Tumor lysis Syndrome in a Patient with Metastatic Breast Cancer Treated with Alpelisib

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ABSTRACT

PURPOSE: Tumor lysis syndrome (TLS) is a rare but life-threatening phenomenon that occurs mainly in patients with aggressive hematologic or highly chemotherapy sensitive solid tumors such as high-grade neuroendocrine carcinoma or testicular cancer. Tumor lysis syndrome is exceedingly rare in hormone receptor-positive, HER2-negative breast cancer. Furthermore, TLS following treatment with alpelisib, a novel phosphatidylinositol 3-kinase (PI3K) inhibitor used to treat *PIK3CA*-mutated (gene encoding p110α subunit of PI3K), hormone receptor positive advanced breast cancer, has never been described in patients with nonhematologic malignancies.

METHODS: In the following case, we present a patient with hormone receptor-positive, HER2-negative, *PIK3CA*-mutated metastatic breast cancer who developed TLS 12 days after starting fulvestrant and alpelisib.

RESULTS: Patient was promptly treated with improvement in her renal function to baseline without requiring renal replacement therapy. Alpelisib was resumed at a reduced dose with no further complications.

CONCLUSION: Through this case, we discuss the potential complications of TLS and the importance of prompt recognition and treatment.

KEYWORDS: Alpelisib, tumor lysis syndrome (TLS), metastatic breast cancer (MBC), oncology

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Introduction

Tumor lysis syndrome (TLS) is the constellation of metabolic derangements associated with extensive tumor lysis and represents an oncologic emergency. Characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, TLS can cause acute renal injury due to the precipitation of uric acid crystals in the renal tubules. In addition, severe electrolyte derangements predispose to cardiac dysrhythmias, seizures, and sudden cardiac death. Tumor lysis syndrome is more commonly a complication of treatment of hematologic malignancies, but there are rare cases reported in adult solid tumors, in particular in patients with poorly differentiated neuroendocrine carcinoma and testicular cancer.[1,2] Aggressive intravenous (IV) fluid resuscitation and correction of electrolyte abnormalities such as hyperkalemia are essential to management in the acute setting.[2] Urate lowering therapy with rasburicase (recombinant urate oxidase) and xanthine oxidase inhibitors, such as allopurinol, can reduce the risk of further renal damage through uric acid crystal deposition. Occasionally, hemodialysis may be required in patients who are refractory to the above strategies.

Alpelisib is a novel orally bioavailable inhibitor of p110α subunit of phosphoinositol-3-kinase (PIK3CA) used in the treatment of patients with *PIK3CA*-mutated, hormone receptor positive (HR+), HER2-negative advanced breast cancer.[3] Recent phase-III SOLAR-1 trial demonstrated a progression-free survival of 11.0 months (95% confidence interval [CI], 7.5-14.5) in previously treated patients with metastatic hormone receptor-positive, *PIK3CA*-mutated breast cancer who received fulvestrant and alpelisib as their subsequent therapy, as compared with 5.7 months (95% CI, 3.7-7.4) in the placebo-fulvestrant group.[3] Frequent adverse effects were hyperglycemia (36.6% in the alpelisib-fulvestrant group vs 0.7% in the placebo-fulvestrant group) and diarrhea (6.7% vs 0.7%), but grade 3 or greater nephrotoxicity was less frequently reported (2.8% vs 0.7%). Moreover, there were no reported cases of hyperuricemia or TLS.[3]

While prompt recognition and treatment are essential to successful patient outcomes, TLS is an exceedingly rare and underrecognized phenomenon in HR+, HER2-negative

*Both authors contributed to this work equally.

Table 1. Blood work during hospitalization showing elevated uric acid, elevated lactate dehydrogenase, acute renal failure, and electrolyte abnormalities consistent with tumor lysis syndrome.

