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Spontaneous tumor lysis syndrome: acute presentation in a patient with a suspected case of non-hodgkin lymphoma and a neuroendocrine tumor

Análisis de caso

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RESUMEN

El síndrome de lisis tumoral (SLT) constituye una emergencia médica que se observa comúnmente con la administración de fármacos antineoplásicos en escenarios de malignidad con alto grado de recambio; su presentación espontánea es una entidad médica rara que ocurre sin la evidencia de un evento precipitante, y está asociada con pobres respuestas homeostáticas y alta morbilidad y mortalidad si no se instaura tratamiento inmediato. Presentamos el caso de un paciente masculino de setenta y cinco años de edad con ascitis, falla renal aguda, hipercalemia e hiperuricemias consistentes con el diagnóstico de síndrome de lisis tumoral espontánea (SLTs) en un probable diagnóstico de linfoma no-Hodgkin y un tumor neuroendócrino. El diagnóstico de SLTs requiere un alto grado de sospecha, puesto que sus manifestaciones clínicas no son específicas y la malignidad subyacente puede no estar diagnosticadas en el momento de la presentación. Puesto que el pronóstico del paciente depende del reconocimiento temprano de la enfermedad, así como del tratamiento temprano, este trabajo destaca la importancia los criterios diagnósticos, el tratamiento extrapolados al paciente presentado y al trabajo diagnóstico realizado.

Palabras clave: Síndrome de lisis tumoral espontánea, linfoma no-Hodgkin, ascitis, carcinomatosis peritoneal, hipercalemia, hiperuricemia

ABSTRACT

Tumor lysis syndrome (TLS) constitutes a medical emergency commonly observed with the administration of antineoplasic drugs in the treatment of high burden malignancies; its spontaneous presentation is a rare medical entity that occurs without evidence of any precipitating event, and is associated with poor homeostatic responses and high morbidity and mortality if not treated promptly. We present the case of a seventy-five-year-old male patient with ascites, acute renal failure, hyperkalemia and hyperuricemia consistent with the diagnosis of spontaneous tumor lysis syndrome (sTLS) in a suspected case of non-Hodgkin lymphoma and a neuroendocrine tumor. Diagnosis of sTLS requires a high index of suspicion, as clinical manifestations are not specific and malignancy at the time of presentation may have not been diagnosed previously. As patient prognosis depends on early recognition of the disease and appropriate treatment, this paper highlights current diagnostic criteria and early treatment approaches, extrapolated to the patient presented and the differential diagnostic work that was performed.

Keywords: spontaneous tumor lysis syndrome, non-Hodgkin lymphoma, ascites, peritoneal carcinomatosis, hyperkalemia, hyperuricemia

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Background

Tumor lysis syndrome (TLS) is an acute medical life-threatening condition, considered an oncological emergency which results from tumor cells releasing its intracellular components into the bloodstream, thus its characteristic laboratory findings of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. (1,2,3). Metabolic anomalies lead to organ dysfunction and poor homeostatic response mechanisms with poor outcomes if not treated promptly (1,2). It is mainly triggered by the initiation of antineoplastic drugs as the mainstream of treatment in malignancies, however it can occur spontaneously: this phenomenon is rare and is mainly associated with high burden hematological tumors such as acute lymphoblastic leukemia (ALL) and non-Hodgkin Lymphoma (NHL), nonetheless in recent years its spontaneous variant has been reported in solid tumors such as ovarian epithelial cancer, small cell lung cancer and prostate cancer (2,3,4,5,6). It has been proposed that the risk for TLS is based on two factors: first, tumor factors – size, other organ involvement such as bone marrow and proliferative ability of the malignancy itself – and second, patient factors such as dehydration and previous renal failure play an important role; in kidney injury the clearance of metabolites is more difficult therefore increasing the likelihood of TLS (2). TLS is a recent entity in medicine, although observed in the 1960's it was not until the 1990's that laboratory and clinical criteria were defined; today the most accepted current definition of TLS is the one established by Cairo and Bishop which is more elaborate, combining pretreatment laboratory and clinical criteria, a time frame up to seven days after the initiation of treatment

and a severity scale (7,8). Although it may be reasonable to think that sTLS (spontaneous lysis tumor syndrome) is the same entity than TLS without any evident trigger of cytotoxic therapy, hyperphosphatemia is significantly less common as the phosphate released is reused by neoplastic cells in the generation of the new cells, an event unlikely in the setting of chemotherapy, and thus hypocalcemia is less likely since the binding of calcium to phosphate is much less common because there is a lower serum phosphate concentration that is available to bind to calcium than in TLS (2). There are two proposed theories for sTLS in the absence of an evident trigger: hyperthermia and an excessive secretion of endogenous glucocorticoids, although proper mechanisms are still poorly understood (11).

Case presentation

A previously healthy 75-year-old hispanic man until three months prior to admission, presented with a three-week course of severe and worsening epigastric and mesogastric non-radiating abdominal pain which was sharp, intermittent associated with a continuous sensation of fullness. The patient reported nausea but no vomiting, loss of appetite, unintentional weight loss, cough, dyspnea, abdominal distention, change in stool patterns since the previous week with constipation lasting four days, and a twenty-four-hour course of subjective fever. There were no associated night sweats, syncope, chest pain, orthopnea, paroxysmal nocturnal dyspnea, edema in lower limbs, melena, bright red stool per rectum, urinary symptoms, jaundice, acholia or choluria. His past medical history was pertinent for a hospitalization in another hospital one month prior to current admission for abdominal distention, non-specific abdominal pain and weight loss; contrast computer tomography showed evidence of an abdominal mass adhered to omentum of approximately 12x5 cm and ascitic fluid. A biopsy of the mass was taken for histopathological studies, and the patient was discharged home with loop and potassium sparing diuretics. His surgical and family history was negative for any

significant disease. His social history was negative for alcohol, tobacco or any other illicit drug use. He lived with his wife and children in Quito, Ecuador, worked in the leather industry and as a builder, was monogamous with his wife, and had no history of blood transfusions.

