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Case Report

Spontaneous Tumor Lysis Syndrome, an Unusual Complication of Metastatic Neuroendocrine Carcinoma of Unknown Primary

Georges El Hachem[1]* and Ziad El Ali[2]

[1]*Fellow in Medical Oncology at Institut Jules Bordet, Université libre de Bruxelles, Belgium*

[2]*Medical Oncology Department, Institut Jules Bordet, Université libre de Bruxelles, Brussels, Belgium*

***Corresponding Author:** Georges El Hachem, Fellow in Medical Oncology at Institut Jules Bordet, Université Libre de Bruxelles, Belgium.

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Abstract

Tumor lysis syndrome is one of the life threatening oncologic emergencies, occurring much more frequently in hematologic malignancies compared to solid tumors. It is described following administration of cytotoxic chemotherapy. It is called spontaneous if it occurs before initiating any antineoplastic treatment, and is usually seen in hematologic malignancies with high turnover rates.

Here we report the case of a 61 years old man, who was referred to our hospital for management of a hypermetabolic, retroperitoneal mass of 20 x 10 x 11 cm with retroperitoneal adenopathies. Laboratory tests showed a normal creatinine, high LDH (1056 IU/L; normal > 225 IU/L), normal electrolytes and uric acid values. Unfortunately, he developed oliguric acute kidney injury, with concomitant rising in LDH (2038 IU/L), and hyperuricemia (8.4 mg/dL); however, the phosphorus and calcium levels remained normal. The pathology came back in favour of a high grade, poorly differentiated neuroendocrine carcinoma, Ki-67 of 40%. After excluding all other causes of renal failure, our patient was diagnosed with spontaneous tumor lysis syndrome. He received an adequate supportive treatment (hydration, hypouricemic agents) and adequate cytotoxic chemotherapy. Ten days later, he was discharged with normal renal function and near normal LDH.

To date and to the best of our knowledge, this is the first case of spontaneous tumor lysis syndrome in metastatic neuroendocrine carcinoma of unknown primary. It is a rare entity that should be considered whenever we have a bulky high grade, chemo sensitive metastatic disease, with new onset of acute kidney injury and concomitant high LDH, hyperuricemia without hyperphosphatemia. Incidence of spontaneous tumor lysis syndrome is undetermined in solid tumors and its prognosis is usually poor.

Keywords: Tumor Lysis Syndrome; Metastatic Neuroendocrine Carcinoma

Introduction

Tumor lysis syndrome (TLS) is one of the life threatening oncologic emergencies. It occurs much more frequently in hematologic malignancies compared to solid tumor where some cases have been already described following administration of cytotoxic chemotherapy. However, it is called spontaneous if it occurs before initiating any anti-neoplastic treatment, and is usually seen in hematologic malignancies of high turnover rates mainly acute lymphoblastic leukaemia, Burkitt lymphoma, or other high-grade lymphomas. Nevertheless, it may occur in solid tumors if these are bulky, poorly differentiated, highly proliferative and known to be sensitive to chemotherapy.

Here we report a case of spontaneous tumor lysis syndrome (STLS) seen in a patient diagnosed with bulky, metastatic, high grade, poorly differentiated neuroendocrine carcinoma of unknown primary before initiation of chemotherapy.

Case Report

Our patient is a 61 years old man, known hypertensive and type II diabetes mellitus, who was admitted to our institution to continue the investigations for a newly discovered retroperitoneal mass. The patient was suffering from unintentional weight loss, around 20 kg over the last year, with new onset of right sided abdominal pain and distention over the last two months. He was initially admitted to a peripheral hospital where he underwent a chest abdomen pelvis CT scan revealing a heterogeneous, retroperitoneal mass of 20 x 10 x 11 cm, with areas of necrosis, compressing the right kidney, the liver posteriorly and infiltrating the right diaphragm. It was associated with centimetric retroperitoneal lymphadenopathies, and right pleural effusion, without any mass seen in the liver, kidneys, pancreas or adrenal glands. They completed their investigations with a nephrogram, revealing a decreased clearance of 40 mL/min/1.79m^2, a right kidney functioning at 26% and left kidney at 74%, with a compressive effect on the upper third of the right kidney; however, there were no obstruc-

tive process seen on the nephrographic curves. His laboratory tests showed a normal complete blood counts, normal creatinine, high LDH (1060 IU/L; normal < 225 IU/L).