	REFERENCE RANGE	BASELINE PRIOR TO ALPELISIB (12 DAYS PRIOR TO ADMISSION)	ADMISSION (HOSPITAL DAY 0)	ICU TRANSFER (HOSPITAL DAY 1)	DISCHARGE (HOSPITAL DAY 6)
Sodium	133-143 mmol/L	133	125	129	140
Potassium	3.5-5.0 mmol/L	3.9	8.2	6.0	3.2
BUN	7-22 mg/dL	14	129	114	47
Creatinine	0.5-1.2 mg/dL	0.69	15.15	13.83	1.00
Glucose	70-99 mg/dL	111	124	152	85
Albumin	3.5-5.0 g/dL	3.8	3.8	3.8	3.4
Calcium	8.6-10.5 mg/dL	9.6	9.0	8.5	8.8
Phosphate	2.2-4.6 mg/dL	2.1	8.2	6.2	2.9
Uric acid	2.8-6.0 mg/dL	Unknown	16.2	3.8	<1.5
Lactate dehydrogenase	100-190 U/L	Unknown	226	190	177

Abbreviations: BUN, blood urea nitrogen; ICU, intensive care unit.

breast cancer. We report here for the first time a case of TLS in the setting of metastatic breast cancer treated with alpelisib.

Case Description

The patient is a 66-year-old woman with HR+, *PIK3CA* mutation-positive (E542K), breast cancer metastatic to bone, brain, peritoneum, pleura, and liver and a baseline Eastern Cooperative Oncology Group performance status of 1. Her oncologic course was complicated by the development of new brain metastases while receiving letrozole and palbociclib. Twenty-one days after completing brain radiation, patient's systemic therapy was changed to fulvestrant and alpelisib. Twelve days following the start of this therapy, she presented to the hospital with altered mental status. Her mental status had worsened over the preceding days and on admission, she endorsed hallucinations. The patient also had asterixis on a physical examination. The results of patient's blood work were notable for creatinine of 15.15 (baseline < 1.0), blood urea nitrogen (BUN) of 129 (baseline 14), uric acid 16.2 (baseline unknown), lactate dehydrogenase (LDH) 226, phosphate of 8.2 (baseline 2.1), potassium of 8.2 (baseline 3.9), and glucose of 124 (baseline 111, Table 1). Electrocardiogram showed widening of the QRS complex with acute T-wave changes (Figure 1) that resolved after electrolyte normalization (Figures 2 and 3). Renal ultrasound did not demonstrate obstructive uropathy. Urinalysis revealed amorphous and calcium oxalate crystals. She received aggressive fluid hydration and was started on allopurinol and rasburicase within the first 12 hr of her hospital course. She developed worsening hypotension and decreased urine output requiring transfer to the intensive care unit (ICU). Rheumatologic testing including C3, C4, antinuclear antibody (ANA), rheumatoid factor (RF) levels, hepatitis serologies, and serum/urine protein electrophoresis (SPEP/UPEP) were within normal limits. Her hypotension, mental status, and urine output slowly improved without requiring renal replacement therapy. Creatinine continued to downtrend and normalized to 1.00 on hospital day 6 (Table 1 and Figure 4). All other clinically significant laboratory abnormalities also resolved (Figure 4). After discharge, alpelisib was resumed at a reduced dose of 250 mg daily which was well tolerated. Repeat staging scans after 2 cycles of fulvestrant and alpelisib showed a mixed response with stable diffuse osseous and peritoneal metastatic disease, progression of pleural metastases, and resolution of liver metastasis.

Discussion

While TLS remains a rare complication in the treatment of solid tumor malignancies, there have been no reported cases in the setting of PI3K inhibitors in patients with nonhematologic malignancies.[1,2] Rare cases of TLS in metastatic breast cancer are predominantly those treated with cytotoxic chemotherapy. Alpelisib has never before been implicated as a causative agent TLS. This case of TLS cannot be correlated to central nervous system (CNS) penetration as this patient received radiation therapy 20 days prior to initiating alpelisib, it would be difficult to quantify degree of CNS response to alpelisib. Breast cancer is a very radiosensitive malignancy and hence the previous radiation was likely a big contributor to response in the CNS. Although there was likely a component of volume depletion contributing to renal decline in this patient, the combination of laboratory abnormalities at the time of presentation and rapid improvement with uric acid lowering therapy and volume

