First case report of tumor lysis syndrome after third line systemic therapy with gemcitabine and pazopanib in a patient with lower extremity soft tissue sarcoma

Edith Norela Benitez-Escobar[1,2,3]^, Duvan Arley Galindes-Casanova[1,2,3]^, Luis Álvaro Melo-Burbano[1,2,3]^, Diana Marcela Bonilla-Bonilla[1,2,3]^, Luis Miguel Osorio-Toro[1,2,3]^, Jorge Enrique Daza-Arana[1]^, Santiago Leandro Escobar-Dávila[2,4]^, Giovanna Patricia Rivas-Tafurt[1,2,4]^

[1]Specialization Program in Internal Medicine, School of Health, Universidad Santiago de Cali, Santiago de Cali, Colombia; [2]Research and Education Department, Clínica de Occidente S.A., Santiago de Cali, Colombia; [3]Genetics Physiology and Metabolism Research Group (GEFIME), Universidad Santiago de Cali, Santiago de Cali, Colombia; [4]Comprehensive Cancer Center, Clínica de Occidente S.A., Santiago de Cali, Colombia

Contributions: (I) Conception and design: DA Galindes-Casanova, EN Benitez-Escobar, GP Rivas-Tafurt, JE Daza-Arana; (II) Administrative support: None; (III) Provision of study materials or patients: DA Galindes-Casanova, EN Benitez-Escobar, GP Rivas-Tafurt, JE Daza-Arana; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Duvan Arley Galindes-Casanova, Physician, senior resident in the internal medicine program. Specialization Program in Internal Medicine, School of Health, Universidad Santiago de Cali, Santiago de Cali, Colombia; Research and Education Department, Clínica de Occidente S.A., Santiago de Cali, Colombia; Genetics Physiology and Metabolism Research Group (GEFIME), Universidad Santiago de Cali, Avenida 8va Norte, # 18-30, Santiago de Cali, Colombia. Email: duvan.galindes00@usc.edu.co.

Background: Tumor lysis syndrome (TLS) is recognized as an oncologic disorder with a variable incidence. TLS can cause the rapid destruction of tumor cells in response to oncologic therapy and is characterized by multiple electrolyte disturbances as well as its secondary complications, including death. This disease is common among patients with hematologic neoplasms, but very rare among those with solid tumors, as is the case with sarcomas. Such patients have a poor prognosis and increased risk of mortality. In the patient's particular case, this occurred after initiating third-line systemic therapy with gemcitabine associated with pazopanib, an event not previously described in the literature.

Case Description: We report the case of a patient with a history of high-grade sarcoma of the left lower limb T4N1M0 stage IIIB undergoing surgical management and exhibiting tumor progression with the need for third-line systemic therapy with pazopanib and gemcitabine. The patient presented with pain at the amputation site, inflammatory changes, and a tumor mass of large components on admission. They later developed electrolyte imbalance and acute renal injury compatible with TLS after systemic therapy was initiated. Pharmacological therapy, including rasburicase, was initiated based on the clinical and laboratory findings. Due to the progression of renal involvement, it was necessary to initiate haemodialysis, and during her hospital stay, the patient presented febrile syndrome associated with pancytopenia. The patient showed a favourable clinical response to the proposed antibiotic therapy and recovery of renal function, for which reason therapy was restarted with pazopanib and gemcitabine, the latter with a 20% reduction for the following cycles. Outpatient follow-up continued, completing eight cycles of treatment with good tolerance and partial clinical response; the patient died of respiratory complications eight months after discharge.

Conclusions: There is limited evidence for TLS in patients with high-grade sarcoma in the literature

^ ORCID: Edith Norela Benitez-Escobar, 0000-0002-0399-9476; Duvan Arley Galindes-Casanova, 0000-0003-0460-2466; Luis Álvaro Melo-Burbano, 0000-0002-3342-8519; Diana Marcela Bonilla-Bonilla, 0000-0001-6950-6817; Luis Miguel Osorio-Toro, 0000-0002-1971-6354; Jorge Enrique Daza-Arana, 0000-0002-4936-1507; Santiago Leandro Escobar-Dávila, 0000-0003-1057-0683; Giovanna Patricia Rivas-Tafurt, 0000-0002-9709-6656

related to the oncologic therapy used; this indicates that early risk evaluation along with prompt initiation of effective therapies is required to prevent the appearance of this type of complications in the short and long term.

