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| RESEARCH ARTICLE

A Diagnostic Paradox: Spontaneous Tumor Lysis Syndrome in a Patient with Undiagnosed Malignancy

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| ABSTRACT

Tumor lysis syndrome entails a life-threatening metabolic complication that may progress swiftly if not recognized at an early stage, and in the absence of a prior cancer diagnosis or history of recent chemotherapy, a diagnostic dilemma arises. Although most cases are chemo-induced, spontaneous tumor lysis syndrome is a well-documented complication of aggressive tumors with a high turnover burden, as in the context of leukemia, for instance. This case study reports on a previously healthy 51-year-old Saudi male who presented with laboratory abnormalities fulfilling the criteria for laboratory and clinical tumor lysis syndrome. This patient was successfully stabilized, achieving improvement in his previously deteriorating renal functions without the need to escalate to renal replacement therapy. Circulating blasts and pancytopenia emerged as significant findings raising the suspicion of leukemia, which warranted an urgent bone marrow biopsy, revealing later findings consistent with acute myeloid leukemia. After stabilization, he was transferred to a tertiary center with a haemato-oncology unit to resume his management plan.

| KEYWORDS

Tumor Lysis Syndrome, Acute Kidney Injury, Hyperkalemia, Hypocalcemia, Hyperphosphatemia, Leukemia, Malignancy.

| ARTICLE INFORMATION

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1. Introduction

Tumor lysis syndrome is a potentially life-threatening acute oncologic emergency mediated by the rapid turnover and breakdown of malignant cancer cells, resulting in the rapid release of intracellular contents into the bloodstream and hence a cascade of metabolic derangement [1][2]. Biochemically, tumor lysis syndrome is characterized by the typical combination of hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia [1]. These physiological changes would then alternate and affect the body's natural homeostasis and equilibrium, resulting in a wide range of possible consequences such as acute kidney injury, heart rhythm disturbances, seizures, and even death [2][3]. The kidney's attempt to eliminate excess uric acid and phosphate through excretion, combined with buffering, can lead to the formation of urate stones, calcium-phosphate crystals, and ultimately, kidney failure and electrolyte imbalances [2]. In real-life practice, the high morbidity and mortality associated with tumor lysis syndrome make it one of the most feared metabolic complications in cancer treatment. It is most common for tumor lysis syndrome to happen in the context of cytotoxic cancer therapy. Aggressive high-grade hematological cancers with substantial tumor burden, such as acute lymphoblastic leukemia or aggressive non-Hodgkin lymphomas, are

particularly susceptible to developing tumor lysis syndrome when chemotherapy or radiation is administered [4]. In such scenarios, the quick turnover of cancer cells caused by chemotherapy or radiotherapy releases intracellular potassium, phosphate, and nucleic acids into the bloodstream [2][4]. Clinically, the onset of tumor lysis syndrome is usually within days of initiating cancer treatment [4][5]. The occurrence of therapy-induced tumor lysis syndrome is often predictable and preventable by proactive measures like aggressive hydration and urate-lowering medications in high-risk patients [4][5]. By contrast, tumor lysis syndrome is rare outside this context. Spontaneous tumor lysis syndrome refers to tumor lysis syndrome that arises without any prior cytotoxic therapy [6]. In such a condition, the rapidly dividing cancer cells undergo "natural" death, or under other stresses, unleash the same intracellular contents that are observed with therapy-induced tumor lysis syndrome [6]. Spontaneous tumor lysis is not triggered by recent chemotherapy or radiation and thus occurs in an untreated malignancy setting. Since no therapy has been administered, it is often unpredictable and unpreventable [6]. While classic tumor lysis syndrome is characterized by hyperphosphatemia, a key distinction point that has been noted is that spontaneous tumor lysis syndrome often shows little or no hyperphosphatemia as the high-turnover tumor reuses released phosphate for new cell growth, leading to less hyperphosphatemia [5]. Overall, spontaneous tumor lysis syndrome is exceedingly rare in comparison to therapy-associated tumor lysis syndrome [7][8]. Epidemiologically, spontaneous tumor lysis syndrome constitutes only a minor percentage of all tumor lysis syndrome events. For instance, in a study involving hematologic cancer patients, the incidence of spontaneous tumor lysis syndrome was estimated to be at roughly 1.1% [7], whereas chemotherapy-induced tumor lysis syndrome can be substantially higher, affecting 10% to 40% of high-risk patients in certain studies [5]. Most of the available evidence on spontaneous tumor lysis syndrome primarily comes from individual case reports and small studies, showing its presence in only a few numbers of patients across multiple cancer types, thereby emphasizing its extreme rarity. The occurrence of spontaneous tumor lysis syndrome is almost always seen in the context of highly aggressive hematologic malignancies. The hematological cancers most connected to spontaneous tumor lysis syndrome are Burkitt lymphoma and acute leukemias [6]. In addition, it has been noticed that diffuse large B-cell lymphoma and plasma cell leukemias can also trigger spontaneous tumor lysis syndrome [5]. Overall, it can be stated that malignancies that exhibit and feature aggressive and rapid proliferation along with a large tumor bulk could potentially result in spontaneous tumor lysis syndrome. While less common, spontaneous tumor lysis syndrome has been observed in certain solid cancers such as hepatocellular carcinoma and metastatic melanoma, but these instances are even rarer and typically discussed within the context of broader tumor lysis syndrome reviews for solid neoplasms. No matter what the cause, tumor lysis syndrome is a critical condition that poses a serious threat to life, necessitating urgent identification and management. Metabolic disturbances associated with tumor lysis syndrome can rapidly advance and progress into multi-organ dysfunction. Specifically, uric acid crystallization within the tubules of the kidney may trigger acute kidney injury, while hypocalcemia may result in tetany or seizures [3]. Furthermore, high potassium levels within the bloodstream along with calcium-phosphate abnormalities may cause abnormalities such as cardiac arrhythmia and neuromuscular irritability [3]. If tumor lysis syndrome is unrecognized it can be fatal, hence making tumor lysis syndrome a true oncological emergency [2][3]. Spontaneous tumor lysis syndrome diagnosis can be particularly challenging, as it often represents the first or one of the earliest signs of an occult cancer [9]. In the absence of prior therapy to signal the risk, physicians may not initially suspect tumor lysis syndrome. As noted by Opyrchal and colleagues, "tumor lysis syndrome can occur in the absence of chemotherapy and may even be the first symptom of underlying malignancy" [9]. According to medical literature, rapid recognition and management of spontaneous tumor lysis syndrome is crucial to avoid the sequelae of electrolyte catastrophe [9]. The current case is particularly noteworthy for demonstrating these principles, as spontaneous tumor lysis syndrome in a previously undiagnosed hematologic malignancy is very uncommon. By manifesting prior to any tumor therapy, it emphasizes how spontaneous tumor lysis syndrome can point to an underlying tumor. Recognizing spontaneous tumor lysis syndrome under these circumstances is especially difficult yet essential, because prompt management may be lifesaving.

