Concurrent acute spontaneous tumor lysis syndrome complicated with multiple organ failure in a patient with pre-existing undiagnosed lung cancer

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Abstract Acute kidney injury, a common complication associated with malignancy, occurs in various clinical situations for numerous reasons. Acute tumor lysis syndrome (TLS) is possibly the most significant cause of acute kidney injury in cancer patients, because it is fulminant at onset and associated with severe metabolic derangements. Acute spontaneous tumor lysis syndrome is rare and most of the related malignancies belong to hematologic malignancies but it has seldom been investigated as bulky or advanced metastatic non-hematologic malignancies. TLS comprises a clinical laboratory derangement of cellular metabolism which can lead to acute renal impairments, cardiac arrhythmia, seizures and patient demise. Prevention and treatment of tumor lysis syndrome depends on early recognition of at-risk patients, volume repletion and xanthine oxidase inhibitors. In addition, in patients with high risk tumor types, prophylactic use of rasburicase before chemotherapy is required. If dialysis is required, continuous modalities may be favored, particularly in patients with more severe TLS. This case report discusses a 79-year-old man with controlled Alzheimer's disease presented with picture of septic shock and multiorgan dysfunction (acute kidney injury, acute lung injury, acute brain injury) pulmonary suppuration in the right lung field due to aspiration pneumonia with infection-induced systemic inflammatory response (SIRS) was diagnosed. Further work-up revealed lung cancer on chest CT scan. Antibiotic, respirator and hemodialysis treatment improved his

condition but died several days later. Acute spontaneous TLS may present in association with infectious SIRS and multiple organ failure, the combination of which results in significant mortality.

Keywords Lung cancer · Multiple organ failure · Spontaneous tumor lysis syndrome

Introduction

Acute tumor lysis syndrome (TLS) is possibly the most significant cause of acute kidney injury in cancer patients. Tumor lysis syndrome is the development of an array of metabolic disturbances that may occur spontaneously or in response to cancer therapies. Hande and Garrow classified TLS as laboratory and clinical TLS. Laboratory TLS (LTLS) has defined to be present if two or more serum values of uric acid, potassium, phosphate or calcium are above or below normal and if they change by 25 % within 3 days before the start of the therapy or 7 days after the commencement of the treatment [1]. Clinical TLS (CTLS) requires LTLS to be present along with one or more clinical complications such as renal insufficiency, cardiac arrhythmia and seizures. TLS is often associated with hematological malignancies but is also observed in various solid tumors with high proliferative rates and high response rate to cytotoxic therapy. Acute kidney injury and dramatic electrolyte imbalances should prompt consideration of spontaneous tumor lysis syndrome, even in the absence of a previous diagnosis of malignant disease. This article presents acute spontaneous TLS with pulmonary suppuration-induced systemic inflammatory response syndrome/multi-organ dysfunction in a patient with pre-existing undiagnosed lung cancer.

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Case report

A 79-year-old man with Alzheimer's disease for the last 5 years presented to emergency room with gradually decreased level of consciousness of 2 days duration. Since 10 days prior to admission, he developed respiratory difficulty, swallowing difficulty, carpopedal spasm during blood pressure measurement, myoclonic jerk. For the patient started ceftizoxime and he developed seizure during first ten minutes and then discontinued. 3 days later, he developed decreased level of consciousness and then referred to emergency room. He had history of long-standing lung disease, systemic hypertension, hyperlipidemia, benign prostatic hypertrophy and normal renal function. His routine medications included memantin, donepezil, seretide spray, theophylline ER tablet, prazosin and tamsulosin. Moreover, past history of patient revealed a black wart on abdomen that consultant dermatologist suggested seborehmic wart and recommended skin biopsy.