Pertinent physical examination on admission showed blood pressure of 120/89 mmHg, heart rate of 119 BPM, respiratory rate of 36 per minute, temperature of 36.5 °C, and oxygen saturation of 94%. There were decreased breath sounds on both pulmonary bases; abdomen was distended, tender to palpation in the epigastric and mesogastric areas, dullness to percussion on the left and right flanks, positive fluid ascitic wave and an increase in bowel sounds; no masses were palpated, nor hepatosplenomegaly or lymphadenopathy, possibly due to the accumulation of fluid. Other system examination was grossly normal. Initial laboratory test at the time of presentation are presented in table no. 1.

Subsequent CT scan of the abdomen and pelvis without contrast demonstrated a solid mass of 10x5 cm, localized in the pelvis dependent of intestinal loops, with multiple densities including fluid, and free fluid in the abdominal cavity with thickening of the peritoneum suggestive of carcinomatosis. Diagnostic paracentesis was immediately scheduled: cloudy yellow liquid was obtained with white blood cells: $15 \times 10^3/mm^3$, neutrophil and lymphocyte percentages of 11.6% and 88.4% respectively, albumin: 2.4 g/dL, Lactate-dehydrogenase: 4475 U/L; Gram and Zhiel Nielsen stains were negative and the fluid was sent for cultures and fluid adenosine deaminase measurement. Complementary laboratory tests were obtained: serum Lactate-dehydrogenase: 1807 U/L and serum albumin 3.00 g/dL.

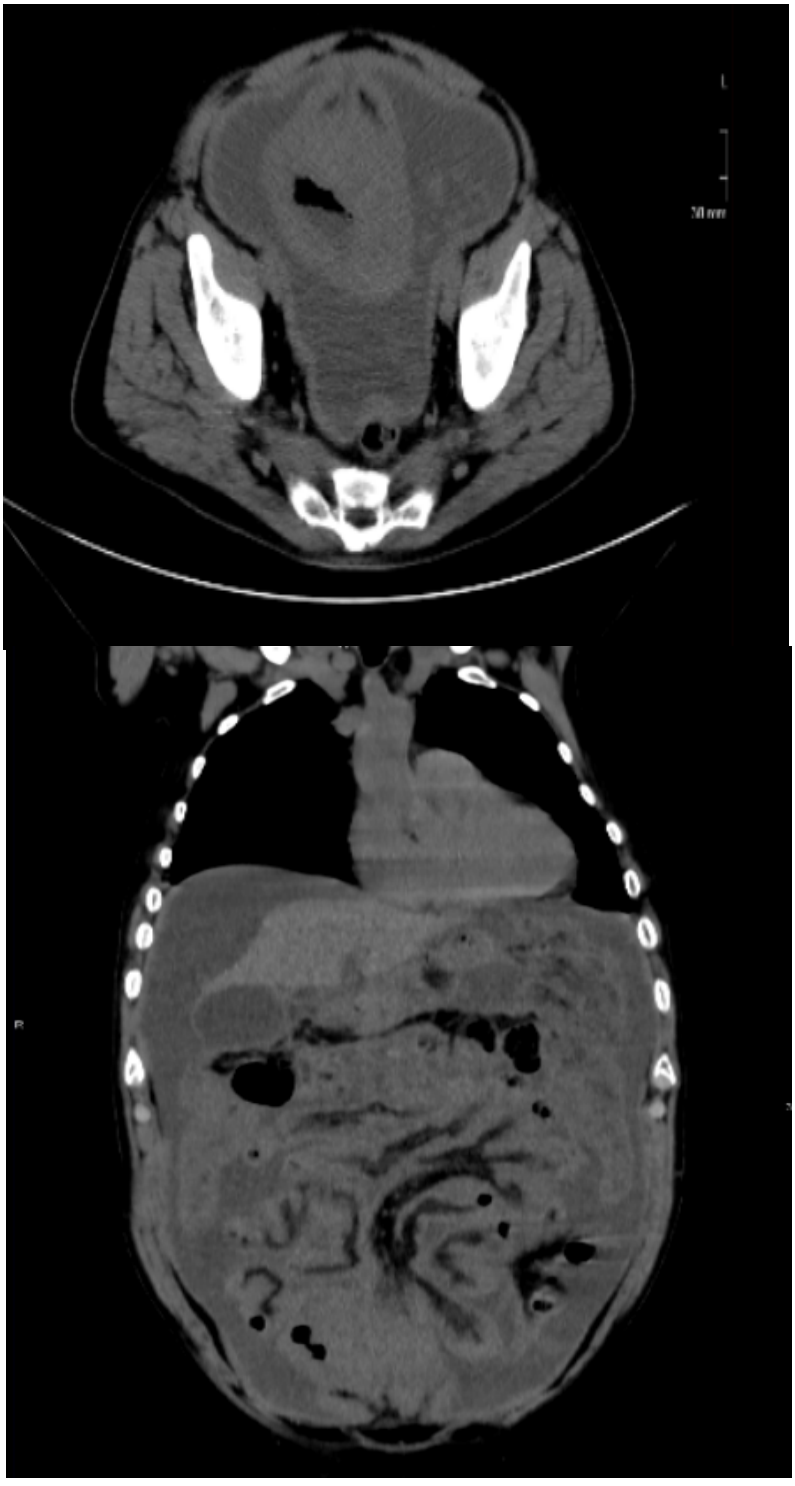

Figure 1. Abdominal computed tomography

The hospital in which the patient had been previously hospitalized was contacted to initiate chemotherapy; the tissue sample that was analyzed by histopathology had a cellularity consistent with non-Hodgkin Lymphoma nonetheless the sample was insufficient for

immunochemistry studies; chemotherapy was delayed, and a new biopsy of the mass was scheduled. Meanwhile the patient's health progressively started to deteriorate over the following twenty-four hours, with altered mental status, worsening dyspnea and tachypnea and new onset of lower extremity edema. At this time new laboratory tests were performed which showed serum creatinine (Cr): 3.27 mg/dL, blood urea nitrogen (BUN): 100 mg/dL serum urea: 214.4 mg/dL, lactic acid: 1.9 mmol/L, potassium: 7.0 meq/L and sodium: 147 meq/L. At this point, a high suspicion of a spontaneous lysis tumor syndrome was considered due to rising serum creatinine and serum potassium levels despite the fact that potassium sparing diuretics were discontinued the day the patient was admitted. Complementary laboratory tests were ordered: serum calcium: 7.8 mg/dL phosphorus: 5.80 mg/dL and uric acid 21.9 mg/dL. Based on the Cairo and Bishop definition proposed in 2004 our patient met one clinical criterion and two laboratory criteria for the diagnosis of sTLS along with high LDH serum levels.