2. Case Presentation

2.1 Patient's history and Physical Examination

Our patient is a 51-year-old Saudi male who was known to be a nonsmoker and previously healthy with an insignificant family history. He presented to our emergency department with vague and non-specific symptoms like tiredness, fatigue, nausea, and numbness over the past four days. Despite the ambiguous symptomatology, it was concerning owing to the progressive nature of his symptoms. Thorough history taking demonstrated loss of appetite and reduced urine output. Apart from that, the patient denied any cough, fever, unintentional weight loss, night sweats, chest pain, palpitations, dyspnea, change in bowel movement, abdominal pain, skin rash, headaches, visual changes, altered mental status, seizures, or neurological deficits. Our patient was ill-appearing, mildly dehydrated, non-drowsy, and vitally stable. Local examinations of the chest, heart, and abdomen were unremarkable; however, bruising was notable during the skin examination. No lymph nodes were detected by physicians.

2.2 Laboratory results

Extensive lab work was done for this patient (Table 1).

Test	Result	Normal Range
Sodium	142 mmol\L	135-145
Potassium	6.7 mmol\L	3.5-5.0
Chloride	102 mmol\L	98-107
Bicarbonate	19 mmol\L	22-29
BUN	40 mg\dL	7-20
Creatinine	3.4 mg\dL	0.5-0.9
Uric Acid	14.5 mg\dL	3.5-7.2
Fasting glucose	80 mg\dL	70-100
Calcium	7.1 mg\dL	8.5-10.2
Phosphate	4.6 mg\dL	2.5-4.5
Hemoglobin	8.4 g\dL	12-16
WBC	$2.1x10^9$\L	4-10
Platelets	$66x10^9$\L	150-400
MCV	85 fL	80-100
Reticulocytes	0.6%	0.5-2
ESR\CEP	Mildly elevated	-
LFTs	Normal	-
LDH	1754	<250
Peripheral smear	Blasts seen	-

Table 1: results of lab work.

2.3 Management course

While the recognition of tumor lysis syndrome without prior history of cancer or chemotherapy is quite challenging, this patient's laboratory findings scream tumor lysis syndrome. Notable red flags in this case included circulating blasts on peripheral blood smear and pancytopenia, raising the concern for potential hematological malignancy. With overt renal dysfunction and hyperkalemia, rapid deterioration up to cardiac arrest was the major concern that prioritized stabilizing the patient first. Thus, further investigations to find the root cause or explanation for these metabolic abnormalities were delayed to achieve this ultimate priority. Cardiac monitoring, intravenous rasburicase and aggressive intravenous hydration (250mL\h) were all initiated while aiming for a urine output >100mL\hr. Owing to the fact that he did not exhibit any specific symptoms of hypocalcemia, like muscle spasms or seizures, hypocalcemia did not require any immediate intervention. Yet, with severe hyperkalemia, intravenous calcium gluconate in addition to insulin and dextrose was mandatory. The administration of bicarbonate was avoided, as the metabolic acidosis was not severe, with a pH of 7.32 shown in his venous blood gases results. After improvement of renal functions and normalization of electrolytes within 72 hours without the need of hemodialysis, a bone marrow biopsy was done, revealing hypercellular bone marrow showing >60% of nucleated cells being immature myeloid precursors, raising strong suspicion for AML (Acute Myeloid Leukemia). To confirm this diagnosis, flowcytometry to assess blast immunophenotype as well as cytogenetic and molecular testing for AML-defining abnormalities were all done. A blast count of more than 20% and the presence of specific genetic mutations alongside the whole clinical picture made the diagnosis of acute myeloid leukemia well established. Eventually we referred the case to a tertiary center with a haemato-oncology unit.