Upon arrival to our hospital, FDG-PET CT Scan was done and confirmed the 20 x 10 cm retroperitoneal mass and lymphadenopathies that were hypermetabolic, with the right pleural effusion being metabolically avid. No lesions were seen in the lungs, pancreas or kidneys.

Upper and lower gastro-intestinal endoscopies didn't reveal any lesion. We also underwent a bronchoscopy that didn't show any primary lung tumor and right pleural effusion thoracentesis was performed: the effusion turned to be a transudate with absence of malignant cells. An ultrasound guided biopsy was done from the retroperitoneal tumor.

Figure 1 : ACT scan showing the necrotic, heterogenous, bulky retroperitoneral mass of 20x10x11cm compressing the right kidney and liver with infiltration of right diaphragm.

Figure 2: A The described primary retroperitoneal mass described on figure 1, appearing hypermetabolic (SUV of 23.5) on the fluoro-D-glucose positron emission tomography (FDG PET).

Unfortunately, the patient became confused during his hospital stay, and developed rapid cognitive deterioration. A complete metabolic and infectious work up were negative. EEG didn't reveal any epileptic activity; it only showed non-specific rapid and slow waves activity that could be of metabolic origin.

There was no brain metastasis or ischemic or haemorrhagic lesions. A symptomatic treatment was given with anti-psychotics, benzodiazepine, and complex multi-vitamin B trying to treat a suspected alcohol withdrawal syndrome although he stopped alcohol consumption for 4 weeks. The next day, he developed an oliguric acute kidney injury, with a serum creatinine rising progressively from 0.8 mg/dL to 1.4 mg/dL to 2.16 mg/dL, with an associated increase in potassium and uric acid. However, he didn't develop hyperphosphatemia nor hypocalcaemia. His complete blood counts remained within normal limits. Furthermore, there was a constant concomitant increase in LDH; it increased from 1060 IU/L (normal < 225 IU/L) upon admission up to 2060 IU/L when his serum creatinine was 2.16 mg/dL. Abdominal ultrasound was done and ruled out an obstructive nephropathy, with a homogeneous prostate of normal size.

At that time, we got the pathology result that was in favour of a high grade, poorly differentiated neuroendocrine carcinoma, Ki-67 40%, negative for thyroid transcription factor-1 (TTF1), islet-1 (ISL1) and homeobox protein CDX2 on immunohistochemistry. Retrospectively, his neuron specific enolase was 326.7 µg/L (normal < 16 µg/L).

No primary lesions were identified by radiological or endoscopic evaluation in the lungs, pancreas, or gastro-intestinal system. Thus, the primary retroperitoneal tumor was a high grade neuroendocrine carcinoma of unknown primary with lymph nodes metastasis.

The patient was transferred to ICU and received an aggressive hydration, Allopurinol, and a chemotherapy consisting of Carboplatin and Etoposide was started.

His renal function improved, his uric acid started decreasing, and concomitantly, he had recovery of his cognitive function. To note that his LDH kept rising while he was receiving his chemotherapy, and reached 3060 IU/L at day 5, then dropped back to 380 IU/L before his discharge one week later.

Finally, we made the diagnosis of spontaneous tumor lysis syndrome that occurred before initiation of chemotherapy treatment

in this case of metastatic, high grade, bulky, poorly differentiated neuroendocrine carcinoma of unknown primary. The patient developed an oliguric acute kidney injury, with simultaneous increase in potassium, uric acid, LDH, and normal phosphate level. These clinical and laboratory abnormalities are characteristic of STLS.

Figure 3: Evolution of Laboratory Tests During the Hospital Stay.

The patient had normal creatinine and high LDH upon admission. When he developed the oliguric acute kidney injury, he had concomitant increase in LDH and uric acid level, but the phosphorus remained normal. Cytotoxic chemotherapy lead to further and continuous LDH rising due to cell destruction. However, his renal function and uric acid level remained stable due to aggressive supportive care he received. Upon discharge, he normalized his kidney function, and his LDH dropped to near normal.

