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CASE REPORT

Treatment of refractory/relapsed extranodal NK/T cell lymphoma with decitabine plus anti-PD-1: A case report

Lin-Jie Li, Jun-Yu Zhang

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Abstract

BACKGROUND

Extranodal natural killer/T cell lymphoma, nasal type (ENKL) is a highly aggressive malignancy characterized by its association with Epstein-Barr virus (EBV) and extranodal involvement, which shows a poor clinical outcome. Although L-asparaginase-based chemotherapy has improved the response rates of relapsed/refractory (R/R) ENKL, relapse occurs in up to 50% of patients with disseminated disease.

CASE SUMMARY

Immune evasion has emerged as a critical pathway for survival in ENKL and may be effectuated *via* STAT3-driven upregulation of programmed cell death ligand 1 (PD-L1) or other molecular pathways. Anti-PD-1 is effective for R/R ENKL with EBV-driven upregulation of PD-L1 expression. Anti-PD-1 combined with decitabine showed positive preliminary results in a patient with R/R ENKL and resistance to anti-PD-1.

CONCLUSION

The treatment experience, in this case, demonstrated the potential ability of decitabine combined with PD-1 inhibitor to treat R/R ENKL, thus providing a new treatment strategy for this tumor.

Key Words: NK-T cell lymphoma; Refractory/relapsed; Anti-PD-1; Decitabine; Case report

Core Tip: Extranodal natural killer/T cell lymphoma nasal type is a highly aggressive malignancy characterized by its association with Epstein-Barr virus and extranodal involvement, which shows a poor clinical outcome. Now, we report a rare case of relapsed/refractory classic Hodgkin lymphoma with resistance to anti-PD-1 in which anti-PD-1 combined with decitabine showed positive preliminary results. Our findings support the potential benefit of anti-PD-1 combined with decitabine in this type of refractory T-cell lymphoma.

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INTRODUCTION

Extranodal natural killer/T cell lymphoma (ENKL) is a rare T-cell lymphoma with a poor prognosis and poor response to conventional chemotherapy. ENKL is more prevalent in China than in Western countries[1,2]. It is a highly aggressive lymphoma with poor efficacy and prognosis by traditional treatments[3,4]. The treatment options for relapsed/refractory (R/R) ENKL are still limited, and improving the treatment is an urgent requirement. Some studies have shown that ENKL cells avoid immune surveillance and the consequent killing of ENKL, resulting in a poor outcome[5].

CASE PRESENTATION

Chief complaints

A 54-year-old male patient was admitted to our hospital with a diagnosis of ENKL for > 4 years.

History of present illness

About 4 years ago, the patient visited our hospital for recurrent gingival bleeding accompanied by night sweats and a recent weight loss of > 10 kg. Positron emission tomography/computed tomography (PET/CT) showed multiple lymphadenopathies in the bilateral neck and supraclavicular area (especially in the right neck), strip-shaped soft tissue density shadow in the right nasal cavity, and significantly increased fluorodeoxyglucose (FDG) metabolism (Figure 1). Biopsy of the right nasal septum mucosa was performed postoperatively, and the pathology showed ENKL. Immunohistochemistry showed CD3 +, CD4 +, CD56 +, granzyme B +, CD8 -, CD20 -, Pax5 -, and Ki-67 + (about 80%). Molecular *in situ* hybridization demonstrated positivity for EBER (Figure 2).

History of past illness

The patient had no history of past illness.

Personal and family history

No personal or family history was available.

Physical examination

There were multiple lymphadenectasis in the bilateral neck especially in the right neck. No palpable enlargement of the liver or spleen was noted.

Laboratory examinations

The liver function, renal function, routine blood tests, myocardial enzymes, and coagulation function were normal. Bone marrow puncture was not performed.

Imaging examinations

On March 3, 2018, PET/CT showed multiple lymphadenopathies in the bilateral neck and supraclavicular area (especially in the right neck), strip-shaped soft tissue density shadow in the right nasal cavity, and significantly increased FDG metabolism and a high standard uptake value (SUV) with a Deauville score of 7.6 (Figure 1).

