Síndrome de Lise Tumoral em Carcinoma Hepatocelular Multifocal sob Sorafenib e Infeção SARS-CoV-2

Tumor Lysis Syndrome in Multifocal Hepatocellular Carcinoma under Sorafenib and SARS-CoV-2 Infection

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Resumo:

A síndrome de lise tumoral é a uma emergência médica potencialmente fatal decorrente da lise celular maciça que ocorre em neoplasias malignas com grande carga tumoral. Ocorre sobretudo em neoplasias hematológicas sob quimioterapia, sendo menos frequente em tumores sólidos, os quais apresentam geralmente um menor índice proliferativo. A síndrome de lise tumoral no carcinoma hepatocelular tratado com sorafenib, um inibidor oral multicinase, é extremamente rara, descrevendo-se apenas nove casos na literatura. Tanto quanto sabemos, não existem casos descritos na população europeia. Apresentamos um caso de síndrome de lise tumoral num doente com carcinoma hepatocelular multifocal sob tratamento com sorafenib e infeção SARS-CoV-2.

Palavras-chave: Carcinoma Hepatocelular; COVID-19; Rasburicase; SARS-CoV-2; Síndrome de Lise Tumoral; Sorafenib;

Abstract:

Tumor lysis syndrome is a potentially fatal medical emergency resulting from massive tumor cell lysis that occurs in high tumor burden malignant neoplasms. It occurs mainly in hematological neoplasms undergoing chemotherapy, being less frequent in solid tumors, which generally have a lower proliferative index. Tumor lysis syndrome in hepatocellular carcinoma treated with sorafenib, an oral multi-kinase inhibitor, is extremely rare, with only nine cases reported in the literature. As far as we know, there are no cases described in the European population. We present a case of tumor lysis syndrome in a patient with multifocal hepatocellular carcinoma under treatment with sorafenib and SARS-CoV-2 infection.

Keywords: *Carcinoma, Hepatocellular; COVID-19; Rasburicase; SARS-CoV-2; Sorafenib; Tumor Lysis Syndrome.*

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Introduction

Tumor lysis syndrome (TLS) is characterized by the rapid onset of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia resulting from the massive lysis of tumor cells, generally occurring after cytotoxic treatment, although several cases of spontaneous lysis have been described. Acute kidney injury is often associated and results mostly from the deposition of uric acid and calcium phosphate crystals in renal tubules. Cairo and Bishop described clinical and laboratory criteria for the diagnosis and classification of TLS, providing useful tools for its early recognition and approach. In the appropriate context, diagnosis is based on the presence of two or more laboratory abnormalities (hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia) associated with at least one of the clinical criteria (elevated creatinine level, cardiac dysrhythmia, seizure or death).[1] The withdrawal of the pharmacological insult and the rapid correction of laboratory alterations associated with TLS are associated with a better prognosis, preventing a probable fatal outcome. Sorafenib was the first therapeutic option with proven benefit approved in advanced stage hepatocellular carcinoma (HCC), with rare serious side effects reported.[2] Nevertheless, clinical suspicion for TLS should be increased in the case of high tumor burden solid neoplasms, where it occurs less frequently and with a delayed presentation.[3,4]

Case Report

We report the case of a 55-year-old male with ethanolic and chronic hepatitis C-associated cirrhosis (Child-Pugh B - 8) with multifocal HCC (BCLC C) under treatment for three months with sorafenib 400 mg/day, a reduced dose considering dermatological toxicity. Pre-treatment arteriography evaluation revealed extensive tumor infiltration not amenable to chemoembolization, and no locoregional therapy was performed. The patient was admitted with complaints of asthenia, prostration, bitemporal headache and dry cough with worsening in the previous week. In the preceding follow-up visit, 17 days before, the patient was clinically stable and the abdominal computed tomography (CT) scan showed diffuse hepatic infiltration by the neoplasm, with no evolution in relation to previous exams and without peritoneal carcinomatosis (Fig. 1). SARS-CoV-2 RT-PCR screening for hospital admission confirmed a positive rapid antigen test performed 3 days before.