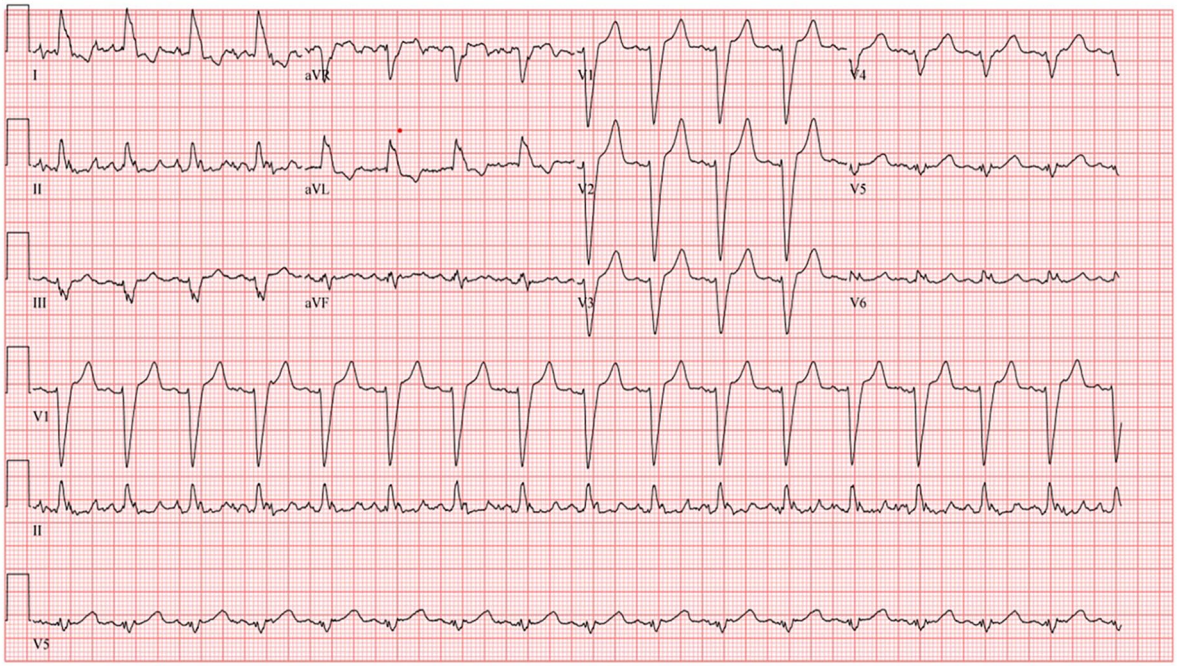

Figure 1. Twelve-lead electrocardiogram (ECG) of the patient. ECG showed wide QRS complexes and peaked T waves consistent with hyperkalemia at the time of patient's admission to the hospital.