Laboratory Data				
Blood				
	Reference Range	Day 1 (on admission)	Day 2	Day 7 (on discharge)
Hemoglobin (d/dL)	13.6-17.5	14.5		10.1
Hematocrit (%)	44	44		31.7
White Cell Count (per mm^3)	4400-11500	10770		9700
Differential count (%)				
Neutrophils	50-70	86.4		75
Lymphocytes	25-40	3.8		20.3
Monocytes	2-10	9.5		2.3
Eosinophils	2-4.5	0.0		0.1
Basophils	0-1	0.1		0.1
Platelet count (per mm^3)	150,000-400,000	165		150
Sodium (meq/L)	132-146	142	147	141
Potassium (meq/L)	3.7-5.4	6.0	7.0	4.2
Phosphorus (mg/dL)	2.50-4.50		5.80	
Calcium (mg/dL)			7.8	
LDH (U/L)	313-618	1807	1623	
Blood Urea Nitrogen (mg/dL)	6-23	76	100	
Urea (mg/dL)	10-70	162.6	214.4	
Creatinine (mg/dL)	0.60-1.30	2.64	3.27	0.66

Uric Acid (mg/dL)	3.50-8.50		21.9	
Total proteins (g/dL)	6.30-8.20	5.70	4.90	
Albumin (g/dL)	3.50-5.00	3.00	2.60	
Amilase (U/L)	30-110	198		
Lipase (U/L)	23-300	356		
Alkaline phosphatase (U/L)	38-126	153		
AST (U/L)	9-50	17		
ALT (U/L)	15-59	4		
Total bilirubin (mg/dL)	0.20-1.30	0.63		
Direct bilirubin (mg/dL)	0.00-0-40	0.42		
INR	0.80-120	1.10		
TTP (seg)	23.4-36.2	39.6		
VDRL		Non-reactive		
HIV		Non-reactive		
Anti-HCV	≥1	0.33		
HBsAg	≥1	Less than 1		
Urine				
Color		Yellow		
pH		5.0		
Specific gravity		1.012		
Protein		Negative		
Glucose		Negative		
Ketones		Traces		
Blood		Traces		
Bilirubin		Negative		
Nitrite		Negative		
Leukocyte esterase		Negative		
Red cells		Negative		
Leukocytes		2-4 HPF		
Bacteria		Traces		
Casts		Negative		
Crystals		Uric Acid ++		
Ascitic Fluid				
Color		Yellow		
White blood cells		15,000 mm^3		
Red blood cells		20,000 mm^3		
PMN		11.6%		
Lymphocytes		88.4%		
Albumin		2.4 g/dL		
LDH		4475 U/L		
Gram		No bacteria		
Zhiel-Nielsen		Negative		
Culture		Negative		
Adenosine deaminase	0-30	24		

Table 1. Laboratory data obtained during patient hospital stay

Differential diagnosis

This seventy-five-year-old male presented two major problems from which a differential diagnosis can be constructed: ascites and progressively declining kidney function - acute kidney injury.

Ascites

To determine the cause of ascites, the single most useful exam is to calculate the SAAG (serum to ascites albumin gradient), which has replaced the protein-based exudate/transudate to objectively identify portal hypertension; the gradient which is calculated by subtracting the ascitic albumin concentration from the serum albumin concentration, can identify with 97% accuracy the presence of portal hypertension when it`s ≥1.1 g/dL (17). Hepatic cirrhosis is one of many causes of portal hypertension and other etiologies should also be considered when accurately defining the cause of ascites with a high SAAG gradient like heart failure, alcoholic hepatitis, portal thrombosis, Budd-Chiari syndrome, constrictive pericarditis, massive hepatic metastases and idiopathic portal fibrosis; low gradient SAAG <1.1 g/dL should raise suspicion for peritoneal carcinomatosis, peritoneal tuberculosis, serositis, pancreatitis and nephrotic syndrome (18). The patient did not have other signs suggestive of portal hypertension other than ascites, such as upper gastrointestinal bleeding from esophageal varices, caput medusae or hemorrhoids. Initial laboratory studies showed no alteration in bilirubins and coagulation synthetic function, making hepatic insufficiency from portal hypertension a diagnosis to exclude; other laboratory tests showed no abnormalities in cytolytic hepatic enzymes and brain peptide natriuretic making alcoholic hepatitis and heart failure less likely causes. Additionally, the CT without contrast showed no hepatic masses, and even though a contrast CT with arterial and portal phases would have been required to accurately determine portal vein thrombosis, initial workup excluded these etiologies as the cause of ascites. The SAAG calculated in our

patient was a low gradient of 0.6 g/dL which in correlation with the findings described previously, turned diagnostic workup to ascites of non-portal hypertension etiologies: following the algorithm proposed by Sleisenger & Fordtran (See Supplementary Appendix No.1), the correct approach would be first, to quantify the number of WBC in the ascitic fluid, and the percentage of polymorphonuclear leukocytes: our patient had total WBC of 15,000 with 11.6%, which in hand with the low SAAG levels calculated previously, leaves two major diagnostic possibilities: peritoneal carcinomatosis, in search of a primary tumor and peritoneal tuberculosis (20). Other non-portal hypertension causes of ascites would have been less likely as a urine sample analysis showed no traces of protein, even though a twenty-four-hour sample would have been necessary to completely rule out nephrotic range proteinuria or in turn urine/creatinine ratio in a single urine sample. On the other hand, pancreatic enzymes showed no abnormalities thus making nephrotic syndrome and pancreatitis less likely diagnosis. In correlation with the findings obtained in the CT without contrast, our patient was later scheduled for diagnostic laparoscopy, and both cultures and ADA measurement were ordered to rule out either malignancy or tuberculosis.