Discussion

Tumor lysis syndrome (TLS) is an oncologic emergency. It typically develops within 12 to 72h of treatment with cytoreductive therapy. However, it rarely occurs spontaneously before any anti-neoplastic treatment. Rapid cellular breakdown leads to massive release of intracellular content overwhelming the homeostatic and excretory mechanisms of the body [1]. The major signs of TLS are hyperuricemia resulting in uric acid nephropathy, hyperphosphatemia with secondary hypocalcaemia and hyperkalaemia with all its cardiac consequences. Clinical complications such as acute kidney injury, cardiac arrhythmias and seizures can develop and lead to multiorgan failure and death [2,3].

Clinically aggressive non-Hodgkin lymphomas and acute lymphoblastic leukemia (ALL), particularly Burkitt lymphoma/leukaemia are the leading causes of TLS [4,5]. Other hematologic malignancies commonly associated with TLS are anaplastic large cell lymphoma, T-cell or B-cell precursor ALL, acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), and plasma cell disorders, including multiple myeloma and isolated plasmacytomas [6].

TLS has been rarely described after treatment of some non-hematologic solid tumors, including breast carcinoma, small cell carcinoma (mostly involving the lung), neuroblastoma, germ cell tumors, medulloblastoma, sarcoma, ovarian cancer, squamous cell carcinoma of the vulva, metastatic colorectal cancer, urothelial cancer, gastrointestinal stromal tumors, melanoma, and hepatocellular carcinoma [3,7-10].

Spontaneous acute kidney injury associated with marked hyperuricemia prior to the initiation of anti-neoplastic therapy has been described in lymphomas and acute leukaemia's [6,11]. It usually occurs in patients with bulky, rapidly proliferating, treatment-responsive tumors. In the literature, there were cases reporting STLS in inflammatory breast cancer, metastatic hepatocellular carcinoma, metastatic small cell lung carcinoma and metastatic merkel carcinoma [12].

The prevalence and incidence of STLS in solid tumors is very difficult to know, because the collection of the data is limited to case reports and small case series.

Neoplasms that are rapidly growing with high cell turnover rates produce high serum uric acid levels through rapid nucleoprotein turnover, leading to the release of intracellular potassium and phosphorus. However, the tumor is able to reutilize released phosphorus to maintain its replication. In contrast, TLS after chemotherapy is due to cell destruction in the absence of reuptake of phosphorus, and thus, hyperuricemia with hyperphosphatemia[6,13,14].

After reviewing the literature, some risk factors predicting the onset of STLS were identified, particularly: large tumor burden, renal insufficiency, elevated LDH, hyperuricemia, metastatic disease (especially liver and bone marrow involvement), extrinsic compression of urinary tract by tumors, and pre-treatment azotaemia [13,14].

It is usually better to prevent than to treat the tumor lysis syndrome. The preventive measurements classify tumors as high, moderate and low risk for tumor lysis syndrome. The solid tumors are in the category of moderate risk for STLS. Whenever there is high LDH, metastatic bulky disease and a known sensitive tumor to cytotoxic treatment, it is better to start aggressive adequate hydration and a hypo-uricemic agent: Allopurinol in moderate and low risk; Rasburicase in high risk [15,16,17]. When tumor lysis occurs, it will be difficult to manage electrolyte disturbance and mainly hyperuricemia.

Small cell carcinomas and high grade neuroendocrine carcinomas are known to be very chemo-sensitive and patients are at risk of developing TLS once they receive the standard chemotherapy regimen consisting of Platinum and Etoposide, especially if there is an extensive metastatic disease. However, our patient who had a bulky high grade aggressive neuroendocrine carcinoma of unknown primary, developed an oliguric acute kidney injury with concomitant increase in LDH, hyperuricemia and normal phosphorus level, before initiation of cytotoxic chemotherapy. After ruling out pre-renal causes and obstructive etiologies, the diagnosis was in favor of spontaneous tumor lysis syndrome.

Figure 4: Risk Stratification, Prevention and Treatment of Tumor Lysis Syndrome [15].

Conclusion

To date and to the best of our knowledge, this is the first case of spontaneous tumor lysis syndrome in metastatic neuroendocrine carcinoma of unknown primary. Although it is a rare entity, it should be considered whenever we have a bulky, high grade, chemosensitive metastatic disease, with new onset of acute kidney injury and concomitant high LDH, hyperuricemia without hyperphosphatemia. Incidence of spontaneous tumor lysis syndrome is undetermined in solid tumors and its prognosis is usually poor.

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