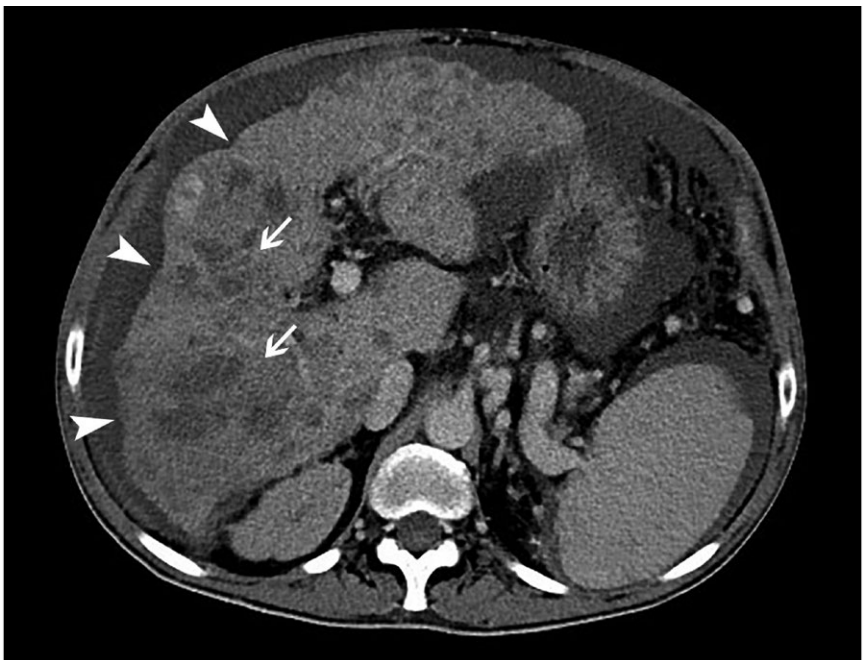

Figure 1: Contrast abdomen computed tomography scan one month before tumor lysis syndrome; axial view. Wavy nodular liver margins (arrowheads) and poorly defined extensively infiltrative masses (thin arrows).

On admission, he was slightly confused, with no signs of meningeal irritation and no flapping. Vital signs within the normal range and no need for supplemental oxygen therapy. He was hydrated, without jugular venous distention and without peripheral edema. The abdomen was slightly distended with signs of ascites, but soft and painless.

Laboratory tests performed on admission highlighted bicytopenia (Hb 11.4 g/dL, VGM 99 fL, platelets 101 x10^9/L), d-dimers 3622 µg/L, alkaline phosphatase 515 U/L, gamma-glutamyl transferase 129 U/L, aspartate aminotransferase 168 U/L, alanine aminotransferase 144 U/L, LDH 282 U/L, total bilirubin 2.82 mg/dL, alpha-fetoprotein 1666 ng/mL, serum creatinine 1.94 mg/dL, hyperuricemia 11.6 mg/dL, hyperphosphatemia 4.9 mg/dL, ionized calcium 1.23 mmol/L and hyperkalemia 8.18 mmol/L, refractory to initial correction measures with insulin, fluid and diuretic therapy, cation-exchange resin and inhaled beta-2 adrenergic agonist. Arterial blood gas presented compensated metabolic acidosis (pH 7.38, pCO2 29.2, pO2 83.5, HCO3 17.2, lactate 2). Chest radiography revealed bilateral perihilar reticular infiltrate. ECG in sinus rhythm, heart rate 80 bpm with peaked T waves in V2-3 leads (Fig. 2). Paracentesis was performed, excluding spontaneous bacterial peritonitis.