On June 6, 2017, PET/CT showed that the original lesions in the right nasal cavity, bilateral neck, and supraclavicular area had subsided and become inactive compared to the scan on March 3, 2017. However, there was new large, curved wall thickening of the gastric body, multiple nodules of the

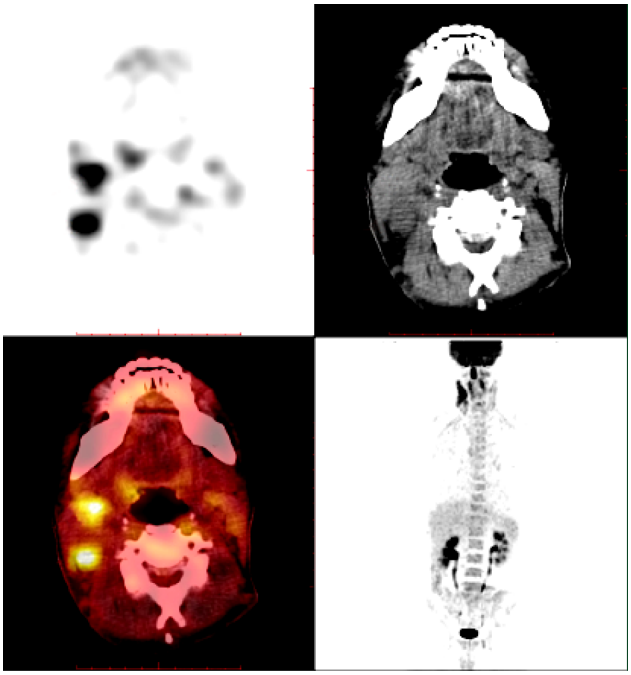

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Figure 1 Multiple lymphadenopathies in the bilateral neck and supraclavicular area (especially in the right neck), strip-shaped soft tissue density shadow in the right nasal cavity, and significantly increased fluorodeoxyglucose metabolism as revealed by standard uptake value (SUV) with a Deauville score of 7.6.

spleen, multiple lymphadenopathies around the stomach, mediastinum and left hilum, and increased FDG metabolism (Figure 3).

On November 9, 2021, PET/CT showed that right mediastinal paratracheal, right main bronchial, and subcarinal lymph nodes and ileocecal small nodules subsided and became inactive, and the metabolism of left lower lobe nodules was decreased significantly (SUVmax decreased from 10.2 to 3.8) (Figure 4).

FINAL DIAGNOSIS

According to the above medical history, the final diagnosis was ENKL.

TREATMENT

After diagnosis, the patient was given SMILE regimen for two cycles (methotrexate 4.5 g d1, dexamethasone 40 mg d1–4, ifosfamide 2 g d2–4, etoposide 160 mg d2–4, L-asparaginase 3200 U d5) on March 10 and April 8, 2017, respectively. Since May 2, 95% planned target volume at 54Gy/28f was irradiated to the local lesion and irregular large-area fields on both sides of the neck. PET/CT on June 6, 2017 showed that the original lesions in the right nasal cavity, bilateral neck, and supraclavicular area have subsided and become inactive compared to the scan on March 3, 2017. However, there was new large, curved wall thickening of the gastric body, multiple nodules of the spleen, multiple lymphadenopathies around the stomach, mediastinum, and left hilum, and increased FDG metabolism (Figure 3). Gastroscopic pathological biopsy suggested ENKL. Then, DDGP regimen plus methotrexate (gemcitabine 1.63 g d1 and 8, methotrexate 3.20 g d1, dexamethasone 30 mg d1–4, L-asparaginase 3750 U d5) chemotherapy was administered for two cycles. On August 30, after SMILE regimen was repeated, stem cells were prepared for autologous stem cell transplantation, but the collection failed. On October 27, modified SMILE regimen (dexamethasone 32 mg d1–4, etoposide 100 mg d2–4, methotrexate 3.6 g d1, L-asparaginase 3750 U d5) chemotherapy was administered. Compared to June 6, 2017, the PET/CT on November 17 showed that the original lesions of the left lung, great curvature of the gastric body, perigastric, spleen, mediastinum, and left hilum had subsided and become inactive, but there were new lesions on the pancreatic head and right lung, with increased FDG metabolism. The patient revisited our hospital, and he was considered with refractory lymphoma. Thus, pembrolizumab 200 mg was administered every 21 d. The follow-up PET/CT after 6 mo showed complete remission of lymphoma. So, the maintenance treatment was continued for > 2 years. However, in July 2021, PET/CT

