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A Case Report of Atezolizumab Induced Tumor Lysis Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
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Literature Search F
Funds Collection G

BCDEF Faisal Fa'ak
BCDEF Diego Vanegas
ABDEFG Kofi M. Osei

Department of Internal Medicine, Piedmont Athens Regional Medical Center, Athens, GA, U.S.A.

Corresponding Author: Kofi M. Osei, e-mail: kali_bonite@hotmail.com
Conflict of interest: None declared

Patient: Female, 67
Final Diagnosis: Atezolizumab induced tumor lysis syndrome
Symptoms: Generalized weakness • hematuria • nausea • vomiting
Medication: Atezolizumab
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: Advanced urothelial carcinoma has been associated with poor prognosis due to high resistance to chemotherapy and radiation until immunotherapeutic agents, such as atezolizumab, emerged as an option and have shown improved survival. However, atezolizumab is associated with side effects, which were mainly autoimmune. In this case study, we report on a rare case of atezolizumab-induced tumor lysis syndrome.

Case Report: A 67-year-old female with a primary diagnosis of metastatic urothelial carcinoma who presented to the emergency department with generalized weakness associated with nausea and vomiting 8 days after her first cycle of atezolizumab. Laboratory values showed hyperphosphatemia, hyperuricemia, hypocalcemia, and acute kidney injury consistent with tumor lysis syndrome.

Conclusions: In our report, we highlight tumor lysis syndrome as a potential reaction to atezolizumab; a condition that requires prophylaxis and close laboratory monitoring.

MeSH Keywords: Immunotherapy • Programmed Cell Death 1 Ligand 2 Protein • Tumor Lysis Syndrome • Urinary Bladder Neoplasms

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Background

Platinum-based chemotherapies have been the primary treatment for metastatic urothelial neoplasms, until the more recent advent of immunotherapy which has shown improved survival [1–3]. Atezolizumab is a programmed cell death-ligand 1 (PD-L1) blocking antibody that was approved by the US Food and Drug Administration (FDA) for the treatment of locally advanced or metastatic urothelial carcinoma in 1) patients not eligible for platinum-containing therapy regardless of PD-L1 expression status; 2) patients not eligible for cisplatin-containing therapy in PD-L1 expressing tumors, and 3) patient who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy [4,5]. Cancer cells evade immune cells by expressing PD-L1 on the cell surface; blocking this expression by atezolizumab allows the body to mount an immune response against cancer cells [6–8].

Several adverse events have been associated with atezolizumab as seen in Phase 1 or Phase 2 clinical trials in urothelial cancer, but to the best of our knowledge, there is only 1 reported case of tumor lysis syndrome in a patient treated with atezolizumab for urothelial carcinoma [9]. We herein describe a case of tumor lysis syndrome following a single dose of atezolizumab for metastatic bladder cancer.

Case Report

A 67-year-old Caucasian female presented to her primary care physician complaining of hematuria associated with feeling

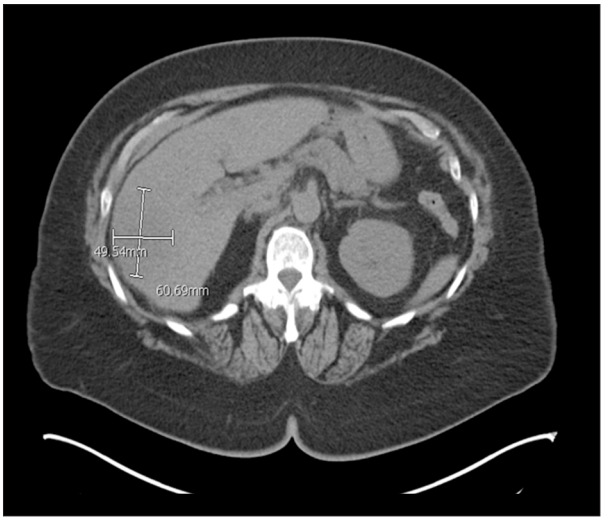

Figure 1. Computed tomography abdomen showing large ill-defined liver lesion in the right lobe difficult to measure secondary to its irregular borders and large size.