Keywords: Tumor lysis syndrome (TLS); sarcoma; gemcitabine; pazopanib; case report

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Introduction

Tumor lysis syndrome (TLS) is an oncologic emergency with a variable incidence depending on the type of neoplasm, therapy, and the patient's risk factors. Nevertheless, given the risk of life-threatening multisystemic complications, it requires early recognition and multidisciplinary management (1).

TLS symptoms can occur during oncological therapy, generally 7 days after initiation. However, it can also present up to 3 days prior to initiation (2), especially in hematologic neoplasms due to high cellular proliferation. The occurrence of TLS in patients with solid tumors (ST) is very rare, but such patients have a poor prognosis and higher mortality risk (3), especially when associated with rare tumors, such as sarcomas, or when it occurs spontaneously (4).

Highlight box

Key findings

- Tumor lysis syndrome (TLS) is an oncologic emergency with high rate mortality, usually develops after the initiation of chemotherapy treatment.
- Early recognition of the renal and metabolic alterations related with TLS and quick initiation of treatment can save a patient's life.

What is known and what is new?

- TLS is most common in patients diagnosed with leukemia and high-grade lymphomas.
- There are few case reports in the literature in solid tumors.
- This is the first report of TLS after third line systemic therapy with gemcitabine and pazopanib in a patient with lower extremity soft tissue sarcoma.

What is the implication, and what should change now?

- Although TLS occurs rarely in patients with sarcomas, if the disease is bulky or highly sensitive to systemic treatment, the patient should be monitored closely and treated with rehydration and allopurinol to prevent its development.

TLS occurs after the rapid destruction of tumor cells with the systemic release of their multiple intracellular products that alters normal homeostasis (5). The main laboratory findings of TLS are hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, which considerably increase the risk of renal injury and cardiac arrhythmias, along with neurological complications and finally death (6).

At present, reports on TLS associated with sarcomas are extremely rare. This limited literature suggests that the risk of presenting this event could be associated with advanced stages, the presence of metastasis, as well as previous renal involvement (7).

The most recent scientific evidence has reported this complication in cases of metastatic undifferentiated pleomorphic sarcoma of the buttock (8), gallbladder carcinoma (9), primary retroperitoneal soft tissue sarcoma (10), and childhood rhabdomyosarcoma metastatic to bone (11).

We report the case in of a patient with a history of high-grade sarcoma of the left lower limb who presented with TLS after third-line systemic therapy with gemcitabine and pazopanib was initiated according to the PAPAGEMO protocol (12). This report adheres to the CARE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-111/rc).

Case presentation

The patient was a 64-year-old woman of mixed ethnicity with a history of arterial hypertension under pharmacological management with losartan/amlodipine and high-grade sarcoma, with mixed hemangiopericytoid and cellular histological patterns of epithelial and fusiform of left lower limb T4N1M0 stage IIIB diagnosed in 2020, who was admitted to our institution on 06 February 2022. She had been surgically treated at another institution with supracondylar amputation with early relapse requiring

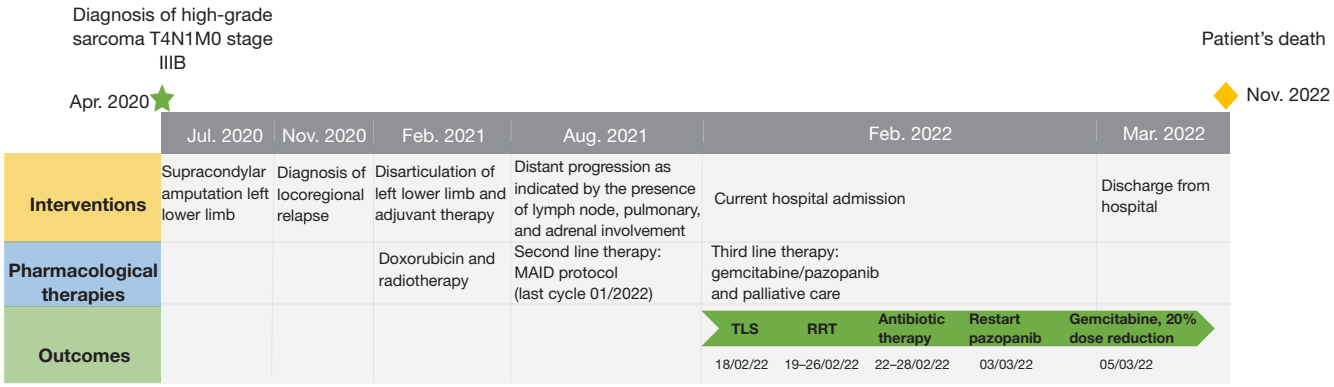

Figure 1 Timeline interventions and relevant clinical events. MAID, mesna, doxorubicin, ifosfamide, and dacarbazine; TLS, tumor lysis syndrome; RRT, renal replacement therapy.