Acute Kidney Injury

The patient´s creatinine levels rose in a twenty-four-hour period from 2.64 mg/dL to 3.27 mg/dL, which according to the KDIGO criteria, accurately defines acute kidney injury (AKI) as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours was objectively mesaured; our patient baseline creatinine levels were not available which made it difficult to categorize the stage of kidney failure (21). The most important question to be answered in this scenario is if the insult is due to a prerenal, intrinsic renal or post-renal obstructive component (21). The CT scan performed without contrast showed kidneys with normal morphological features, and no obstructive components, thus making a post-renal case a highly unlikely

diagnosis; in the same sense, an abdominal ultrasound was also performed which exhibited normal appearing kidneys without evidence of hydronephrosis corroborating this criterion. A prerenal condition with low intravascular effective volume could have been suspected the moment the patient presented to our hospital, however initial laboratory testing and clinical examination made diseases such cardiac failure, cirrhosis and nephrotic syndrome less likely diagnosis. Our patient renal function did not respond acutely to volume repletion with normal saline, and drugs that affect glomerular filtration were not administered (NSAIDs), corroborating that a prerenal cause was a less probable cause of this patient`s AKI, however calculating the fraction of sodium excreted in the urine (FeNa) could have helped in diagnosis (20). The urine sample sediment that was performed showed no casts: the absence of red cell casts almost excluded glomerulonephritis as the cause of our patient`s renal injury; in the same sense the absence of white cell blood casts excluded acute interstitial nephritis as a probable diagnosis of AKI (21). Less likely possibilities that could have been considered at the time were viral glomerulonephritis, however results of HIV, HCV and HBV were all negative (21). The only abnormality in the urine sample examined was the presence of acid uric crystals. The progressive decline in kidney function continued to be unanswered to our team: the electrolyte abnormalities and the observation of uric acid crystals in the urine sample raised a high index suspicion of an hyperuricemic condition like TLS, thus measuring serum uric acid levels was the next appropriate step in diagnosis. Acute uric acid nephropathy behaves very much like a post renal insult, as uric acid crystals precipitate in the tubules, which clinically manifests as oligo/anuria and the presence of AKI by rapidly rising creatinine levels (22); it`s different in the sense that its acute presentation does not cause any morphological changes in image studies such as the CT and the echography that were performed in our patient, unlike a true postrenal cause of AKI (22). The overexcretion of uric acid can be documented with a ratio of uric acid/creatinine ratio in a random urine sample when values are ≥ 1 (22). It should also be noted

that concurrent electrolyte abnormalities as the ones observed TLS such as hyperkalemia contribute independently to the progress of AKI.

In summary, our patient`s symptoms of ascites and progressively declining kidney function, could be explained by acute uric acid renal nephropathy in the scenario of a spontaneous tumor lysis syndrome of an abdominal mass with peritoneal carcinomatosis causing ascites.

Diagnostic criteria

The diagnosis of TLS is made clinically or by laboratory, meeting the definitions proposed by Cairo and Bishop in 2004: it is required that two or more laboratory criteria are met three days previous or up to seven days after the initiation of cytotoxic therapy which include hypercalcemia, hyperphosphatemia, hyperuricemia or hypocalcemia; clinically it is diagnosed when increase creatinine levels, seizures, cardiac abnormalities or death is accompanied by one laboratory criteria (9,10). Howard et. al proposed in 2011 that a few refinements could improve the proposition made by Cairo and Bishop which include that two or more laboratory criteria be met at the same time, as one may not be related to the other in a significant time frame, second that a 25% change in baseline should not be considered a criterion because they are seldomly significant within the normal range and third that any symptomatic hypocalcemia be considered a clinical TLS (1). In contrast to TLS, there are no criteria to define sTLS, and the ones established by Cairo and Bishop are used in the setting of TLS without any evident precipitating event such as cytotoxic therapy; the considerations made by Weeks & Kimple about the laboratory abnormalities should be present at the time of diagnosing a sTLS: phosphate levels may not rise as expected in a classic setting of TLS

because they are reused by tumor cells for the generation of new cells, and hence hypocalcemia is a less likely finding (2).

Definitions of Laboratory and Clinical Tumor Lysis Syndrome		
Metabolic Abnormality	**Criteria for Classification of Laboratory Tumor Lysis Syndrome**	**Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperphosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/liter) in adults or >6.5 mg/dl (2.1 mmol/liter) in children	
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute Kidney Injury		Increase in the serum creatinine level of 0.3 mg/dl (26.5 µmol/liter) (or a single value >1.5 times the upper limit of the age appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hours for 6 hours

Table 2. Cairo and Bishop Criteria: Definitions of Laboratory and Clinical Tumor Lysis Syndrome

In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter).

Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome.

- Table reproduced from "The tumor Lysis Syndrome", Howard et.al, NEJM, 2011 (1)

Management

The cornerstone of treatment of TLS is the identification of patients at the highest risk of developing it, so prophylactic measures can be implemented before any cytotoxic therapy is administered (8). Most complications can be managed when they are identified early, so the burden of disease and costs can be reduced (1,8). Though true for patients with known malignancies and current oncological treatments, sTLS behaves differently: there is no identifiable trigger and as in our patient it can be an acute presentation which requires a high index of suspicion and insight. Despite this consideration, it is known that sTLS is more common in malignancies that have scenarios with higher risk factors (12):

Characteristic	Risk Factor
Type of tumor	Burkitt Lymphoma Lymphoblastic Lymphoma Diffuse Large Cell Lymphoma Acute Lymphoblastic Leukemia Solid tumors with high turnover rate
Characteristics of tumor	Tumoral mass > 10 cm Highly sensible tumors to chemotherapy Leucocytes > 25 × 10^3/μL LDH > 2N
Kidney function	Preexisting acute kidney injury or chronic kidney disease Oligo/anuria
Baseline Uric Acid levels	Baseline uric acid >7.50 mg/dl