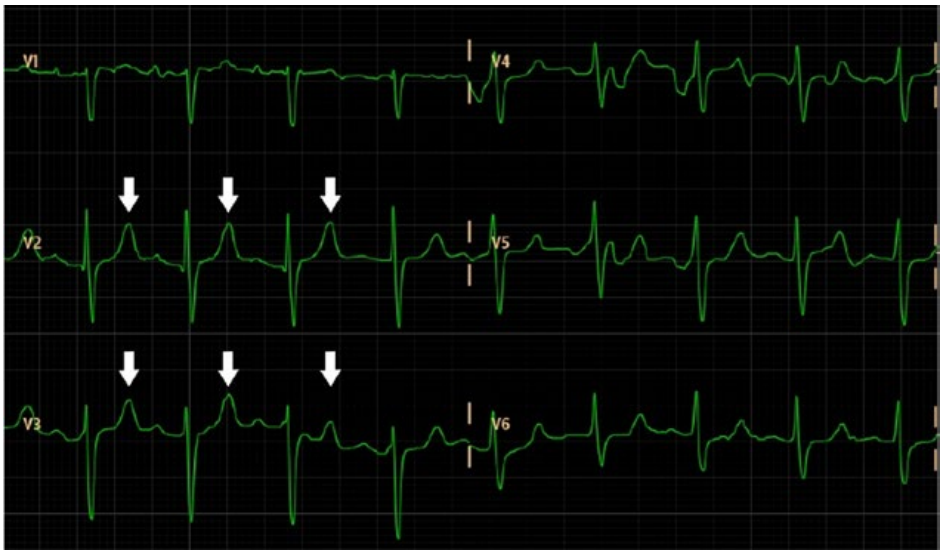

Figure 2: Patient's electrocardiogram at hospital admission. Normocardic and sinus rhythm tracing showing spiked T waves (white arrows) in association with hyperkalemia.

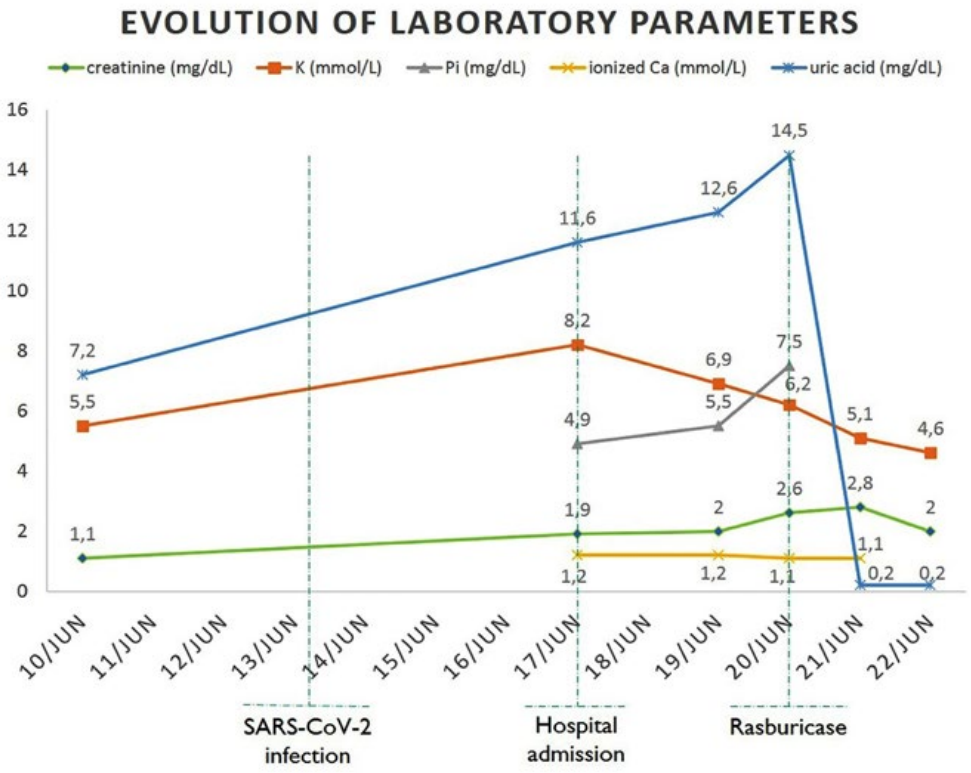

Figure 3: Line graph showing kinetic evolution of laboratory parameters used in the Cairo-Bishop classification considering our case (x-axis show dates since the last follow-up appointment). Dotted lines indicate date of diagnosis of SARS-CoV-2 infection, hospital admission and rasburicase administration.

