

Case Report

Tumor Lysis Syndrome in a Super-responder to Chemoimmunotherapy for Nasopharyngeal Carcinoma: A Case Report

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Abstract

We present the case of a 54-year-old male with nasopharyngeal cancer accompanied by huge liver metastasis, an extremely high Epstein-Barr virus viral load, and B symptoms. Despite aggressive hydration and close laboratory monitoring, he developed tumor lysis syndrome (TLS) and acute kidney injury after the first cycle of chemoimmunotherapy. Although the tumor exhibited an excellent response, the patient became dialysis dependent for 8 months. This case highlights the risk of TLS in patients with nasopharyngeal carcinoma with high tumor burden, a rare but easily overlooked complication.

Keywords: Acute kidney injury, case report, nasopharyngeal carcinoma, tumor lysis syndrome

INTRODUCTION

Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency typically associated with highly proliferative hematologic malignancies. TLS is rare in most nonhematologic malignancies.

We present the case of a patient with metastatic nasopharyngeal cancer (NPC) who developed severe TLS shortly after the initiation of pembrolizumab combined with gemcitabine and cisplatin therapy, despite aggressive prophylactic measures. This case highlights the potential risk of TLS in patients with solid tumors such as chemosensitive NPC,

especially in the setting of high tumor burden and rapid treatment response.

CASE REPORT

A 54-year-old male patient with well-controlled type 2 diabetes mellitus presented with fever and night sweats 2 weeks before hospital admission. He visited the emergency department, where a 15-cm hepatic mass was identified

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on abdominal ultrasound. The alpha-fetoprotein level was within the reference range; however, the initial lactate dehydrogenase (LDH) level was high (4857 U/L), raising the concerns of a rapidly proliferative tumor such as high-grade lymphoma. An extremely high Epstein–Barr virus (EBV) viral load (2,491,133 IU/mL) was also detected during workup.

A liver biopsy revealed a poorly differentiated carcinoma. Immunohistochemical staining revealed strong positivity for cytokeratin (CK), focal and weak positivity for p40 and GATA3, and negativity for TTF-1, arginase-1, HepPar-1, and CK7 [Figure 1a and b]. Epstein–Barr encoding region (EBER) *in situ* hybridization was positive in most of the tumor cells [Figure 1c]. Whole-body positron emission tomography imaging revealed fluorodeoxyglucose-avid lesions in the right nasopharynx, bilateral cervical lymph nodes, liver, and abdominal nodes [Figure 2]. An otolaryngologic examination identified a nasopharyngeal lesion, and a biopsy confirmed a histological pattern consistent with the liver tumor. A final diagnosis of *de novo* metastatic NPC, EBER-positive, poorly differentiated, Stage IV disease with extensive liver, and lymph node metastases was made.

The patient received palliative chemoimmunotherapy with pembrolizumab (100 mg, reduced dose due to financial concerns), gemcitabine (1000 mg/m²), and cisplatin (80 mg/m²). Prophylactic hydration with 2000 mL/day of normal saline for 3 days and febuxostat 40 mg/day were also administered. The fever and night sweats resolved the day after chemotherapy, and remarkable clinical and biochemical responses were observed soon after treatment, including resolution of B-symptoms and a rapid decline in EBV viral load (before treatment: 2,491,133 IU/mL; day 5: 87,772 IU/mL; day 17: 1,552 IU/mL).

While the treatment was effective, it was also accompanied by serious complications. According to the Cairo-Bishop definition,^[1] he had laboratory TLS. Electrolyte imbalances included hyperphosphatemia (from 4.4 mg/dL to 5.7 mg/dL;

+29%), hyperuricemia (from 7.5 mg/dL to 9.2 mg/dL; +22.6%), hypokalemia (from 2.21 mmol/L to 1.89 mmol/L; –14.5%), and an increase in potassium level (from 4.1 mmol/L to 4.9 mmol/L; +19.5%). He received salvage treatment with rasburicase, which quickly corrected hyperuricemia but failed to prevent the progression to clinical TLS. He developed acute kidney injury requiring dialysis, with an increase in serum creatinine level from 0.84 mg/dL to 2.99 mg/dL within 2 days after initiating chemoimmunotherapy, accompanied by metabolic acidosis, hyperkalemia, azotemia, and oliguria. Renal replacement therapy was initiated.

Given his compromised renal function and concerns about platinum-associated nephrotoxicity, further platinum-based chemotherapy was withheld. A mild biochemical rebound of EBV viral load and LDH levels occurred 1 month later. The treatment regimen was switched to three cycles of weekly high-dose 5-fluorouracil (2400 mg/m²) and leucovorin infusion, followed by maintenance oral chemotherapy with tegafur-uracil (UFUR). After 8 months of dialysis dependence, renal replacement therapy was successfully discontinued.