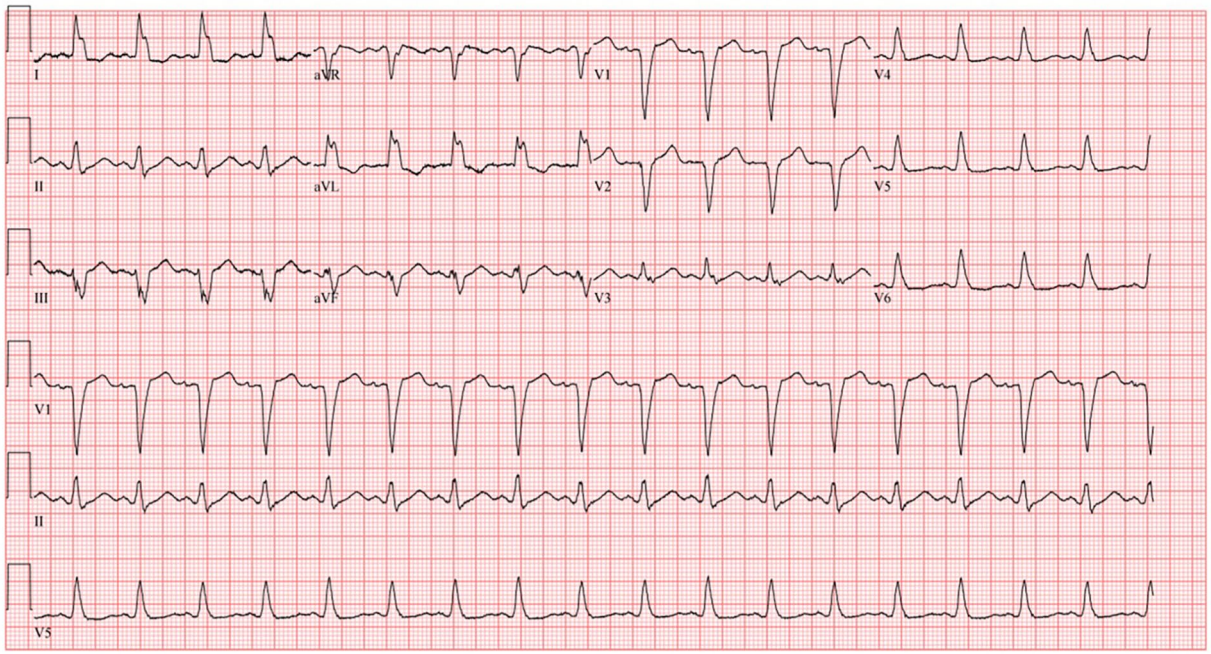

Figure 2. Peaked T waves resolved after the patient's potassium normalized following treatment.

expansion are consistent with TLS. In addition, the patient met the Cairo-Bishop definition of laboratory TLS and grade-IV clinical TLS.[4] She did not have any arrhythmias during her stay but did have acute T wave changes as demonstrated in Figure 1. Given that these resolved with the resolution of metabolic derangements, this was unlikely to be due to alpelisib alone. While the patient did receive radiation for new brain metastases, treatment was completed about 4 to 5 weeks prior to presentation making this an unlikely precipitating factor. The patient in this case had additional risk factors for TLS including large disease burden and low volume state given her poor oral intake in the days leading up to hospitalization.[5] This case illustrates the need to include TLS on the list of differential diagnosis for a patient with metastatic, HR+ breast cancer treated with alpelisib and presenting with acute renal insufficiency associated with electrolyte derangement.

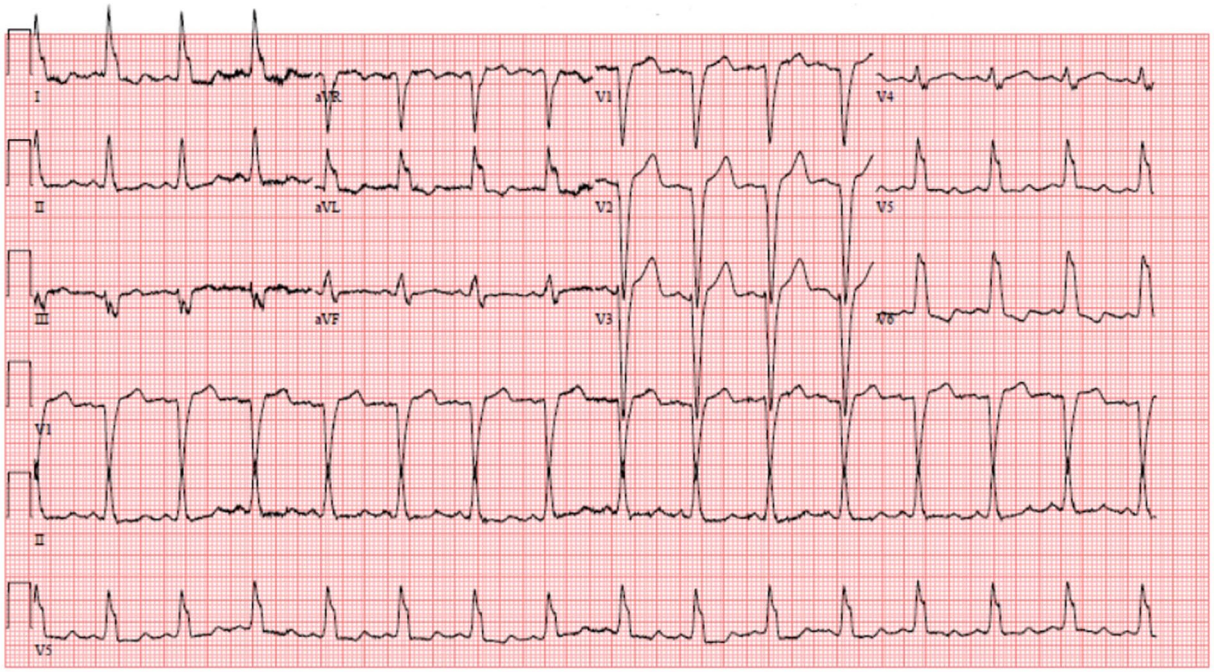

Figure 3. Electrocardiogram (ECG) after resumption of alpelisib. Remains at baseline without return of acute T wave abnormalities.