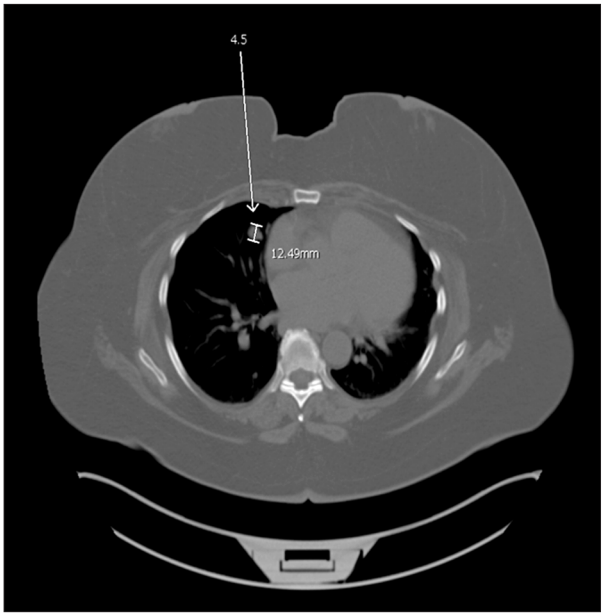

Figure 2. Computed tomography chest showing lung nodule in the medial right middle lobe measures 1.2 cm.

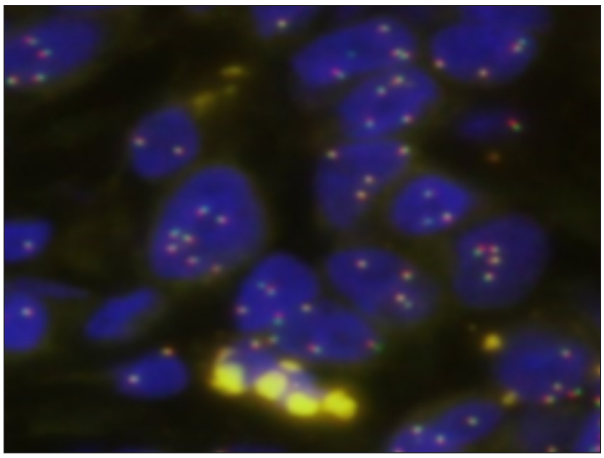

Figure 3. MYC (8q24): the sample is considered positive for c-MYC gene rearrangement if >10% of nuclei show a break-apart pattern (1R1G1F).

of incomplete bladder emptying. The patient was referred to a urologist who did cystoscopy which appeared normal. Computed tomography (CT) of the abdomen/pelvis with and without contrast showed irregular bladder wall thickening anteriorly, 2 pulmonary nodules, and a very small lesion in the right lobe of her liver. Her renal function was normal with creatinine was 0.97 mg/dL. A month after initial presentation, the oncology consultant evaluated her condition with CT scan and liver biopsy. CT scan showed irregular bladder wall thickening anteriorly as well as enlarging bilateral lung nodules, liver lesion, and small left periaortic lymph node (Figures 1, 2); Liver biopsy immunoperoxidase staining was positive for GATA3 and uroplakin II but negative for glypican 3, GCDFP-15, and arginase

