL patients for whom L-Asp-base chemotherapy regimens failed. Kwong et al<sup>19</sup> study demonstrated that the overall response rate of the anti-PD-1 antibody pembrolizumab was 100% after a median of seven cycles of treatment in refractory/relapsed NKTCL patients. In another study<sup>20</sup> using the anti-PD-1 antibody pembrolizumab in refractory/relapsed NKTCL patients, the overall response rate was 57% with a median of four cycles of pembrolizumab. Anti-PD-1 therapies work by targeting the overexpression of the immune checkpoint programmed cell death protein ligand 1 on NKTCL cells<sup>21</sup>. In our study, fortunately, the patient received treatment with the anti-PD-1 antibody camrelizumab as a salvage therapy and achieved a progression-free survival of 34 months without severe adverse effects. Hence, in this patient, the anti-PD-1 antibody camrelizumab showed encouraging efficacy and a manageable safety profile.

## Conclusions

Advanced NKTCL with multifocal small intestine involvement complicated by recurrent bowel perforation is a rare condition with an extremely poor prognosis. Bowel perforation can lead to serious complications with high morbidity, including severe peritonitis, intestinal hemorrhage, and delayed treatment for lymphoma. There is no standard treatment strategy for this rare condition. Individual treatments should be based on the patient's tolerance to chemotherapy, combined with the physician's experience and close attention to the high risk of perforation during the period of the treatment. Novel anti-PD-1 antibody therapies may have potential for treating this type of intractable NKTCL. Further observations and future research are required to identify and confirm the efficacy and safety of new agents.

## Ethics Approval

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

## Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Availability of Data and Materials

All data are fully available without restriction.

## Conflict of Interest

The authors indicated no potential conflicts of interest.

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## Authors' Contributions

Liling Zhang and Fang Zhu designed the research. Tao Liu, Huaxiong Pan collected the data. Qiuhui Li and Xinxu Liu performed analysis. Fang Zhu and Xia Yun wrote the manuscript. Liling Zhang reviewed the manuscript.

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