Case Report

Tumor Lysis Syndrome Due to Pembrolizumab Use in Metastatic Nasopharyngeal Carcinoma

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Cite this article as: Turhan A, Hannarici Z, Büyükbayram ME, et al. Tumor lysis syndrome due to pembrolizumab use in metastatic nasopharyngeal carcinoma. Arch Basic Clin Res. 2024;6(1):73-76.

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ABSTRACT

In this case, we report tumor lysis syndrome (TLS) in a patient with metastatic nasopharyngeal carcinoma treated with pembrolizumab. There are only a few studies reporting the development of TLS associated with pembrolizumab, but this is the first report to include a patient with nasopharyngeal carcinoma. We think that this case report may help us to improve our current understanding of TLS in solid tumors, particularly nasopharyngeal carcinoma. We also believe that there should be a multidisciplinary treatment and prophylactic approach for TLS, a potentially fatal complication associated with pembrolizumab treatment.

Keywords: Pembrolizumab, nasopharyngeal carcinoma, tumor lysis syndrome

INTRODUCTION

Programmed cell death protein-1 (PD-1) is a cell surface receptor belonging to the immunoglobulin superfamily proteins expressed on T cells, B cells and natural killer cells.¹ Blockade of PD1 is used as an important immunotherapeutic strategy for cancers.² Pembrolizumab is a humanized monoclonal antibody that can restore antitumor immune activity in solid tumors and hematological malignancies by blocking the interaction between PD-1 and its ligands (PD-L1).³ Tumor lysis syndrome (TLS) following pembrolizumab use has been reported in several malignancies.4-6 Tumor lysis syndrome is an oncological emergency with a high mortality rate, resulting from metabolic disorders attributed to the lysis of malignant cells and the massive release of intracellular materials into the circulation.⁷ The characteristic findings of TLS include cardiac arrhythmia, seizures, uremia, acute renal failure (ARF), and various forms of electrolyte imbalance, including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, which can jointly lead to sudden death.8 The earlier TLS is detected and treated, the less likely it is to result in severe outcomes.7

In this report, our purpose was to present a case that developed TLS after pembrolizumab use for the treatment of metastatic nasopharyngeal carcinoma.

CASE PRESENTATION

A 49-year-old female patient with type 2 diabetes mellitus and squamous cell nasopharyngeal carcinoma was admitted to our clinic. In the examinations performed on admission, it was determined that the patient had liver, bone, and lymph node metastases. The patient was diagnosed with cancer in another center and received chemoradiotherapy for the mass in the nasopharynx. Gemcitabine+cisplatin treatment was started after the disease progressed. However, when the disease progressed again, a docetaxel + capecitabine course was applied once. At this stage, the patient applied to our clinic. The last chemotherapy treatment protocol that the patient received was given 2 more cycles and we requested the PD-L1 test. Docetaxel + capecitabine treatment was completed for 3 cycles and good response was obtained. As we got a good response, 3 more cycles of docetaxel + capecitabine were given. In the evaluation made after 6 cycles of treatment,

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progression was detected. Numerous metastases were detected in the cervical lymph nodes, liver, and bones in the positron emission tomography. The patient with liver and bone metastases was hospitalized to be kept under close observation due to a high bilirubin concentration and severe pain. The patient's PD-L1 test was positive. Tumor proportion score was >50 and combined positive score was >60%. Pembrolizumab was planned to be administered as a single agent to the patient with an Eastern Cooperative Oncology Group performance score of 1. Before the treatment, the patient's detailed blood values and vital parameters were measured. The patient's systolic/diastolic blood pressure was 130/80 mm Hg, and oxygen saturation was 93%. Biochemical analyses showed that corrected calcium was 7.8 mg/dL, phosphate was 1.8 mg/dL, potassium was 3.4 mmol/L, uric acid was 6.1 mg/dL, blood urea nitrogen was 21.3 mg/dL, and creatinine was 0.6 mg/dL. Calcium replacement was performed, and pembrolizumab was administered intravenously at a dose of 200 mg.

One day after the patient was given pembrolizumab treatment, nausea, vomiting, weakness, dizziness, and tachycardia developed in addition to her current complaints. The patient's blood values were re-evaluated and hypocalcemia (corrected calcium: 7.2 mg/dL), hyperphosphatemia (5.4 mg/dL), hyperuricemia (14.6 mg/dL), and elevation in creatinine (2.1 mg/dL) were detected. From these results, it was understood that TLS-induced acute renal failure developed. Treatment with aggressive intravenous fluid infusion and allopurinol was started immediately, and urine output was closely monitored. Electrocardiography (ECG) revealed that the patient was mildly tachycardic and in sinus rhythm. Calcium replacement was done. When blood parameters were re-measured 6 hours after intravenous treatment, hyperphosphatemia (8.2 mg/dL), hyperuricemia (15.8 mg/dL), hypocalcemia (corrected) calcium: 7.2 mg/dL), and hyperkalemia (6.4 mmol/L) developed. Creatinine (2.4 mg/dL) and blood urea nitrogen level (39.6 mg/dL) increased. T waves were normal in the re-examined ECG. Insulin+dextrose treatment was started for hyperkalemia. The patient was admitted to

MAIN POINTS

- Pembrolizumab is used in the treatment of nasopharyngeal carcinoma.
- Tumor lysis syndrome (TLS) has been reported following the use of pembrolizumab in several malignancies.
- Tumor lysis syndrome is an oncological emergency with a high mortality rate.
- If pembrolizumab is used in the treatment of patients with metastatic nasopharyngeal carcinoma, tumor lysis syndrome should be kept in mind.

the intensive care unit to be closely monitored for ARF and TLS and was consulted to nephrology for hemodialysis because of decreased urine output, fluid overload, and metabolic acidosis. The patient was taken to hemodialysis in the intensive care unit. Later, unfortunately, our patient died due to sudden cardiac arrest.