On physical examination, the patient was cachectic and had respiratory gasping and undetectable blood pressure. He had 3+ pitting edema in both upper extremities and atrophic muscles in lower extremities. The patient was intubated and removed large amount of pussy discharge from endotracheal tube and underwent ventilator with synchronized intermittent mandatory ventilator mode. He received 1000 cc normal saline and started intravenous dopamine and blood pressure gradually raised to 70 mmHg in less than 1 h. Urinary output with internal Foley catheter insertion was 100 cc. Venous blood gas revealed mixed metabolic and respiratory acidosis (pH 7.12, $p\text{CO}_2$ 70 mmHg, HCO_3^- 14 mEq/l) at first hour and then changed to metabolic acidosis and respiratory alkalosis post endotracheal intubation and mechanical ventilation. A chest radiograph showed patchy infiltration in right lower lung field. Several hours after admission, the patient developed one brief, generalized tremor that stopped spontaneously.

Laboratory analysis showed anemia (Hb 10 g/dl), leukocytosis (WBC $15 \times 10^3/\mu\text{l}$), platelet count ($214 \times 10^3/\mu\text{l}$), elevated erythrocyte sedimentation rate (ESR 105 mm/h), elevated C-reactive protein concentration, hyperglycemia (blood sugar 300 mg/dl), elevated serum creatinine [cr 3.5 mg/dl (baseline 0.8 mg/dl)], hyperkalemia (K^+ 5.6 mEq/l), severe hyponatremia (Na^+ 188 mEq/l), significant hyperuricemia (uric acid 14 mg/dl), severe hyperphosphatemia (P 11 mg/dl), hypocalcemia (Ca 6.2 mg/dl, albumin 2.2 g/dl). For the patient started regular insulin, half-saline and broad spectrum antibiotic (meropenem and clindamycin) with suspicion to sepsis due to aspiration pneumonia. Moreover, water through nasogastric tube was given. Due to anuria, the patient received intravenous furosemide 100 mg and response to it and found urinary output.

Fig. 1 Coronal chest computerized tomography scan shows bilateral pleural effusion and pulmonary collapse, right hilar mass and an irregular round mass with infiltrating outline in left peripheral lung

During third day, because of positive Chvostek's and Trousseau's signs, generalized myoclonic jerk and laboratory hypocalcemia, intravenous calcium gluconate was given and had improvement. Brain CT scan without contrast performed and revealed atrophic changes. Chest CT scan showed bilateral pleural effusion and pulmonary collapse, right hilar mass and a round lesion about 23×17 mm with an irregular, infiltrating (spiculated) edge in left peripheral lung and then transferred to ICU (Fig. 1). Urinalysis was normal with pH of 5 and blood and urine cultures did not grow microorganism. Because of uremic encephalopathy, elevated serum creatinine (cr 5.5 mg/dl) and persistent hyperuricemia, for the patient inserted left femoral vein catheter and performed hemodialysis for 3 session of 2 h duration after 5 days and had improvement and level of consciousness increased but unfortunately expired 4 days later.

Discussion

Acute kidney injury is common among cancer patients and cancer is the second leading cause of death in the United States and survival rates significantly are lower in patients with cancer and AKI compared with patients with similar disease severities who do not have cancer. Moreover, acute kidney injury is an important complication of cancer and its treatment [2].

Tumor lysis syndrome is an intrinsic cause of AKI in the patient with malignancy and is considered as an oncologic emergency. TLS comprises a clinico-laboratory derangement of cellular metabolism which can lead to acute renal impairments, cardiac arrhythmia, seizures and patient

Fig. 2 Cairo-Bishop classification of tumor lysis syndrome in adults. Patients must meet more than two serum values of laboratory criteria within a 24-h period or a >25 % increase from baseline laboratory values within 3 days before the start of therapy or 7 days after the commencement of the treatment. Symp.hypocalcemia, other symptomatic hypocalcemia; TLS, tumor lysis syndrome

demise. According to Cairo-Bishop classification, TLS can be defined as laboratory TLS, when clinical TLS is silent, as well as clinical TLS; laboratory evidence of TLS is complicated by clinical manifestations such as arrhythmias, renal insult, seizures and ultimately death. Laboratory TLS is defined as the presence of at least two or more biochemical variables within 3 days before chemotherapy or 7 days after chemotherapy in the face of adequate hydration and use of uric acid-lowering agent. Clinical TLS is defined as the presence of at least one clinical criterion that is not believed to be attributable to chemotherapy agent (Fig. 2).