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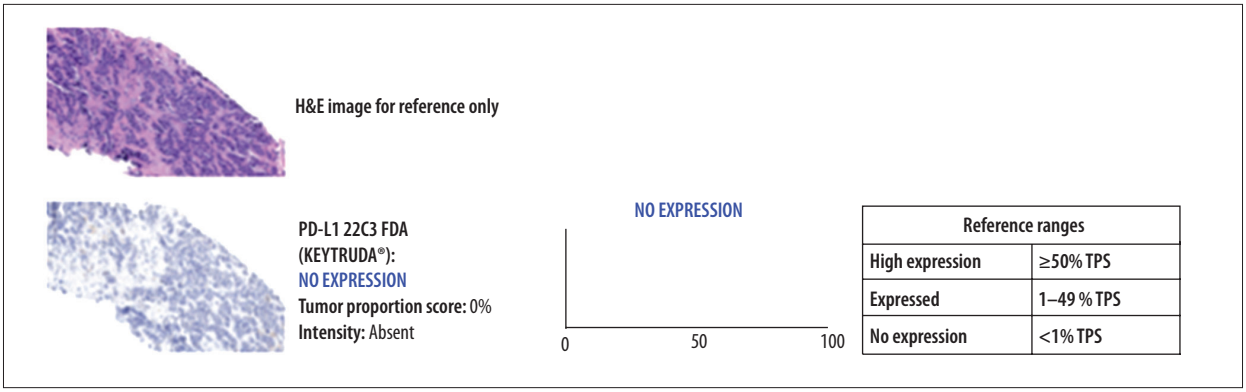

Figure 4. Qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1, clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed samples.

representing poorly differentiated carcinoma with urothelial primary; genomic studies showed Myc amplification and no PD-L1 expression (Figures 3, 4). A diagnosis of stage IV metastatic urothelial cancer was made. Given her poor performance status and Eastern Cooperative Oncology Group (ECOG) score of 2; the decision was made to treat this patient with atezolizumab instead of first-line chemotherapy.

Eight days after the first dose of atezolizumab, she presented to the Emergency Department complaining of shortness of breath associated with right upper quadrant pain, nausea, vomiting, swollen legs, hematuria, difficult urination, and progressive weakness. During the physical examination, the patient was in moderate distress due to abdominal pain in the right quadrants and short of breath and tachycardic, her lungs were clear to auscultation, her abdomen was distended and tender to palpation in right upper quadrant, and there was significant bilateral pitting edema +3 up to the knee, and joints without effusions. Her laboratory results are shown in Table 1. Chest x-ray was normal.

A diagnosis of tumor lysis syndrome was made using the widely accepted Cairo-Bishop Criteria [10]. The patient had hyperphosphatemia, hypocalcemia, and hyperuricemia complicated by elevated creatinine with previously normal renal function. She was treated with normal saline at 200 cc/hour for the first 10 hours and then continued at 75 cc/hour; rasburicase, broad-spectrum antibiotics piperacillin-tazobactam, and vancomycin were started empirically due to possibility of sepsis in the setting of immunocompromised state. She remained anuric despite receiving 7.5 L normal saline. The nephrologist started her on renal replacement therapy without significant improvement in creatinine levels. Ultimately, given her poor prognosis, the palliative care team had a discussion with the patient and her family who decided to withdraw care; and eventually discharged the patient with home hospice.

Table 1. Laboratory values.

Laboratory	Result	Reference range
BUN	91 mg/dL	6–20 mg/dL
Creatinine	7.52 mg/dL	0.4–1 mg/dL
Potassium	4.9 mEq/L	3.3–5.1 mEq/L
Phosphorus	5.8 mg/dL	2.6–4.5 mg/dL
Uric Acid	20.1 mg/dL	2.6–8 mg/dL
Calcium	7.9 mg/dL	8.4–10.2 mg/dL
Sodium	130 mg/dL	133–145 mg/dL

Discussion

Metastatic urothelial carcinoma is associated with high mortality due to the limited treatment options; until recently, platinum-based chemotherapy has been the main treatment but has shown poor outcomes [11,12].

In 2016, the FDA initially approved atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma which has progressed despite platinum-based chemotherapy after a Phase 2 IMvigor210 (Cohort 2) trial showed overall response rate of 14.8% (95%CI: 11.2, 19.3) compared to historical controls with overall response rate of 10%. With a median follow-up of 11.7 months, and 84% (38 out of 45 cases) of responders continued to show improvement beyond the median follow-up period. Out of a total of 310 patients who received atezolizumab, 5% reported grade 3–4 immune-based adverse events with pneumonitis and transaminitis being the most common. Other reported adverse events were pruritus, fatigue, nausea, diarrhea, constipation, decreased appetite, dyspnea, pyrexia, arthralgia, insomnia, musculoskeletal pain, and anemia [13].