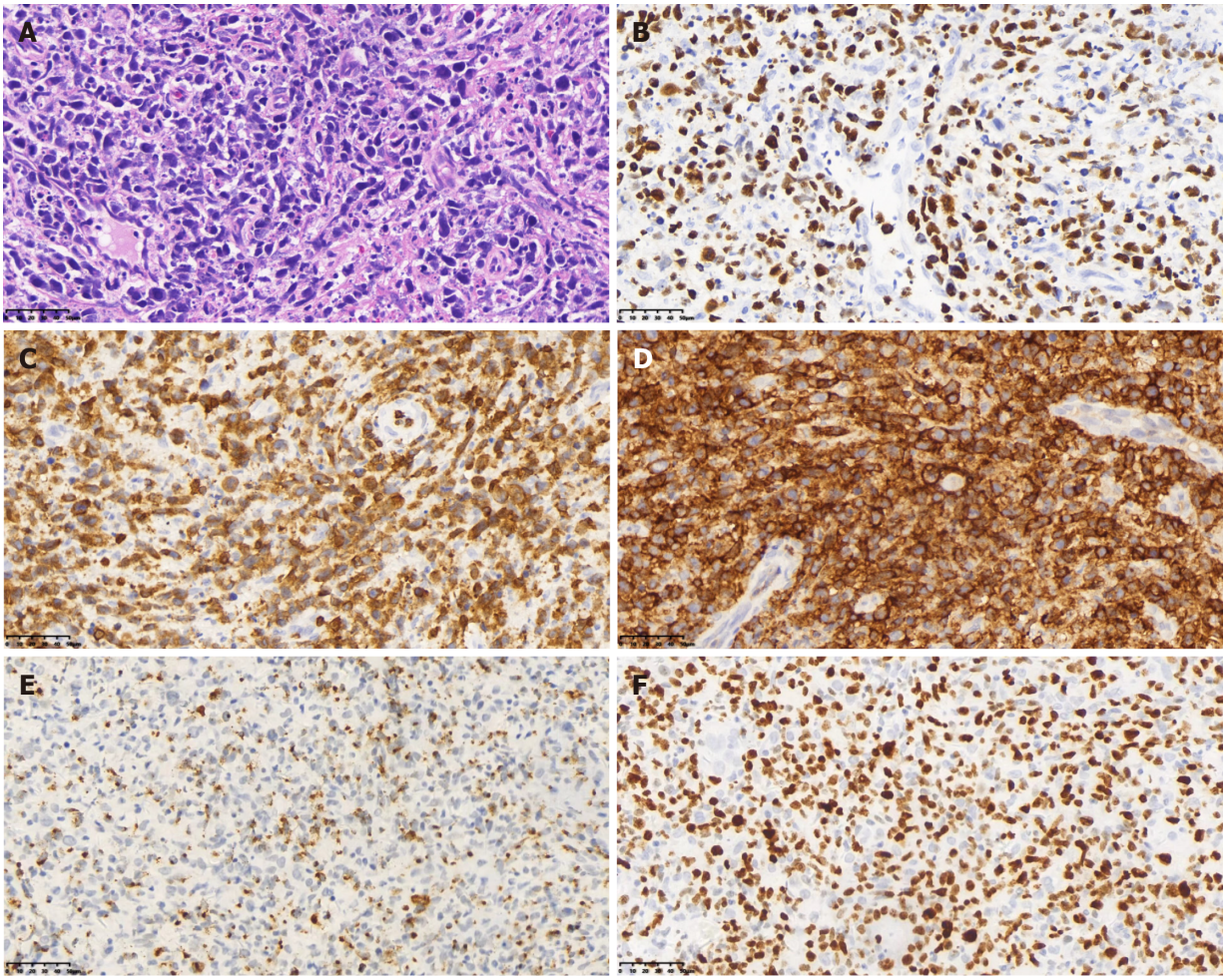

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Figure 2 Molecular *in situ* hybridization demonstrated positivity for EBER. A: Tumor cells are large, nucleus pleomorphic or elongated, deeply stained, diffuse, and patchy (hematoxylin-eosin staining, × 400); B: EBER positivity (*in situ* hybridization, × 400); C: CD3 positivity (Envision two-step immunohistochemical staining, × 400); D: CD56-positivity (Envision two-step immunohistochemical staining, × 400); E: Granzyme B positivity (Envision two-step immunohistochemical staining, × 400); F: Ki-67 positive expression rate of 80%.

