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TUMOR LYSIS SYNDROME WITH HYPERCALCEMIA IN DIFFUSE LARGE B CELL LYMPHOMA

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ABSTRACT: *Tumor lysis syndrome (TLS) is characterized by hyperkalemia, hyperuricemia, hypophosphatemia and hypocalcemia from massive tumor cell turnover. It can rarely present with hypercalcemia. It is known to occur most commonly in lymphoproliferative disorders, either spontaneously or in response to cytotoxic therapies. TLS is an oncological emergency and if not promptly treated, can lead to multi-organ failure, seizures, and cardiac arrhythmias secondarily to electrolyte abnormalities. We present the case of a 79 year old female with newly diagnosed diffuse large B cell lymphoma who presented with hypercalcemia manifesting as TLS.*

KEYWORDS: *Hypercalcemia, tumor lysis syndrome, Diffuse large B cell lymphoma, Lymphoma*

CASE PRESENTATION

A 79 year old female with a past medical history of hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, anxiety, presented with a chief complaint of shortness of breath for 2 weeks. She also had been having abdominal discomfort associated with poor appetite and constipation. She had a history of imbalance with multiple falls, the last one being a week prior, when she stumbled while using her walker. She hit her knees and developed left knee hematoma. Her vitals at the time of admission were as follows: afebrile, heart rate 110, blood pressure 149/81 mm Hg, requiring 4 Litre oxygen by nasal cannula. Physical examination revealed mild diffuse abdominal tenderness, ecchymosis on the left knee, ecchymosis of the right breast area, and rash under the right breast. EKG showed sinus tachycardia at 119 bpm, normal axis, and no ST-T elevation. Laboratory tests revealed anemia (Hb 11.1), thrombocytopenia (platelet count 71,000), hyperkalemia (Potassium 5.5), hypercalcemia (Calcium 11.9), hyperphosphatemia (Phosphorus 5.1), hyperuricemia (Uric acid 11.9), along with elevated serum creatinine (1.3). Further endocrinological workup demonstrated low PTH (5.0) and low PTH-related protein (<2.0).

She was admitted to the hospital around 11 months ago, when she presented with a complaint of abdominal pain. At that time, she was found to have chronic hemoperitoneum, splenomegaly, and multiple periaortic retroperitoneal lymph node enlargements. No acute intervention was done at that time. She was discharged to follow up with Oncology and General Surgery as an outpatient. The underlying cause of her condition had not been found yet.

Imaging done during her hospitalization was reported as follows:
-Chest CTA- 1. No evidence of PE. 2. Small moderate bilateral pleural effusions. Adjacent compressive atelectasis. 3. Extensive adenopathy increasing in size. Stable bilateral lung nodules.

-CT abdomen pelvis- Increasing adenopathy, mesenteric and retroperitoneal, with subtle lytic deformities involving the bones suggesting bone marrow involvement.

-Echocardiogram- EF Calculated: 68 %. Mildly sclerotic aortic valve. Trace to mild tricuspid regurgitation. Trace pulmonary hypertension. Pericardial fat pad or hemodynamically insignificant small pericardial effusion.

The patient was admitted to the hospital under general medical ward service with multidisciplinary input being received from relevant specialties like oncology, nephrology and palliative medicine through consultations. She was suspected to have tumor lysis syndrome, given the rapid increase in lymph node size, so she was started on allopurinol 200 mg daily. Her hypercalcemia was suspected to be secondary to Hypercalcemia of Malignancy. She was given one dose of IV zoledronic acid 4 mg and was started on I/V normal saline at 200 cc/hr. During her hospital stay, she underwent CT-guided biopsy of mesenteric lymphadenopathy, which revealed diffuse large B-cell lymphoma, high grade: CD20+, Bcl-2+, Bcl-6+ She was started on dexamethasone 10 mg IV for 4 days, and was recommended outpatient treatment with CD20 directed antibody and chemotherapy, for which a mediport was placed.

Outpatient, she received 3 cycles of combination therapy with Rituximab, Polatuzumab vedotin, Cyclophosphamide, Doxorubicin and Prednisone. On follow-up visit after 1 month, CT scan showed significantly decreased adenopathy compatible with treatment. Hypercalcemia and hyperuricemia had resolved as well. LFTs were normal. Hemoglobin was trending up. Plan is to do a total of 6 cycles every 3 weeks, after which, the patient will undergo a PET scan.

DISCUSSION

Tumor lysis syndrome is an emergency in oncology associated with significant morbidity and mortality. It is typically recognized to happen either on its own or after cytotoxic chemotherapy in hematological cancers with a substantial tumor burden, like lymphoblastic leukemia, acute myeloid leukemia, and Burkitt lymphoma [1]. It is also recognized to occur in other large tumors that are highly sensitive to chemotherapy [1,2].

TLS occurs due to tumor cells quickly releasing their intracellular contents into the extracellular environment, exceeding homeostatic capabilities. This sudden and rapid event is the mechanism behind hyperphosphatemia in TLS, which is subsequently worsened by acute kidney injury (AKI). The hyperphosphatemia then leads to hypocalcemia by binding to calcium, creating phosphate-calcium crystals that deposit in the renal parenchyma, resulting in the AKI that is commonly seen [3].

Cairo-Bishop proposed a criterion to assist in the diagnosis of TLS. It requires laboratory results showing two or more abnormal serum findings, which include: Uric acid level >8mg/dl, potassium level >6meq/L, phosphorus level >4. 5mmol/dl, and/or calcium level <7mg/dl, either 3 days before, or 7 days after chemotherapy. Clinical features of TLS, fulfilment of laboratory conditions, and one or more of AKI (serum creatinine > 1. 5x the upper limit of normal), cardiac arrhythmia or sudden death or the onset of seizures.

Hypocalcemia and hyperphosphatemia are observed to arise 24–48 hours following chemotherapy treatment. In TLS, hypocalcemia has been linked to intracellular phosphate creating complexes with free calcium after it enters the bloodstream [4]. Symptoms of hypocalcemia can include muscle cramps, tetany, and seizures. It might also extend the QT interval and lead to impairment in cardiac contractility. Our patient exhibited an atypical case of hypercalcemia in the context of TLS upon presentation, in a situation of newly diagnosed diffuse large B cell lymphoma.

Hypercalcemia is a paraneoplastic syndrome and has been identified in 15% of DLCBL instances [5]. Elevated calcitriol levels in lymphoma are frequently linked to the unregulated activity of vitamin D 1-α-hydroxylase by macrophages in the vicinity of tumor cells [6]. Calcitriol levels need to be assessed as a component of the evaluation of hypercalcemia in these individuals.

The management of TLS should address 3 essential aspects: hydration, correction of metabolic imbalances, and treatment of kidney failure. Robust fluid administration at 3 L per square meter daily has been demonstrated to lower serum levels of dangerous electrolytes, enhance renal blood flow, and avert crystal formation in renal tubules. [7] To inhibit the development of uric acid crystals in renal tubules, agents that lower uric acid, like allopurinol and febuxostat, are administered to prevent renal failure.
In situations of renal failure, a dialysis method is necessary. Continuous dialysis is favored over intermittent hemodialysis to minimize the likelihood of "rebound" buildup of harmful substances. [8]

CONCLUSION

This case underscores the significance of quickly identifying and addressing TLS. The existence of hypercalcemia and the absence of the complete metabolic profile of TLS should not hinder the identification and timely treatment of TLS since it is a condition that poses a threat to life.

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