3. Discussion

Tumor lysis syndrome is a fatal oncological emergency usually triggered by the sudden release of intracellular components from rapid turnover of cancerous cells; in most cases it occurs in response to chemotherapy, but it could also occur spontaneously, as seen in this case. Laboratory tumor lysis syndrome can be defined by the presence of two or more new metabolic abnormalities: hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcemia [7]. Even though tumor lysis syndrome is rare without prior history of cancer and chemotherapy, laboratory findings in this case are highly consistent with spontaneous tumor lysis syndrome, which is a well-documented presenting feature of some aggressive hematological malignancies [1][2]. This event is found to be more common in highly proliferative malignancies like high-grade lymphomas, acute leukemias, and only a few solid tumors [9]. In other scenario, the absence of both leukocytosis and circulating blasts on smear could create a huge diagnostic dilemma in the cases of aleukemic leukemia, but pancytopenia supported by circulating blasts seen by pathologists strongly suggested leukemia to be a major differential diagnosis for the metabolic disturbance in this case. Thus, spontaneous tumor lysis syndrome could be the first sign of undiagnosed malignancy and pose a significant threat for rapid progression and deterioration, emphasizing and stressing the vital role of early recognition to achieve successful stabilization [5][9]. Spontaneous tumor lysis syndrome is an elusive diagnosis that could be easily missed if it occurred before the cancer diagnosis; laboratory abnormalities like markedly high LDH, hyperphosphatemia, and hyperuricemia could serve as early silent markers that appear before all signs of cancer [7]. Because of that, a lower threshold for bone marrow biopsy should be set in this setting, even if it

was isolated pancytopenia without circulating blasts, since it could be an early leukemia [7]. Minimal red flags should be needed to proceed with the bone marrow biopsy mainly due to the seriousness of complications that could happen on account of any diagnostic delay. Additionally, since absence of blasts cannot exclude leukemia by itself, bone marrow biopsy should be warranted even in cases without pancytopenia if the metabolic abnormalities are potentially attributed to spontaneous tumor lysis syndrome. In cases of mild lab abnormalities like isolated hyperuricemia, monitoring while investigating other causes could be justified, but when an alternative diagnosis like gout and CKD (Chronic Kidney Disease), bone marrow biopsy can be dismissed until other red flags arise [3]. Still, bone marrow biopsy remains the ideal tool for establishing a definitive diagnosis in case of atypical presentations of hematological malignancies [7]. In non-oncology centers, immediate management of spontaneous tumor lysis syndrome should be focused on stabilizing the patient by hydration, electrolyte monitoring, uric acid management, and renal support if required [3][4]. Allopurinol can be used for prevention of tumor lysis syndrome in low to intermediate-risk patients [4]. However, rasburicase remains the preferred agent for treatment of established cases and even prophylaxis in high-risk patients [4]. Major differences between rasburicase and allopurinol include the rapid action of rasburicase, which effectively clears uric acid, contrary to the delayed action of allopurinol which could take 24-72 hours to onset [4]. Rasburicase should always be considered whenever it is available if the uric acid levels exceed 8 mg\dL or there is overt renal dysfunction [4]. A limitation for rasburicase is that it is absolutely contraindicated in patients with G6PD (Glucose 6-Phosphate Dehydrogenase) deficiency due to the risk of acute hemolytic anemia and methemoglobinemia, warranting urgent G6PD screen before initiation [4]. Yet, in case of life-threatening tumor lysis syndrome with unknown G6PD status, consideration of low dose rasburicase is reasonable if the patient is not from a high-risk ethnic group for G6PD deficiency, which is not applicable in regions like Africa, South Asia and the Middle East [4]. Usual indications for RRT (Renal Replacement Therapy) still apply here and must be taken into consideration whenever hyperkalemia is unresponsive to medical treatment or there is severe refractory metabolic acidosis [7]. Above all, the crucial role of multidisciplinary teams, including haemato-oncology and nephrologists cannot be ignored in the process.

4. Conclusion

A major takeaway is that the absence of classic features of tumor lysis syndrome, like an obvious solid tumor or leukocytosis, should never dismiss the diagnosis. Another principal message to retain is that metabolic derangements in tumor lysis syndrome could be subtle and not always textbook in numerical values, requiring continuous monitoring for early recognition. This whole thing challenges traditional cancer paradigms and pushes clinicians to consider malignancy even in nonspecific acute illnesses. Finally, the development of sensitive and rapid biomarkers alongside refined risk stratification models might be a futuristic advancement that could help in detecting tumor lysis before the onset of symptoms, ensuring rapid recognition in the future.

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