showed that the right mediastinal paratracheal, right main bronchial, and subcarinal lymph nodes (groups 4R, 10R, and 7) were further enlarged. New nodules were added in the lower lobe of the left lung, and small nodules were added in the ileocecal part; all had significantly increased FDG metabolism (Figure 4). However, no tumor cells were found in the alveolar lavage fluid and bronchoscopic biopsy. Combined with the medical history and clinical presentation, this patient was considered with relapsed ENKL, and AspaMetDex regimen chemotherapy (methotrexate 3 g d1, dexamethasone 40 mg d1–4, L-asparaginase 3400 U d5) combined with chidamide 30 mg orally twice a week was used. Repeat CT showed that the lesions in the lower lobe of the left lung increased in size after two cycles. As the disease progressed, we utilized the regimen of decitabine 25 mg d1–5, sintilimab 200 mg d6, and L-asparaginase 3750 U d10 for combined chemotherapy.

OUTCOME AND FOLLOW-UP

The above scheme was repeated after 4 wk. PET/CT on July 16, 2021 showed that after 8 wk, the right mediastinal paratracheal, right main bronchial, subcarinal lymph nodes, and small ileocecal nodules subsided and were inactive, and the left lower lobe nodules, and FDG metabolism decreased significantly (Figure 4). This patient is still undergoing regular chemotherapy every 4 wk: Decitabine 25 mg d1–5, sintilimab 200 mg d6, and L-asparaginase 3750 U d10. To the best of our knowledge, this is the first case of decitabine combined with anti-PD-1 applied to R/R ENKL.

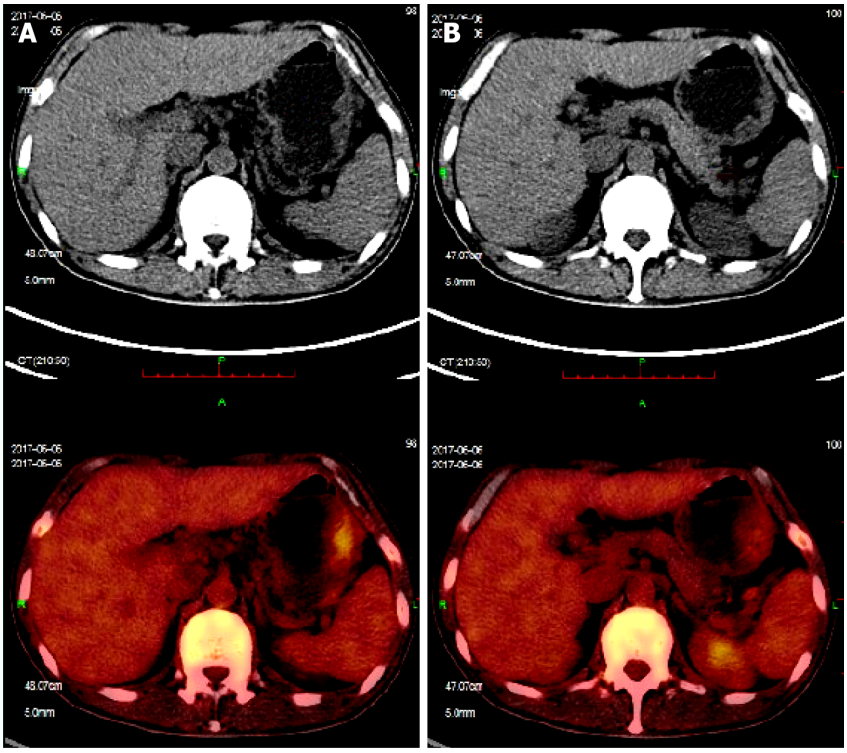

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Figure 3 Positron emission tomography/computed tomography images. A and B: New large-curved wall thickening of the gastric body, multiple nodules of the spleen, and multiple lymphadenopathies around the stomach.