Petrylak et al. conducted the Phase 1 study evaluating the safety and toxicity of atezolizumab. The trial enrolled 95 patients

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Table 2. Review of tumor lysis syndrome case reports secondary to immunotherapy.

Study	Cancer	Metastasis	Treatment	Number of treatment cycle before TLS	Days between treatment and TLS	Outcome
Brunnhoelzl et al. [9]	Urothelial carcinoma	Liver, retroperitoneum, celiac axis, mesentery, paraaortic and mammary lymph nodes.	Atezolizumab	1	14	Death
Sater et al. [18]	Renal cell carcinoma	Lung and retroperitoneum	Nivolumab	1	2	Death
Brunnhoelzl et al. [19]	Melanoma	Lung, liver, kidneys, omentum, adrenal, bones	Nivolumab	3	5	Death
Regnault et al. [20]	Melanoma	lungs, liver, spleen, bones, bladder	Ipilimumab	1	6	Death
Herbst et al. [21]	Solid tumor	Unknown	Atezolizumab	Unknown	Unknown	Unknown

TLS – tumor lysis syndrome.

with metastatic urothelial carcinoma. The study reported no patient experienced severe treatment-related adverse events or death [14]. Thus, tumor lysis syndrome was not reported in either the Phase 1 or Phase 2 clinical trials.

Tumor lysis syndrome is an oncologic emergency characterized by extensive destruction of tumor cells secondary to treatment which results in the release of intracellular content including uric acid, potassium, phosphorus, and calcium resulting in cardiac, renal, and nervous system toxicities [10,15]. It occurs predominantly during the treatment of hematologic malignancies such as lymphoma and leukemia. However, there has been increase of tumor lysis syndrome reports in solid tumors like colorectal carcinoma, small-cell lung carcinoma, sarcoma, and ovarian cancer [16,17].

The risk is higher in the presence of a large tumor burden, high cell proliferation rate, chemosensitive malignancy, and preexisting hyperuricemia, hyperphosphatemia, or kidney injury [15]. Diagnosing tumor lysis syndrome requires the presence of at least 2 abnormal laboratory findings, hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia, complicated by 1 or more of the following: acute kidney injury, seizures, cardiac arrhythmia, and or death [10].

Brunnhoelzl et al. published a case report of a 77-year-old female with metastatic urothelial carcinoma who presented to the hospital with anorexia, fatigue, and abdominal pain 2 weeks after her first cycle of atezolizumab [9]. Our case shares similar characteristics with this previously published case, including gender, race, type of cancer, onset of tumor lysis syndrome after single dose, and outcome. Also, tumor lysis syndrome was reported secondary to other forms of immunotherapy anti-PD1 and anti-CTLA4 in metastatic melanoma and renal cell carcinoma (Table 2) [9,18–21]. In our patient, in the absence of other competing etiologies for tumor lysis syndrome, patient's high tumor burden, lack of tumor lysis syndrome prophylaxis, and the direct relationship between the onset of symptoms and treatment which make atezolizumab the more likely culprit.

Conclusions

In conclusion, tumor lysis syndrome seems to be a relatively unknown adverse event associated with atezolizumab that was not reported by clinical trials. The disease's precise pathogenesis remains unclear in solid malignancies so having a deeper understanding of the characteristic immune response that mediates it may have a tremendous impact on how we manage it, and might unveil a new mode of action. In addition, this case should raise awareness of tumor lysis syndrome as a potential complication in the post surveillance phase of the drug atezolizumab which requires prophylaxis and close laboratory monitoring.

Conflict of interest

None.

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