DISCUSSION

Immune checkpoint inhibitor treatments can induce TLS in both solid and hematological malignancies.⁹ Increasing awareness of the potential complications of anti-PD-1/ PD-L1 immunotherapy can guide clinical decisions by aiding decisions to prevent adverse outcomes.¹⁰ In the current case, TLS was detected after pembrolizumab treatment in a case with metastatic nasopharyngeal carcinoma. While there are a few reports in the literature reporting TLS after pembrolizumab for other malignancies, this is the first to report pembrolizumab-induced TLS in a patient with nasopharyngeal carcinoma.

In a study evaluating pembrolizumab treatment in patients with myelodysplastic syndrome, it was reported that treatment could not be continued due to TLS in 1 of the 28 patients.³ In another study, TLS was reported in a patient with non-small cell lung carcinoma after chemotherapy with pembrolizumab and paclitaxel.⁵ In the study of Hlaing et al.,⁶ it was concluded that TLS developed in a case with endometrial adenocarcinoma after 2 cycles of treatment with pembrolizumab and a tyrosine kinase receptor inhibitor, lenvatinib. In a case report published for a patient with primary metastatic urothelial carcinoma, TLS developed 8 days after a course of treatment with the anti PD-L1 antibody, atezolizumab.¹¹ In a case report of a patient with metastatic triple negative breast cancer, TLS was observed after combined treatment with atezolizumab and nab-paclitaxel.¹² Sugimoto et al.¹³ reported TLS after nivolumab (anti PD-1) treatment in a patient with metastatic melanoma.¹³ Tumor lysis syndrome was reported in a case of hepatocellular carcinoma treated with the combination of nivolumab and sorafenib.¹⁴ Avelino and colleagues reported that a patient with metastatic squamous cell lung carcinoma treated with pembrolizumab was intubated in the ICU due to post-treatment emergence of T-cell prolymphocytic leukemia, dyspnea, hyperviscosity, and TLS.¹⁵ Emergency leukapheresis was initiated due to the TLSinduced development of ARF and hyperviscosity, and the patient also received continuous renal replacement therapy; however, they died as a result of hemodynamic decompensation. Although hematological malignancies secondary to immunomodulators were emphasized in this case report, it is noteworthy that TLS developed after pembrolizumab.¹⁵ In another report, paclitaxel treatment was initiated in a patient with metastatic melanoma after progression despite pembrolizumab and azacitidine treatment, but TLS was observed in the patient. Although the exact cause of TLS in this case is unknown, it was understood that pembrolizumab was used before TLS occurred.¹⁶ A study by Mayer et al.¹⁷ reported that a patient with metastatic prostate carcinoma (who had received pembrolizumab) was started on steroids for the treatment of liver damage and ARF, who then developed TLS. Although the authors speculated that TLS might have been associated with steroids, it is again noteworthy that TLS developed after use of pembrolizumab.¹⁷ In the study of Shah et al.,⁴ it was reported that TLS developed within 8 days after pembrolizumab & axitinib treatment in a patient with metastatic renal cell carcinoma.

Life-threatening TLS has been reported with the use of another anti PD-L1 antibody, atezolizumab, in a metastatic urothelial carcinoma case.¹⁰ In the study of Hayes et al.,¹⁸ TLS was detected after the use of nivolumab, another anti-PD-1 antibody, in the treatment of recurrent small cell lung carcinoma. Tumor lysis syndrome was also reported in another study where nivolumab and a protein kinase inhibitor, pazopanib, were used in a case with metastatic renal cell carcinoma.¹⁹ Our findings in this case are consistent with the results of reported cases of TLS in which the patient had received pembrolizumab (or other anti-PD-1/ PD-L1 antibodies) for malignancy. Since there were no prior reports of TLS development attributed to pembrolizumab in nasopharyngeal carcinoma, no prophylactic treatment was administered in our case. Pembrolizumab-sensitive high metastatic tumor volume resulting in rapid tumor necrosis was thought to be a possible factor contributing to the development of TLS in this patient. In malignancies, especially in cases of nasopharyngeal carcinoma, care should be taken regarding the possible development of TLS when using pembrolizumab. Because TLS may be missed, especially in individuals with metastatic disease, frequent laboratory monitoring and initiation of therapeutic intervention as soon as possible are critical to improving outcomes. Even in cases where TLS development is not expected, initiation of prophylactic treatments for TLS prior to the use of pembrolizumab can prevent adverse events.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.T.; Design – A.T.; Supervision – S.B.T.; Resources – M.E.B.; Materials – Z.H.; Data Collection and/ or Processing – A.T.; Analysis and/or Interpretation – A.A.Ç.; Literature Review – P.Ç.E.; Writing – A.A.Ç.; Critical Review – M.B.; Other – P.Ç.E. **Declaration of Interests:** The authors declare that they have no competing interests.

Funding: The authors declared that this study has received no financial support.

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