DISCUSSION

As an inhibitory receptor, PD-1, expressed on the surface of activated T cells, is involved in immune tolerance and the prevention of tissue damage associated with chronic inflammation. Inflammatory cytokines have been found to induce programmed cell death ligand 1 (PD-L1) expression in many studies. In particular, the involvement of IFN-γ in immune checkpoint induction has been reported. When the expression of proinflammatory cytokines was high, it suggests the possibility that the expression of PD-L1 Therefore, it suggests the possibility that the expression of PD-L1[6].

PD-1 interacts with its ligands PD-L1 and PD-L2 to inhibit T cell receptor signal, downregulate T cell activation and proliferation, and weaken the T cell-mediated anti-tumor immune response[7,8]. Therefore, the PD-1 pathway is an immune checkpoint that suppresses anti-tumor immunity. Other studies have reported the efficacy of anti-PD-1 in R/R ENKL[5,9].

Exhausted T cells, including memory-like exhausted T cells that respond to PD-1 inhibitors, ultimately differentiate into terminal exhausted T cells. These T cells are resistant to anti-PD-1-induced rejuvenation but can still exhibit distinct epigenetic profiles[10-12]. Another study identified low-dose DNA demethylating agents that alter T-cell's epigenetic status and enhance the anti-tumor activity of PD-1/PD-L1 blockade therapy in mouse models[13,14]. Reportedly, T cell phenotype and function and the expression of PD-1 are strongly regulated by epigenetic changes[15,16]. Patients with hematological malignancies treated with hypomethylating agents have demonstrated increased expression of PD-1 transcripts and proteins on the cell surface[17,18]. With the expanding application of immune checkpoint inhibitors in hematological malignancies, immunotherapies targeting the PD-1/PD-L1 axis combined with hypomethylating agents may counteract the upregulation of PD-1/PD-L1 checkpoints and improve the clinical outcomes[18]. While anti-PD-1 alone had modest effects, hypomethylating agents followed by anti-PD-1 therapy inhibited tumor growth and prolonged the survival of the pancreatic cancer mouse model[19]. Wang *et al*[20] found that decitabine combined with anti-PD-1 achieves curative effects in patients with R/R Hodgkin's lymphoma resistant to anti-PD-1 and is a safe and feasible approach. A randomized phase II study of R/R Hodgkin's lymphoma demonstrated that anti-PD-1 plus decitabine was well-tolerated and improved the clinical outcomes compared to anti-PD-1 alone with regard to the duration of response (DOR) and progression-free survival (PFS)[21]. The common treatment-related adverse events, such as a benign and reversible skin condition, reactive capillary endothelial proliferation, and leukocytopenia, but no treatment-related infections, were identified[21]. Although this protocol has achieved good preliminary results in Hodgkin's lymphoma and other tumors, this is the first attempt to use this combination therapy in R/R ENKL. Our patient was resistant to pembrolizumab after continual treatment for 2 years but still achieved near-complete