Table 3. Risk factors for TLS

- Table reproduced from Nature Clinical Practice Oncology 2006

Hydration

The cornerstone of prevention and treatment of TLS is vigorous hydration to increase renal perfusion and consequently glomerular filtration rate which in turns reduces the likelihood of oliguria and reduces the acidity of urine, which promotes uric acid crystal and calcium phosphate precipitation in the renal tubules (1,13). Close monitoring of vital signs and urine output is mandatory in patients with preexisting cardiac or renal conditions, as fluid overload can worsen prognosis; ICU must be considered in this group patients (13). Target hydration is usually achieved by rates of infusion of 2.5-3 L/m^2/day or 200 ml/kg in children weighing $\leq$ 10 kg; likewise, urine output must be strictly measured to achieve diuresis of at least 2 ml/kg/h in both adults and children, and 4-6 ml/kg/h in children weighing $\leq$ 10 kg (13). The choice of fluid is controversial and depends upon the clinical circumstances and the type of cancer, though it seems appropriate for most cases to initiate with isotonic fluids (13). The method of choice to achieve target diuresis is IV hydration, however diuretics or mannitol may be considered to achieve goal urine output levels, even though they are rarely used in patients with normal renal and cardiac functions: loop diuretics like furosemide (0.5-1 mg/kg) are the agent of choice as they achieve the greatest diuresis and excrete the greatest amount of potassium (1,12,13)

Urine alkalinization

Increasing urinary pH with either acetazolamide or sodium bicarbonate was once thought a cornerstone in the treatment of TLS, however it is actually considered controversial, and is highly not recommended: though it increases the solubility of uric acid, it promotes calcium phosphate deposition in the kidney, heart and other organs, especially when hyperphosphatemia develops (1,13). Due to the fact that it is easier to correct hyperuricemia

than hyperphosphatemia, urine alkalinization has been relegated as a therapy measurement. In clinical scenarios where rasburicase is available urine alkalinization is highly discredited (1,13), and in scenarios where allopurinol is available, studies have shown no benefit (1), though if alkalinization is used, it should be initiated when uric acid levels are high, and discontinued when hyperphosphatemia develops (13). In sight of these observations, most experts have concluded that the use of sodium bicarbonate is only indicated in patients with concomitant metabolic acidosis (13).

Hypouricemic agents

Allopurinol: it is an hypoxanthine analog that inhibits xanthine oxidase, blocking the metabolism of the precursors hypoxanthine and xanthine into uric acid formation; it is highly effective in stopping the formation of new uric acid, consequently reducing the incidence of uric acid nephropathy, however its disadvantages are related to the fact that it does not reduce the circulatory uric acid, it increases purine precursors which in turn lead to xanthinuria, which can cause deposition and nephropathy/AKI and it has the potential to interact with many other drugs such as azathioprine, methotrexate and cyclophosphamide (1,13, 14). Additionally, it has been established that uric acid levels may not decrease for up to forty-eight hours after initiating treatment, thus the role in preventing uric acid nephropathy is more controversial as it may still develop after initiating treatment (1). For these reasons, the management of TLS varies upon the risk of developing it (Supplementary Appendix No.1): for patients at low and intermediate risk with pretreatment uric acid levels <8 mg/dL, allopurinol is used as the initial management drug in both adult and pediatric patients (13). Adult dosing is 100 mg/m^2 every eight hours not to exceed 800 mg per day, and in children 10 mg/kg dose not to exceed 300 mg per day. For patients in which oral route is not available, IV allopurinol may be administered at dose of 200-400 mg/m^2 per day divided into one to three doses not to exceed 600 mg per day (1,12).

Allopurinol must be corrected for kidney function to 200 mg/day, 100 mg/day and 100 mg/dose for creatinine clearance of 10-20 mL/min, 3-10 mL/min and <3 mL/minute respectively in the adult population. (13).

Rasburicase: a recombinant enzyme of urate oxidase – an enzyme that it is found in many mammals, but not humans - rasburicase catalyzes the oxidation of uric acid into a more hydrosoluble component – five to ten times the solubility of uric acid – allantoin, which is excreted in urine (2,12,15). It is the drug of choice for the management of adult and pediatric patients with high risk of developing TLS (Supplementary Appendix No.2), uric acid levels > 8 mg/dL, and with patients with impaired renal and cardiac dysfunction (1,13). In contrast with allopurinol, it immediately reduces uric acid levels, it does not have the risk of producing nephropathy related to xanthine accumulation, and it does not interfere with antineoplasic drugs such as methotrexate, although it is contraindicated in patients with G6PD (glucose-6-phosphate dehydrogenase deficiency) as it may cause methemoglobinemia and hemolytic anemia and in pregnancy (1,12). Doses depend upon risk patient stratifications: for intermediate risk patients a single dose of 0.15 mg/kg followed by allopurinol seems a reasonable scheme, and for high risk patients a single dose of 0.2 mg/kg followed by allopurinol (13). Other schemes approved by the FDA, range doses from 0.1-0.2 mg/kg/day depending on the intention to prevent or treat TLS, for up to five-seven days with an average of three days (12,13) and even in cases with a high massive lysis doses may be administered up to two times per day (12). The single dose therapy has been topic of debate, with the intention to evaluate dose responses and in turn minimize costs (12).

Electrolyte management

Guidelines for the management of abnormalities in electrolytes in the scenario of TLS were provided by the 2008 International Expert Panel and are summarized in the tables below (12):

HYPERPHOSPHATEMIA	
MODERATE ≥ 6.5 mg/dL	Restrict phosphate intake (avoid IV and oral phosphate; limit dietary sources) Phosphate binders: 1. Calcium acetate: Adult: 2 to 3 tabs (1334 to 2668 mg) with each meal OR 2. Calcium carbonate: Adult: 1 to 2 grams with each meal; Pediatric: 30 to 40 mg/kg with each meal OR 3. Sevelamer: Adult: 800 to 1600 mg with each meal; Pediatric: 40 to 54 mg/kg with each meal OR 4. Lanthanum carbonate: Adult: 500 to 1000 mg with each meal OR 5. Aluminum hydroxide: Adult: 300 to 600 mg with each meal; Pediatric: 12.5 to 37.5 mg/kg four times daily with meal
SEVERE	Dialysis, Hemofiltration

Table 4. Management of hyperphosphatemia

❖ Table reproduced from *Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26:2767*

HYPOCALCEMIA: calcium ≤ 7 mg/dL or ionized calcium ≤ 3.2 mg/dL	
Asymptomatic	No therapy needed
Symptomatic	Calcium gluconate administered slowly with ECG monitoring; hypocalcemia and hyperphosphatemia should not be treated with calcium until phosphate levels are corrected or unless there is tetany o cardiac arrhythmia 1. Calcium gluconate: Adult: 1 gram (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg. Slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if symptoms or ECG changes persist.