The highest risk of TLS is seen in large volume, highly metabolic malignancies such as B cell ALL and Burkitt's lymphoma, whereas solid tumors and slow-growing hematologic malignancies (such as multiple myeloma) carry lower risks. TLS can be either spontaneous (without cancer targeted treatment) or therapy-related. Spontaneous TLS is even rarer event in patients with solid malignancies and a key distinction between spontaneous tumor lysis and that occurring after therapy is the lack of hyperphosphatemia in the spontaneous form, presumably because of the rapid uptake of extracellular phosphate by the remaining highly active residual tumor cells in the former condition. Hyperphosphatemia in patients with TLS will be further exacerbated by any associated AKI. Of course, this finding in above presented case is inconsistent with suggestion of spontaneous TLS but sepsis-induced AKI can be a reason for hyperphosphatemia [3]. Lung cancer is a common malignancy that severely threatens human health. Patients with early stage lung cancer are asymptomatic in most cases without distinct imaging manifestations. Occurrence of TLS in patients with non-small cell lung carcinoma and small cell lung carcinoma has demonstrated [4, 5]. Carcinoma of the bronchus is one of the most common primary

malignant tumors. It is convenient to consider the radiological features of central and peripheral tumors separately. Presentations of tumor as a hilar mass with or without narrowing of the adjacent major bronchus and collapse and/or consolidation of lung beyond the tumor are the signs of a central tumor. A peripheral tumor usually presents as a solitary pulmonary nodule/mass on plain films or chest CT. A rounded opacity with an irregular border (lobulation, notching and infiltrating edges) and cavitation within the mass are the signs of peripheral primary carcinoma [6]. Serum tumor markers, e.g., NKX2-1 (NKX homeobox-1 gene), also known as TTF-1 (thyroid transcription factor-1) can be considered as a transcription factor for development, diagnosis and prognosis of lung cancer [7]. Risk factors for the development of acute spontaneous tumor lysis syndrome in patients with non-hematological solid tumors include large tumor burden (>10 cm) with necrosis, rapidly proliferating tumor, extensive bone marrow involvement, hepatic metastasis, elevated white cell count ($>50000/\mu\text{l}$), elevated lactate dehydrogenase level, use of potentially nephrotoxic drugs and drugs which inhibit uric acid excretion, elevated uric acid level, impaired renal function, extrinsic compression of the urinary tract by the tumor, underlying problems such as dehydration, infection or urinary obstruction. According to tumor type, lung cancer is in moderate risk of TLS. Nevertheless, clinicians should keep in mind that patients with solid tumors may develop this potentially deadly syndrome [8].

Notable findings with tumor lysis syndrome include AKI, hypocalcemia, hyperkalemia, hyperphosphatemia and hyperuricemia as AKI is central to the development of TLS. Secondary hypocalcemia of TLS is the more immediate threatening of the two electrolytes disorders, leading in severe cases to arrhythmia, seizures, tetany and death. The hypocalcemia of TLS may persist even after phosphate levels normalize, presumably because of deficiencies of 1, 25-dihydroxyvitamin D [9]. In our patient, symptomatic hypocalcemia as focal motor seizures improved with 10 ml of intravenous 10 % calcium gluconate (containing 0.465 mEq/ml elemental calcium) and then inserted on oral calcium carbonate. The primary mechanism of kidney injury includes urate and phosphate nephropathy. Urate nephropathy occurs because of intratubular obstruction and direct toxicity. Emerging and clinical data suggest both a direct and indirect role for uric acid in the development of AKI associated with TLS. AKI associated with TLS due to hyperuricemia may have both a crystal-dependent and a crystal-independent mechanism of renal injury. In malignancy-associated TLS, testing of urine uric acid and calculation of the urine uric acid-to-creatinine ratio to predict the risk for or confirm the presence of TLS is not recommended. Phosphate nephropathy is due to direct toxicity or

