Title- Rare Tumor Lysis Syndrome in a Solid Tumor Presenting as Multisystem Toxicity After Enfortumab Vedotin Plus Pembrolizumab for Metastatic Urothelial Carcinoma

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Introduction (130 words)
According to National Comprehensive Cancer Network (NCCN) guidelines, enfortumab vedotin (EV) combined with pembrolizumab is preferred first line therapy for metastatic urothelial carcinoma, demonstrating a significant survival benefit over chemotherapy alone (median overall survival 31.5 months vs 16.1 months). Although adverse effects of each of the drugs have been documented individually, multisystem toxicity from the combination remains exceedingly rare. Tumor lysis syndrome (TLS) is an uncommon complication in solid tumors and is rarely reported in bladder cancer, particularly after EV plus pembrolizumab therapy. Concurrent presentation of immune mediated pneumonitis, severe transaminitis and TLS has not been well described in literature. We present a rare and severe case of EV-pembrolizumab-associated TLS and multisystem toxicity highlighting the need for early recognition and for surveillance of toxicity patterns in patients on combination therapy.

Case Presentation (216 words)
A 70-year-old male with metastatic bladder cancer, diagnosed one year ago, receiving EV plus pembrolizumab therapy for past four months, presented to the hospital six days after cycle 5, day 1, with generalized malaise, dysphagia and brown sputum production. Vitals signs were stable. Laboratory evaluation revealed creatinine 3.03 mg/dL, potassium 6.8 mmol/L, bicarbonate 10 mmol/L, phosphorus 10.30 mmol/L, uric acid 13.5 mg/dL, LDH more than 2500 U/L, lactate 8.48 mmol/L, total bilirubin 1.54 mg/dL, direct bilirubin 0.83 mg/dL, alkaline phosphatase 266 U/L, AST 4750 U/L, ALT 2737 U/L, hemoglobin 8.6 g/dL, WBC 39.3 $x10^3$/uL. Chest imaging showed multifocal pneumonia and abdominal imaging revealed severe left hydroureteronephrosis and hydroureter.

He was admitted to the ICU with concerns for TLS, acute kidney injury and multifocal pneumonia. Treatment included aggressive intravenous hydration, rasburicase and broad-spectrum antibiotics, followed by initiation of continuous renal replacement therapy (CRRT) for his worsening renal function. Detailed review of the imaging raised concerns for treatment-induced pneumonitis, prompting initiation of high-dose steroids (1mg/kg/day) with six-week taper. A nephrostomy tube was placed for his hydronephrosis. During the hospital stay, the acute injury improved and transaminitis which was suspected to be due to cancer treatment, also gradually resolved. He was safely discharged from the hospital with a close oncology follow-up for reassessment and modification of his cancer treatment.

Case Discussion (154 words)
EV plus pembrolizumab has become a preferred first line option for metastatic urothelial carcinoma, supported by clinical trial data demonstrating significantly prolonged survival. While each drug carries a distinct toxicity profile – immune-related events with pembrolizumab and metabolic or dermatological toxicities with EV – serious overlapping toxicity is uncommon. TLS in bladder cancer is extremely rare, with only isolated cases reported. Our patient's presentation with simultaneous TLS, acute kidney injury, severe

transaminitis, and suspected immune-mediated pneumonitis represents an unusual and severe constellation of toxicities associated with EV plus pembrolizumab. The case highlights the need for vigilance in monitoring patients receiving this regimen as timely recognition and prompt initiation of metabolic support, corticosteroids, CRRT, and placement of nephrostomy tube were critical in the recovery of our patient. This case emphasizes the importance of maintaining high index of suspicion for multisystem toxicity patterns in patient receiving EV plus pembrolizumab, and the need for early intervention to reduce morbidity.

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