disarticulation of the limb and adjuvant doxorubicin administered every 21 days and radiotherapy. At the end of 2021, there was evidence of distant progression as indicated by the presence of lymph node, pulmonary, and adrenal involvement diagnosed using positron emission tomography/computed tomography. Second-line oncological therapy was initiated with MAID protocol (mesna, doxorubicin, dacarbazine on days 1–4 and ifosfamide on days 1–3, every 21 days). The second cycle of therapy was administered 1 month before admission.

The patient was admitted to our department for exacerbation of moderate intensity chronic pain on the visual analog pain scale at the amputation site during the previous week. This exacerbation was accompanied by hyporexia and constipation, but no fever. The evolution of the interventions received and relevant clinical events are summarised in *Figure 1*.

Physical examination revealed hemodynamic stability and evidence of a mass of approximately 20 cm in diameter at the level of the left inguinal region and extending to the hypogastrium and amputation site, along with erythema, pain, and areas of necrosis with an Eastern Cooperative Oncology Group status of 2 and a Karnofsky index of 60 points.

Taking into account these findings, the possibility of soft tissue infection was considered, and blood and urine cultures were performed. Magnetic resonance imaging (MRI) of the pelvis revealed a macrolobulated expansive process affecting the left hemipelvis, showing two dominant and confluent lobulated masses, one of them associated with the hip stump, measuring 12 cm × 10 cm and another in the left iliac fossa measuring 12 mm × 11 mm, which showed cystic changes due to necrosis on its lateral surface (*Figure 2*). Prominent adenopathies in the internal iliac chain and toward the distal para-aortic region were also noted, with moderate ascitic fluid. Laboratory tests upon admission indicated leukocytosis of 13,920 per mm^3, with a predominance of neutrophils, and lymphopenia at 630 per mm^3. Anemia at normal volumes was noted, requiring a transfusion of red blood cells, and reactive thrombocytosis was present as well. Renal function and electrolytes showed no alterations. Due to these findings, empirical antibiotic therapy was started with piperacillin tazobactam and vancomycin.

We monitored the progress of the patient, the pelvic progression of the disease was confirmed on the basis of the results of the MRI scans performed, and the possibility of local surgical control was ruled out. We decided on 07 February of 2022 to start third-line systemic therapy with gemcitabine and pazopanib as palliative care. Pazopanib was indicated orally, once daily, 800 mg, beginning on day 1 of cycle 1, and gemcitabine was indicated intravenously, 1,600 mg (1,000 mg/m^2), over 30 minutes on day 1 and 8 of each 21-day cycle.

As part of the protocol, a transthoracic echocardiogram was performed, which revealed a left ventricular ejection fraction of 60% and no valvular heart disease or contractility disorders. A simple cranial tomography showed incipient signs of hypertensive microangiopathy.

In the 48 hours after the initiation of chemotherapy with gemcitabine (12/02/2022), impaired renal function was evident, associated with episodes of dyspnea and oxygen desaturation. Chest X-ray indicated right pleural effusion; therefore, thoracentesis was performed. Polymerase chain