Serial imaging demonstrated rapid shrinkage of the liver tumor in weeks, followed by calcification of hepatic lesions without evidence of recurrence [Figure 3a-c]. The patient remained progression-free without further platinum-based therapy for 9 months, and the EBV viral load has remained suppressed below 200 IU/mL during ongoing UFUR maintenance [Figure 4].

DISCUSSION

This case highlights the need to recognize high-risk TLS in patients with nonhematologic malignancies. Although TLS prophylaxis is a well-established practice in hematologic cancers, it is often overlooked in nonhematologic tumors.

TLS is a life-threatening oncologic emergency characterized by rapid tumor cell breakdown, release of intracellular contents,

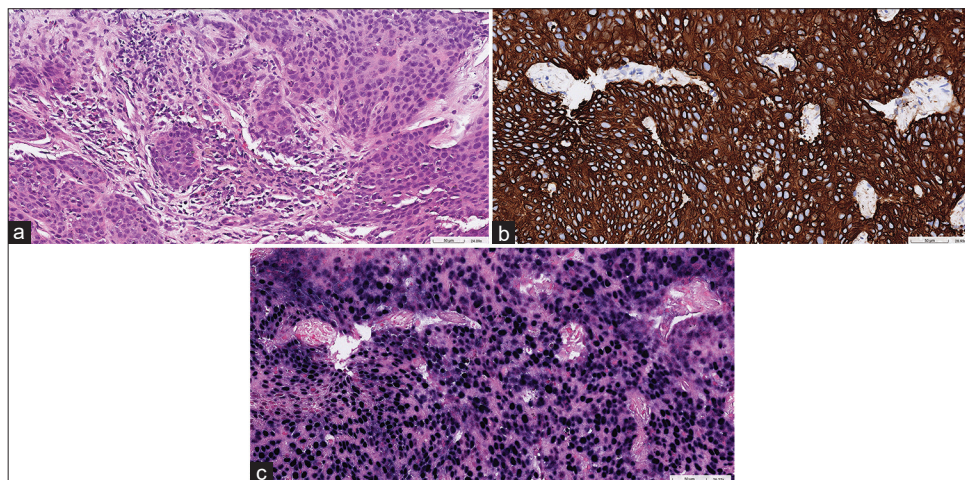


Figure 1: Pathology findings of the liver tumor biopsy. (a) Hematoxylin and eosin staining of the poorly differentiated carcinoma with hyperchromatic nuclei (24x), (b) Immunohistochemistry staining was strongly positive for cytokeratin (29x). (c) Positivity of Epstein–Barr virus-encoded RNA *in situ* hybridization (26x)



Figure 2: Intensely fluorodeoxyglucose-avid lesions in the liver and cervical lymph nodes (positron emission tomography scan)

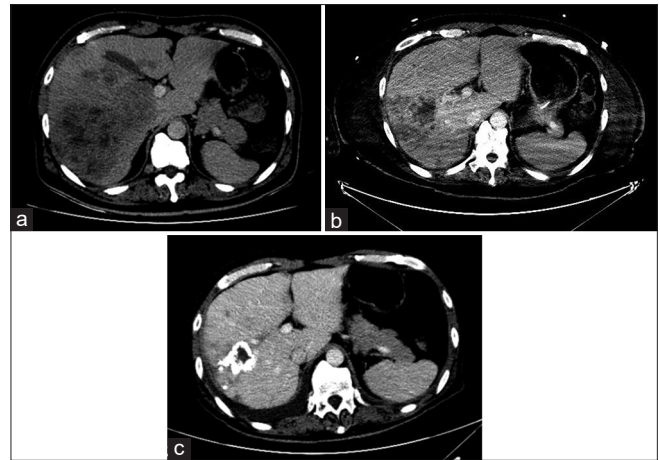


Figure 3: Tumor response before and after chemoimmunotherapy (computed tomography scan). (a) Huge liver tumors before treatment. (b) Rapid liver tumor shrinkage (day 24 after 1st dose of chemoimmunotherapy). (c) Remission of the liver tumors with residual calcifications (8 months after the 1st dose of chemoimmunotherapy)

Table 1: The Cairo-Bishop definition of tumor lysis syndrome

Laboratory TLS	Clinical TLS
Presence of ≥ 2 metabolic abnormalities (serum uric acid, potassium, phosphorus, or calcium) within 3 days before or 7 days after initiation of cytotoxic therapy	Presence of laboratory TLS with any of manifestation mentioned below
Uric acid: ≥ 8 mg/dL or 25% increase from baseline	Creatinine: >1.5 times the upper limit of normal
Potassium: ≥ 6.0 mmol/L or 25% increase from baseline	Arrhythmia
Phosphorus: ≥ 4.5 mg/dL or 25% increase from baseline	Seizure
Calcium: ≤ 1.75 mg/dL or 25% increase from baseline	Sudden death