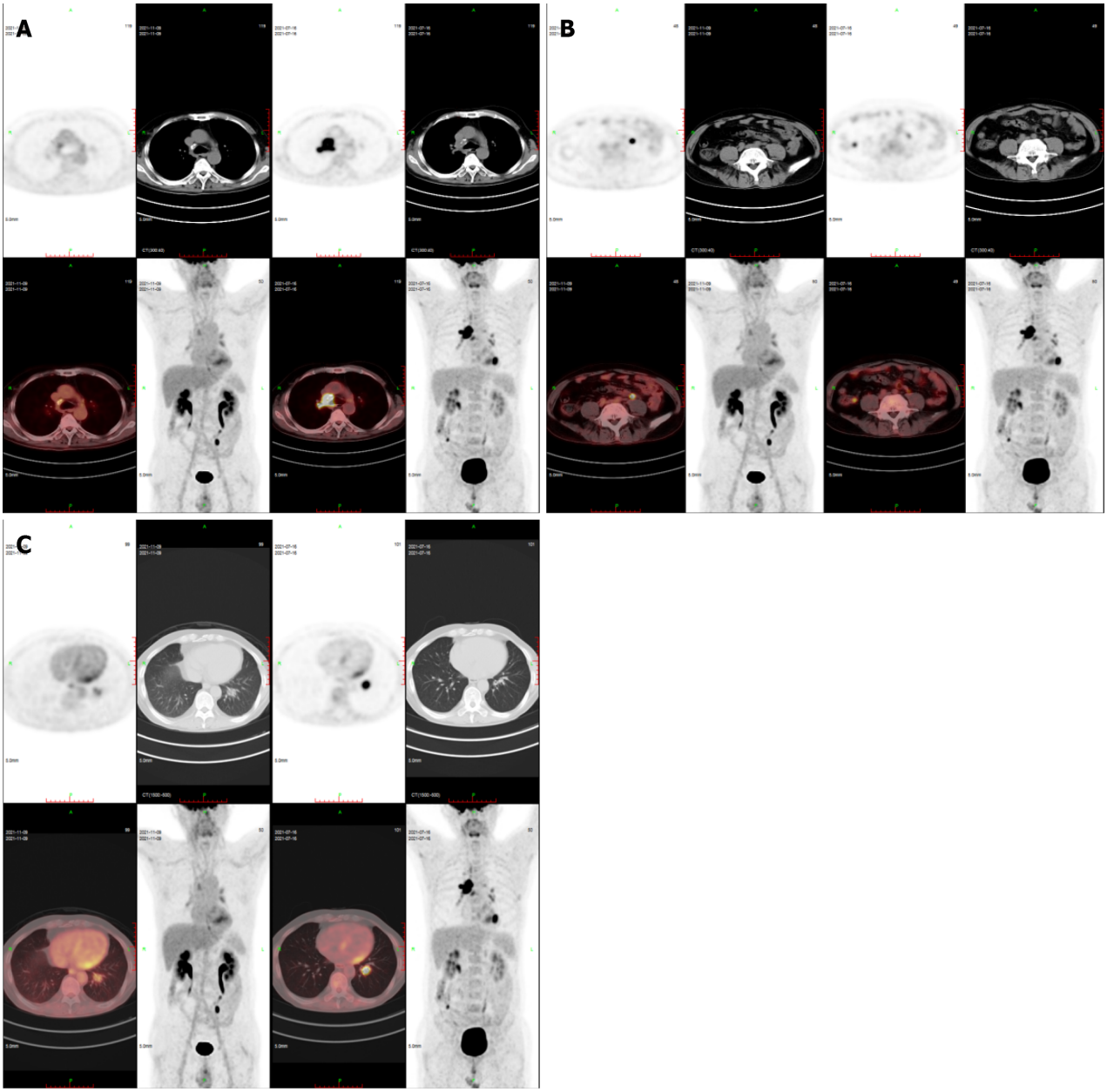

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Figure 4 Positron emission tomography/computed tomography images. A-C: Compared to the film on July 16, 2021, that taken on November 9, 2021 showed that right mediastinal paratracheal, right main bronchial, subcarinal lymph nodes and ileocecal small nodules had subsided and become inactive, and the metabolism of left lower lobe nodules was decreased significantly (SUVmax decreased from 10.2 to 3.8).

remission by decitabine combined with sintilimab. Although the binding sites of the two antibodies are different, more over the Fc side of sinitinib was modified to avoid direct phagocytosis of antibody molecules. These mechanisms maybe result in the different response between these two antibodies. But as far as the current research is concerned, sintilimab has similar anti-tumor effects to other anti-PD-1 [22]. No treatment-related adverse events were noted in our case.

L-asparaginase-based chemotherapy improves the response rate of R/R ENKL. However, no studies have yet reported that L-asparaginase has a synergistic effect with anti-PD-1 or demethylated drugs.

CONCLUSION

The experience of this case offers a new option for the treatment of R/R ENKL resistant to anti-PD-1 and other types of lymphomas. This case is only an empirical report of a single case, and the efficacy of decitabine combined with anti-PD-1 in R/R ENKL needs to be confirmed in more patients.

FOOTNOTES

Author contributions: Zhang JY designed the report and wrote the paper; Li LJ collected the patient's clinical data; all authors have read and approved the final version of this manuscript.

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