calcium phosphate deposition [10]. Acid-base status of patient showed hypercapnic respiratory acidosis due to suppurative pneumonia and metabolic acidosis. Superimposed metabolic acidosis was created because of nonketotic hyperglycemia and lactic acidosis due to circulatory failure. This life-threatening combination (respiratory and metabolic acidosis) represents sepsis. Prevention of TLS may be more effective than treatment. Among patients at medium or high risk of development of TLS, a prophylactic xanthine oxidase inhibitor should be provided. Even among patients with low-risk tumor types, xanthine oxidase inhibition should be considered if other risk factors (elevation of baseline uric acid or lactate dehydrogenase, or underlying kidney disease) are present. In patients with high-risk tumor types, consensus guidelines suggest the prophylactic use of recombinant urate oxidase (Rasburicase) before chemotherapy.

The treatment consists of aggressive hydration, correction of electrolyte disturbances and uric acid-lowering therapy. If dialysis is required, continuous modalities may be favored, particularly in patients with more severe TLS [11]. Continuous therapies did not perform due to unavailable solutions. Although acute kidney injury in this patient has several causes including dehydration due to poor oral intake, infection and drugs, e.g., memantine, it seems that acute TLS is the main cause of acute kidney injury. In spite of good control of infection and hemodynamic stability and drug cessation, clinical and metabolic derangements (uremic encephalopathy and rising of serum creatinine) continued and led to hemodialysis. In adults, hypernatremia developing outside the hospital most often occurs in patients over the age of 60. In addition to an increased frequency of concurrent illness and diminished mental status, increasing age is also associated with diminished osmotic stimulation of thirst, even though the release of antidiuretic hormone (ADH) is maintained. Although most otherwise healthy older patients maintain normal water balance, their response to a given stress may be impaired, increasing the likelihood of their becoming hypernatremic. In our patient, hypernatremia is due to water loss because of insensible loss (respiratory infection) and dehydration due to poor oral intake. SIRS and MOD associated with acute spontaneous tumor lysis syndrome (ATLS) would seem to be physiologically plausible. Soares et al. [12] in a retrospective, small study reported five patients who developed ATLS associated with SIRS and MOD in the absence of clear alternative explanations. The etiology of systemic inflammatory response syndrome in tumor lysis syndrome patients is not fully understood; it is reasonable to hypothesize that cytokines released by the cells during lysis may induce severe SIRS and often multiorgan failure. SIRS has also been reported in cancer patients receiving T cells genetically modified with chimeric

antigen receptors to retarget their specificity to tumor-associated antigens [13]. Moreover, serum uric acid is a potent free radical scavenger and increases in response to oxidative stress [14]. Sepsis is the most common cause of acute kidney injury seen in patients with cancer and this patient presented with an infectious source of SIRS that clearly was determined during endotracheal tube insertion, on plain chest X-ray and with peripheral blood leukocytosis. This event led to septic shock and multiorgan failure. Moreover, both sepsis/MOD and acute TLS can be presented with AKI, seizure, evidence of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. This finding in our patient demonstrated with detection of lung cancer on chest CT scan. However, acute spontaneous TLS should be considered in this patient especially with evidence of lung mass and other clinical and laboratory metabolic disturbances. A search of literature revealed five cases of acute TLS associated with SIRS/MOD, while no account of aspiration pneumonia following lung cancer could be found. This case report, to my knowledge, describes the first case of pulmonary suppuration from aspiration pneumonia leading to multiple organ failure in a patient with acute spontaneous TLS due to lung cancer.

Conclusion

Although in the presented case, definite diagnosis of lung cancer cannot be established through tissue proven biopsy, we can demonstrate that acute spontaneous TLS may present in association with infectious SIRS and MOD, the combination of which results in significant mortality. Furthermore, it is essential that onco-nephrologists to be noticed this point that acute TLS must be considered in the differential diagnosis of any patient with AKI of uncertain etiology, particularly in the setting of hyperuricemia, hyperkalemia and hyperphosphatemia.

Conflict of interest The author declares that there is no conflict of interests regarding the publication of this paper.

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