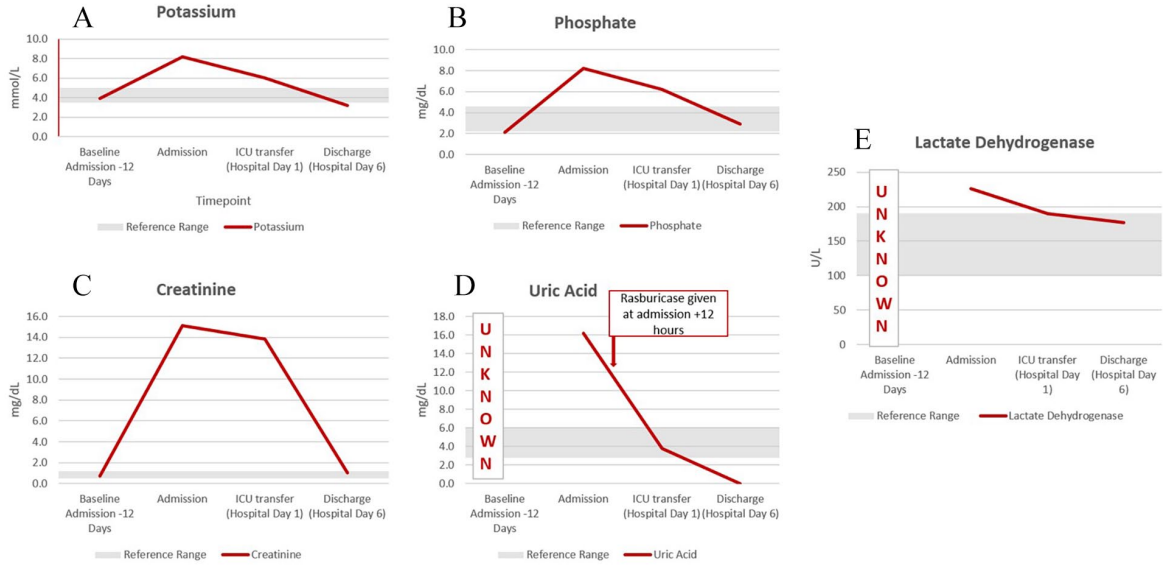

Figure 4. Graphic representation of trends in potassium (A), phosphate (B), creatinine (C), uric acid (D), and lactate dehydrogenase (E) during patient's hospitalization.

Author Contributions

All authors contributed to the study conception and design. Material preparation,and analysis were performed by Caitlin Handy, Robert Wesolowski, Michelle Gillespie, Michael Lause, Sagar Sardesai, Nicole Williams, Michael Grimm, Mahmoud Kassem and Bhuvaneswari Ramaswamy. The first draft of the manuscript was written by Caitlin Handy and Robert Wesolowski, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Taira F, Horimoto Y, Saito M. Tumor lysis syndrome following trastuzumab for breast cancer: a case report and review of the literature. *Breast Cancer*. 2015;22:664-668.
2. Mirrakhimov AE, Ali AM, Khan M, Barbaryan A. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors*. 2014;6:68-76.
3. Rugo HS, Andre F, Rubovszky G, et al. A phase 3 study of alpelisib (ALP) plus fulvestrant (FUL) in men and postmenopausal women with hormone receptor-positive (HR plus), human epidermal growth factor receptor 2-negative (HER2-) ABC progressing on or after aromatase inhibitor (AI) therapy: SOLAR-1. *J Clin Oncol*. 2017;35:5.
4. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3-11.
5. Cairo MS, Coiffier B, Reiter A, Younes A, TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol*. 2010;149:578-586.