Table 5. Management of hypocalcemia

❖ Table reproduced from *Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26:2767*

HYPERKALEMIA	
Moderate and asymptomatic, ≥6.0 meq/L	Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulfonate (Kayexalate): Adult: 15 to 30 grams orally; Pediatric: 1 gram/kg orally. Onset 1 to 2 hours. Repeat every 4 to 6 hours up to four times daily as needed based on repeat serum potassium levels.
Severe (>7.0 meq/L) and/or symptomatic	Same as above, plus: To stabilize cardiac membranes (ECG changes (widening of the QRS complex or loss of p waves but not peaked t waves alone), give calcium gluconate by slow IV infusion to prevent life-threatening arrhythmias) 1. Calcium gluconate: Adult: 1 gram (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg. Slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if symptoms or ECG changes persist. To temporarily shift potassium into cells 1. IV insulin and dextrose: Adult: regular insulin (10 units) IV plus 100 mL of a 50 percent dextrose solution (D50) IV; Pediatric: regular insulin (0.1 unit/kg) IV, plus 25 percent dextrose solution (D25) 0.5 gram/kg (2 mL/kg of D25) IV over thirty minutes. May be repeated after thirty to sixty minutes. Monitor fingerstick glucose closely. 2. Sodium bicarbonate can be given to induce influx of potassium into cells if patient is acidemic. Sodium bicarbonate and calcium solutions should not be administered through the same line due to incompatibility a. Sodium bicarbonate Adult: 45 to 50 mEq; Pediatric: 1 to 2 mEq/kg. Slow IV infusion over five to ten minutes. 3. Albuterol: Adult: 10 to 20 mg in 4 mL saline nebulized over 20 minutes or 10 to 20 puffs per metered dose inhaler over

	10 to 20 minutes; Pediatric: 0.1 to 0.3 mg/kg per nebulization.
	Dialysis

Table 6. Management of hyperkalemia

- Table reproduced from *Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26:2767*

Discussion of management

Our patient was treated with aggressive intravenous fluid with normal saline boluses, followed by maintenance hydration for three days. An EKG was performed which exhibited no abnormalities related to rising serum potassium levels; impending dialysis was postponed and the patient was not transferred to the ICU. A solution of dextrose with ultra-fast-acting insulin was administered to shift potassium into the intracellular space. Other immediate pharmacological therapies used were calcium-gluconate and allopurinol adjusted for glomerular filtration rate was administered orally until patient discharge. Rasburicase was not considered a treatment option as it is seldom available in our hospital. After complementary laboratory tests demonstrated a decrease in serum albumin to 2.6 g/dL and arterial blood gas demonstrated metabolic acidosis, sodium bicarbonate and human recombinant albumin were added to the treatment scheme. Urine quantification revealed oligo/anuria in spite of adequate volume repletion: a solution of furosemide was prepared and target diuresis was achieved during the first twenty-four hours of therapy. The patient's serum potassium level normalized, the uric acid level slowly started to decrease as did the levels of creatine to baseline levels of 8.50 mg/dL and 0.66 mg/dL respectively.

Our patient would have benefited from the administration of rasburicase, given uric acid levels of 21.9 mg/dL, and the high turnover rate of the suspected malignancy (1 12, 13).

This was not considered a pharmacological approach as our hospital does not have it available. Perhaps administration of rasburicase could have potentially produced better short-term outcomes reducing uric acid levels more rapidly (13), even though the patient was successfully managed with a single oral dose of allopurinol, vigorous hydration and furosemide. The efficacy of a single dose of allopurinol in the scene of sTLS vs. multiple doses has yet to be studied, yet in our experience the outcome was favorable with creatinine levels and uric acid levels normalizing.

Follow up

The patient`s general status started to improve: vital signs remained stable, mental status returned to baseline, there was no respiratory distress, lower limb edema completely resolved, and spontaneous diuresis was achieved. Once stabilized diagnostic laparoscopy was scheduled: approximately two liters of ascitic fluid was drained, with findings of the surgical procedure suggestive of peritoneal carcinomatosis, a tumor mass localized in the pelvic inlet dependent of parietal peritoneum and adhered to large intestine and an omentum with morphology suggestive of neoplasm; liver and other abdominal structures appeared normal; biopsies were taken to complete immunochemistry studies. Other procedures that were performed during the hospitalization included an upper gastrointestinal endoscopy in which a gastric polyp in the gastric body suggestive of malignancy was found: biopsies were taken; a transthoracic echocardiogram revealed no important anomalies. The patient was discharged home in overall good conditions with alopurinol, pending results of the biopsies – both the gastric polyp and the peritoneal/omentum samples – and the respective immunochemistry studies of to initiate chemotherapy in a specialized cancer center.

The patient returned to our hospital to the emergency department four months after he was initially discharged: at arrival the patient was at impending cardiorespiratory failure and he was immediately transferred to the Intensive Care Unit where endotracheal intubation and vasopressors where required. Complementary laboratory showed white blood cells 10.69 × 10^3/μL with absolute neutrophils of 9.739 × 10^3/μL and procalcitonin: 27.72 ng/mL. The patient was immediately transferred to the operating room to perform an exploratory laparotomy due sepsis from possible abdominal source: pertinent physical examination showed bilateral crackles on lung auscultation, and the abdomen was tense, dull to percussion with absent bowel movement sounds. During the procedure there was evidence of a tumor mass of 15 cm of small intestine that was perforated with generalized peritonitis of 2500 mL. The mass was resected, ileostomy was placed, drainages were placed, broad spectrum antibiotics were initiated and tissue samples were sent for histopathological studies. The patient remained in the ICU for half a day where unfortunately he died due to cardiorespiratory failure as a complication of sepsis. The family referred that no chemotherapy had been initiated and they didn't wish for an autopsy to be performed.

Pathology

In total five samples were analyzed by the pathology team in our hospital. The ascitic fluid obtained during diagnostic laparoscopy was negative for malignancy; the peritoneal and omentum samples on microscopy and by immunochemistry studies were conclusive of diffuse large B cell non-Hodgkin Lymphoma. On the other hand, the gastric polyp obtained by upper gastrointestinal endoscopy on microscopy and by immunochemistry studies showed a poorly differentiated neuroendocrine tumor. Lastly the small bowel segment that was resected during exploratory laparotomy was in correlation with the findings of the peritoneal and omentum samples of a diffuse large B cell non-Hodgkin Lymphoma.