TLS: Tumor lysis syndrome

and metabolic derangements, which may lead to complications such as seizures, cardiac arrhythmias, acute kidney injury, and even death. The Cairo-Bishop definition [Table 1] is the most widely used diagnostic criterion, classifying TLS into laboratory TLS (presence of ≥ 2 metabolic abnormalities within 3 days before or 7 days after initiating cytotoxic therapy) and clinical TLS, which includes laboratory TLS plus evidence of end-organ dysfunction such as elevated serum creatinine ($\geq 1.5 \times$ upper limit of normal [ULN]), arrhythmia, or seizures.^[1] TLS prevention strategies have primarily focused on hematologic malignancies and certain solid tumors such

as germ cell tumors and small cell lung cancer, which are known for high proliferation rates and marked treatment responsiveness.^[2,3] The occurrence of TLS in nonhematologic tumors other than germ-cell tumors and small cell lung cancer is rare and generally considered low risk, making prophylactic recommendations in these tumors unclear.

In our case, the patient had massive liver metastases and rapidly progressive impending liver failure. We aimed to maximize tumor response, as we believed there may be only one chance to rescue his liver function. In the randomized phase 3 JUPITER-02 trial, the objective response rate was 78.8% in patients with recurrent or metastatic NPC who received toripalimab, an anti-PD-1 monoclonal antibody, plus gemcitabine and cisplatin, compared with 67.1% in those who received chemotherapy alone,^[4] suggesting that chemoimmunotherapy may achieve a higher response rate. Based on these results, the US Food and Drug Administration approved toripalimab in combination with chemotherapy for upfront NPC treatment. In the phase 3 KEYNOTE-122 trial, pembrolizumab monotherapy achieved an objective response rate comparable to chemotherapy.^[5] Because toripalimab has not yet been approved in Taiwan, we believed that the combination of pembrolizumab and chemotherapy would result in a higher response rate and that it would be relatively safe due to their nonoverlapping adverse effect profiles. After shared decision-making with the patient, we chose chemoimmunotherapy with pembrolizumab in combination with gemcitabine and cisplatin to maximize tumor response.

The rapid resolution of B-symptoms and development of typical electrolyte derangements strongly suggested a super-sensitive tumor response to the initial treatment. The renal injury later suggested clinical TLS rather than from underlying disease (well controlled type 2 diabetes mellitus), although it could also have been exacerbated by cisplatin

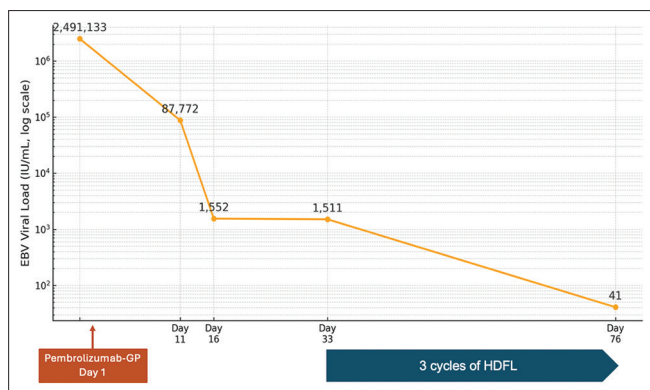


Figure 4: Epstein–Barr virus viral load dynamics during treatment. EBV: Epstein–Barr virus

exposure. However, his baseline renal function was good. Cisplatin is still the best chemotherapy choice for NPC. In addition, elevated serum LDH and uric acid levels prior to therapy may have indicated substantial and preexisting tumor breakdown before treatment initiation, placing the patient at high risk of TLS. Spontaneous TLS is typically characterized by marked hyperuricemia but often an absence of hyperphosphatemia, as viable tumor cells can reutilize released phosphate.^[6] Pretreatment elevations of LDH and uric acid levels (>7.5 mg/dL) have also been identified as risk factors for the development of TLS in hematologic malignancies; however, data remain limited in the context of nonhematologic malignancies.^[7] Clinical judgment is especially critical in such settings.

Given the high-risk profile, prophylactic hypouricemic therapy was initiated in our patient. Unfortunately, we were unable to prevent the development of clinical TLS. It remains uncertain whether the prophylactic use of rasburicase instead of febuxostat could have prevented this complication. To our knowledge, no definitive evidence supports the use of prophylactic rasburicase for preventing clinical TLS.^[8] Nevertheless, more intensive preventive strategies may be warranted in selected high-risk patients with nonhematologic malignancies, such as in our case, characterized by bulky highly responsive tumors and signs suggestive of spontaneous tumor lysis. TLS prophylaxis in such cases may follow the same principles applied to high-risk hematologic malignancies.

This case highlights that TLS can occur in nonhematologic malignancies beyond the traditionally recognized small cell lung cancer and germ cell tumors. As systemic therapies become increasingly potent, more nonhematologic tumors are likely to exhibit high responsiveness to treatment. The risk of TLS in these tumors should not be overlooked, including in future clinical trial settings.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

Kuan-Yu Chen: data collection, literature search, and drafting of the manuscript. Li-Chun Lu: case management, study supervision, and critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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