During a period of monitoring, and despite clinical stability, changes in the patient's analysis persistently worsened (Fig. 3). Assuming a high probability of TLS, sorafenib was suspended and rasburicase 14 mg (single dose, 0.2 mg/kg) was administered with subsequent correction of ionic disturbances and improvement of renal function in less than forty-eight hours with no need for renal replacement therapy. Considering the SARS-CoV-2 infection, the patient remained asymptomatic, without the need for supplemental oxygen therapy and without imaging evidence of pneumonia. He was discharged on the sixth day of hospitalization, clinically improving.

Discussion

TLS is a medical emergency with high morbidity and mortality and its diagnosis requires high clinical suspicion, especially in the context of solid neoplasms. In this rare case of TLS in a patient with multifocal HCC on well-tolerated sorafenib therapy, SARS-CoV-2 infection is presumed to be the trigger. The limitations imposed in the observation of patients with SARS-CoV-2 infection and the pathophysiological changes associated with COVID-19 were, in this case, a complicating and confounding factor in the patient's clinical presentation and evaluation.

The demographic and clinical aspects of our patient were similar to those of the other cases described in the literature where all were male, with a median age of 55 years and the majority (77.8%) in BCLC staging C.[5-13] Our case corresponds to a grade II TLS according to Cairo-Bishop classification, despite by definition not falling within the period between 3 days before and 7 days after the start of treatment.[1] A delayed onset of TLS following sorafenib therapy (median 8 days) compared to other treatment options like transcatheter arterial chemoembolization has been reported, which was observed in our case.[13] We found an unusually late presentation in our patient on well-tolerated sorafenib therapy for approximately 3 months. This fact led to the etiological investigation of a possible trigger, which was only positive for SARS-CoV-2 infection. We also consider that the late presentation in our patient could be due to a delay in resorting to health care, in part attributable to the pandemic context.

Molecular targeted therapies like sorafenib are increasingly used in advanced cancer stages. It was the first approved molecular targeted agent for advanced unresectable hepatocellular carcinoma providing proven survival benefits compared to placebo. Sorafenib acts inhibiting Raf kinase and vascular endothelial growth factor receptor (VEGFR), blocking angiogenesis and tumor cell proliferation. Although mild adverse events were frequently reported in 80% of patients (dermatologic, weight loss and diarrhea), few reports of TLS following sorafenib treatment have been notified.[2]

Whether or not SARS-CoV-2 infection was a trigger for TLS in our patient remains in doubt, as similar cases were not yet reported. Notably, several anticancer drugs that interrupt growth factor receptor signaling, such as sorafenib, have been studied as also inhibiting SARS-CoV-2 replication in vitro, only with experimental results to date. Promising data comes from the fact that clinically achievable doses of these drugs appear to prevent viral RNA replication by modulating virus host cell signaling pathways, but also interfering with the enzymatic machinery necessary for viral proliferation. In addition, sorafenib appears to effectively inhibit the unregulated production of pro-inflammatory cytokines such as IFN-I by controlling the STING pathway, acting as an immunomodulator.[14]

The administration of rasburicase, a urate oxidase used in the prophylaxis and treatment of acute hyperuricemia, has been shown to be highly effective in reducing serum uric acid levels and preventing worsening of renal function. It is also indicated for the prophylaxis of TLS (four hours before and up to five days after treatment) and should not be used in case of glucose-6-phosphate dehydrogenase deficiency.[4,15] In the several cases of sorafenib-induced TLS, different uric acid lowering strategies were used (rasburicase n = 3; allopurinol n = 2; febuxostat n = 1) with no significant difference being found between them13. Despite our initial watch-and--wait approach, progression of TLS was assumed with an optimal response subsequent to rasburicase administration.

Conclusion

We conclude that treatment with sorafenib should be monitored regularly considering that the diagnosis of severe associated conditions such as TLS depends on a recent laboratory evaluation. Late presentations such as the one we described are unusual, require increased level of suspicion and should therefore be reported, especially if in association with possible new atypical precipitating factors such as SARS-CoV-2 infection. ■

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MAF, MF, JP, ZN – Redação e revisão do artigo

Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

MAF, MF, JP, ZN – Drafting and revising the article

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