Discussion

Spontaneous Tumor Lysis Syndrome as a rare medical entity, requires a high index of suspicion for its diagnosis; even though it may be a more common clinical scenario for hemato-oncologists, it's definitely uncommon for practitioners outside this field (1,2,17). Our patient fulfilled the Cairo Bishop Criteria and the modifications for the diagnosis that were recommended by Howard et. al, nonetheless a retrospective study by Hsu et. al proved that the incidence of sTLS may not be an extraordinary medical occurrence as previous literature implies: in the clinical scenario of uric acid nephropathy, elevated lactate dehydrogenase, and biopsy proven malignancy, sTLS had a prevalence of 1.08% in 926 patients with renal failure, making this entity still very rare, but not extremely uncommon (17). This finding in correlation with the observation made by Weeks & Kimple (2) imply that the current criteria for diagnosis of TLS cannot be adequately extrapolated, and are insufficient for the diagnosis of sTLS, this being the reason that this entity is often underdiagnosed (2,11). They suggest a simpler approach for its diagnosis: in absence of cytotoxic therapy, patients with hyperuricemia $\geq$ 8.0 mg/dL in the presence of suspected malignancy with elevated lactate dehydrogenase >2ULN, acute oliguric/anuric renal failure despite adequate volume resuscitation in the absence of a postobstructive cause and urinary uric acid to creatinine ratio > 1.0 be considered spontaneous TLS until proven otherwise (2). In our case our patient fulfilled all but the last criteria proposed by Weeks & Kimple, as no urinary measurement of either creatinine and uric acid were performed. Perhaps as suggested by these authors, more important than establishing criteria for the diagnosis of sTLS, is understanding the pathophysiology of the disease associated with tumor breakdown, and to initiate treatment even in the absence of a clear diagnosis, due to the high morbidity and mortality associated (1,2,3,13). Our approach was simplified and influenced by the fact that the patient had a previous diagnosis, although not confirmed, of a

non-Hodgkin Lymphoma; this provided the team an insight of the likelihood of sTLS being the cause of acute renal failure. As stated by Weeks & Kimple, our patient did not experience either marked hyperphosphatemia nor hypocalcemia, congruent with the hypothesis that in sTLS these two metabolic abnormalities are less likely to be present (2).

The occurrence of both a NET (neuroendocrine tumor) with another malignancy, has been an issue addressed lately: the association of a NET with another form of cancer, commonly described as a second primary malignancy (SPM) is an increasingly recognized phenomenon (24, 25, 26, 27). In a meta-analysis, Habal et. al reported an incidence of SPM of approximately 17% in 5280 patients with a neuroendocrine tumor; their results showed that gastrointestinal neuroendocrine tumors where twice as likely to be associated with SPM than other malignancies (24). Although pathophysiological mechanisms have not been clearly identified, it has been proposed that a common carcinogenic effect, stimulates both the growth of the SPM and the NET; other theories in which both malignancies appear concomitantly suggest a common genetic defect, however the true nature of this particular phenomenon is still a nature to be studied (24). Most cases of NET and SPM have been reported with neuroendocrine tumors and gastrointestinal or genitourinary secondary malignancies (25, 26); there has been one reported case of a NET and a MALT lymphoma but there have not been associations described with other hematological malignancies, such as leukemias or non-Hodgkin lymphomas (24). The case illustrated in this paper could represent one of the first formal associations between a NET and a non-Hodgkin large B cell lymphoma as a SPM; although it would certainly be ideal to evaluate patient follow up, and the clinical course in regards to the natural evolution of the malignancies and their treatment and thus patient prognosis. In this particular scenario this wouldn`t be possible because our patient died, and no further comments can be established.

An important question yet to be completely answered, is the true histological and immunochemical phenotype of the tumor which spontaneously lysed. There have been case reports in medical literature of sTLS in cancers with high turnover rates such as large B cell non-Hodgkin Lymphomas (1,2,3,12), however if indeed the tumor that lysed was a neuroendocrine tumor, to the best of our knowledge, it would be one of the first reported cases in literature. Given some of the characteristics of non-Hodgkin Lymphomas like the high turnover rates, its rapid growing behavior, and the high-risk stratification of suffering TLS (17), it seems very unlikely that a gastric polyp with results of histological and immunochemical studies conclusive of a neuroendocrine tumor, where indeed the cause of this patient's sTLS, when three other histopathological samples where indicative of a large-B non-Hodgkin Lymphoma. Despite the extraordinary likelihood of the neuroendocrine tumor being the primary neoplasm that lysed, the samples that were obtained during the course of the hospital stay should be analyzed in the future for immunochemical markers such as chromogranin and synaptophysin for the implications that they could potentially have in the medical community (23).

Given the nature that NETs are secretory tumors, and that more than forty secretory products have been identified such as serotonin, histamine, prostaglandins etc. (28), we have hypothesized the possibility that a secretory product of the NET could have been the trigger of the TLS. Prommeger et. al have reported that bombesin which is a neuropeptide that can be secreted by NETs, stimulates in vitro growth of human breast cancer cells and additionally has a potential autocrine growth factor in small lung cell cancers; likewise, other growth factors can be secreted by NETs such as fibroblast growth factor (FGF) and transforming growth factor (TGF) (24). Although no formal association can be established in our particular case as no

secretory substance was identified from the NET in our patient, and no relationship can be established in regards to the pelvic tumor mass, we can certainly speculate with the possibility that a given secretory product could have potentially acted as the triggering event, in which case, this would no longer be considered a spontaneous presentation of a tumor lysis syndrome.

Conflict of interest

The authors report no conflict of interest with any of the parts involved in this publication.

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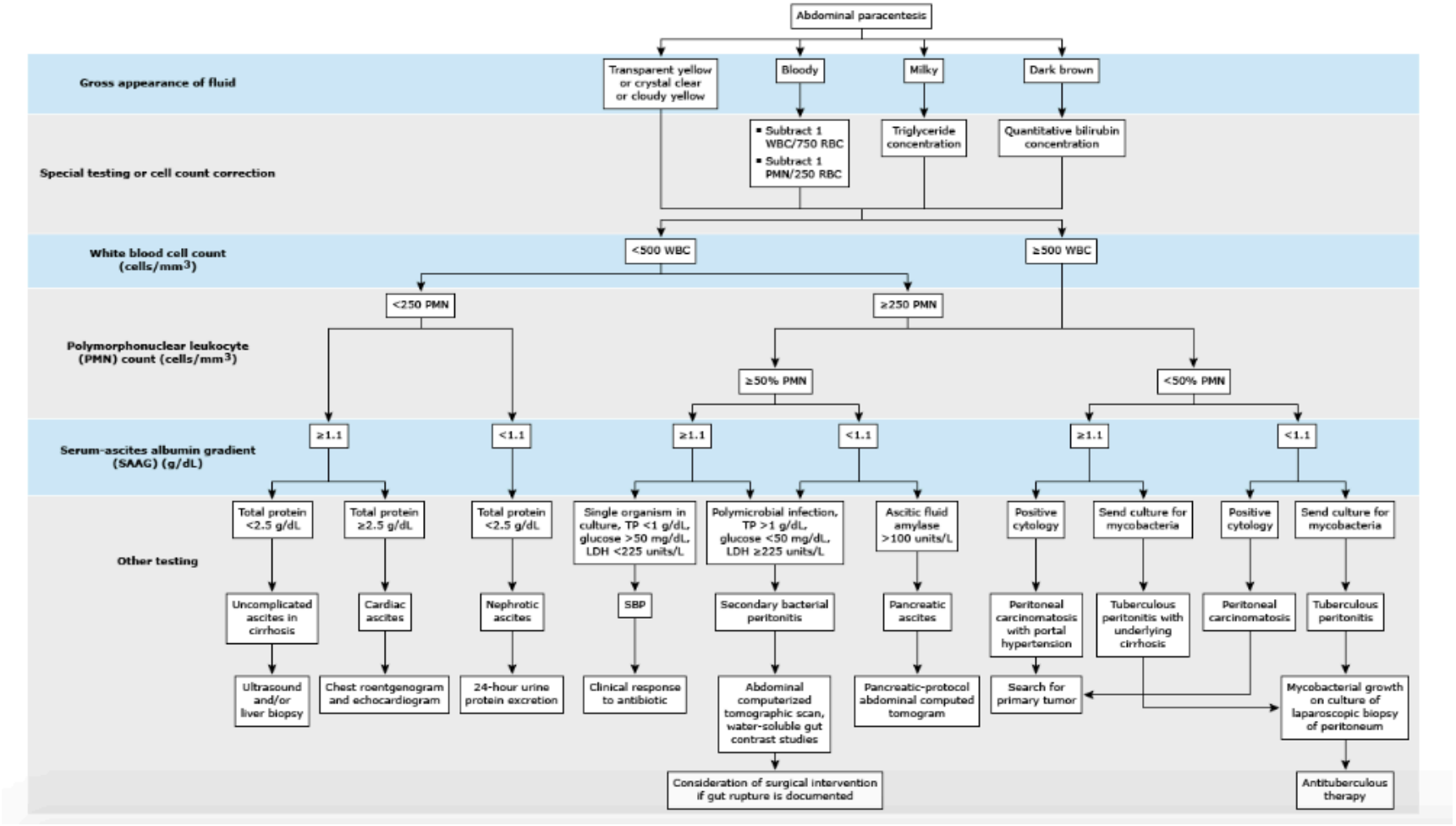
APENDIX A: ASCITES DIAGNOSTIC ALGORITHM



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APENDIX B: TLS PROPHYLAXIS BASED ON TLS RISK

Tumor lysis syndrome (TLS) prophylaxis recommendations based on TLS risk

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
Most solid tumors	Rare, highly chemotherapy-sensitive solid tumors (eg, neuroblastoma, germ cell tumor, small-cell lung cancer) with bulky or advanced stage disease	N/A
MM	Plasma cell leukemia	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL and WBC <50 x 10^9/L treated only with alkylating agents	CLL treated with fludarabine, rituximab, or lenalidomide, or venetoclax and lymph node ≥5 cm **or** absolute lymphocyte count ≥25 x 10^9/L, and/or those with high WBC ≥50 x 10^9/L	CLL treated with venetoclax and lymph node ≥10 cm, **or** lymph node ≥5 cm **and** absolute lymphocyte count ≥25 x 10^9/L and elevated baseline uric acid.
AML and WBC <25 x 10^9/L and LDH <2 x ULN	AML with WBC 25 to 100 x 10^9/L	AML and WBC ≥100 x 10^9/L
	AML and WBC <25 x 10^9/L and LDH ≥2 x ULN	
Adult intermediate grade NHL and LDH within normal limits	Adult T cell leukemia/lymphoma, diffuse large B-cell, transformed, and mantle cell lymphomas with LDH > ULN, non-bulky	Adult T cell leukemia/lymphoma, diffuse large B-cell, transformed, and mantle cell lymphomas with bulky disease and LDH ≥2 x ULN
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH <2 x ULN	Stage III/IV childhood diffuse large B-cell lymphoma with LDH ≥2 x ULN
N/A	ALL and WBC <100 x 10^9/L and LDH <2 x ULN	Burkitt's leukemia
		Other ALL and WBC ≥100 x 10^9/L and/or LDH ≥2 x ULN
N/A	Burkitt lymphoma and LDH <2 x ULN	Burkitt lymphoma stage III/IV and/or LDH ≥2 x ULN
N/A	Lymphoblastic lymphoma stage I/II and LDH <2 x ULN	Lymphoblastic lymphoma stage III/IV and/or LDH ≥2 x ULN
N/A	N/A	Intermediate risk disease with renal dysfunction and/or renal involvement
		Intermediate risk disease with uric acid, potassium, and/or phosphate > ULN
Prophylaxis recommendations		
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
±Allopurinol	Allopurinol	Rasburicase*

N/A: not applicable; MM: multiple myeloma; CML: chronic myeloid leukemia; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; CLL: chronic lymphoid leukemia; WBC: white blood cell count; AML: acute myeloid leukemia; LDH: lactate dehydrogenase; ULN: upper limit of normal; ALCL: anaplastic large cell lymphoma; ALL: acute lymphoblastic leukemia.

* Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

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