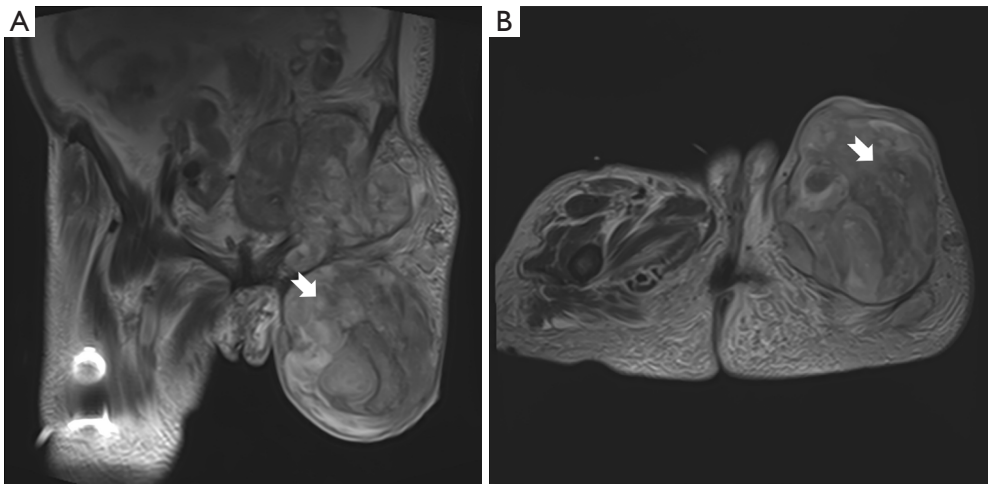

Figure 2 Coronal and axial view of the pelvis, with a mass of heterogeneous signal intensity riding over the pelvis, without signs of bone infiltration. (A) Coronal section at pelvis level including upper and lower segments with evidence of mass, with heterogeneous signal intensity (white arrow). (B) Axial section at the level of the pelvis, showing the upper third of the mass, with heterogeneous signal intensity riding on the pelvis with no signs of bone infiltration (white arrow).

reaction for SARS-CoV2 was negative, hydration was adjusted and, in view of the improvement of the respiratory pattern, pazopanib was started (15/02/2022). The follow-up laboratory tests results are presented in *Table 1*.

On day 7 of gemcitabine initiation and day 3 of pazopanib initiation, marked elevation of urea nitrogen and creatinine was evident, along with the presence of hyperuricemia, hyperphosphatemia, and hypocalcemia of no less than 7 mg/dL. A diagnosis of TLS associated with chemotherapy and secondary acute renal injury was considered, hydration was optimized, and rasburicase was initiated. In the following 48 hours (19/02/2022), there was a need for intermittent hemodialysis, which was suspended after the fifth cycle because of improvement in renal function.

The patient developed fever and pancytopenia; therefore, meropenem and caspofungin was prescribed for the persistent fever, as well as a single dose of pegfilgrastim. Given the stability of the cell lines, the negative cultures and the recovery of renal function, with the antibiotic scheme completed, we decided to restart the proposed therapy with pazopanib (03/03/2022) and gemcitabine (05/03/2022), the latter at a reduced dose of 20% (1,280 mg) for its subsequent cycles, in order to avoid recurrence of the event.

Chemotherapy was restarted with adequate tolerance, no new clinical or laboratory findings during the course of their evolution, reason for which the patient was discharged to outpatient follow-up, completing eight treatment cycles with good tolerance, paraclinical within the normal range and achieved partial clinical response, however, the patient died of respiratory complications eight months after discharge.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

TLS occurs because of the rapid destruction of cancer cells in response to oncologic therapy initiation. However, there is also the possibility of it occurring spontaneously, which worsens the prognosis and increases mortality rate to >60% (13).

The diagnostic criteria of Cairo and Bishop (14) and the additional concepts given by Howard *et al.* currently allow this syndrome to be identified from both the laboratory and clinical points of view (6).

TLS is diagnosed at the laboratory as the presence of two or more electrolyte disturbances occurring simultaneously 3 days prior to initiation of therapy and up to 7 days after initiation of therapy. These include uric acid >8 mg/dL,

Table 1 Paraclinical follow-up of events

Laboratory	Normal range	Admission	First cycle gemcitabine					Start of dialysis	Pancytopenia	Discharge
			Day 1	Day 3	Day 4 (initiation of pazopanib)	Day 6	Day 7	Day 9	Day 12	Day 26
BUN (mg/dL)	9.0–23	13.5	11.5	35	36.9	52.9	58.6	78	71	24
Cr (mg/dL)	0.5–08	0.42	0.84	2.31	2.65	3.17	3.3	3.44	2.17	0.77
P (mg/dL)	2.4–5.7	3.4	–	–	–	–	6.3	7	–	1,3
UA (mg/dL)	2.4–5.7	–	–	–	–	–	10.4	11.4	–	4
K (mEq/L)	3.5–5.1	4.76	4.14	–	4.22	4.65	4.38	4.78	4.8	3.65
Ca C (mg/dL)	8.6–10	8.7	–	–	–	–	7.68	7.48	–	8.2
Na (mEq/L)	136–145	134	137	136	136	138	137	139	140	147
Cl (mEq/L)	98–107	99	–	104	105	–	101	–	–	114
LDH (U/L)	120–246	–	–	–	359	359	358	–	–	391
Leukocytes (mm^3)	4.5–11	13,920	10,560	10,250	13,590	10,000	–	8,610	520	59,180
Lymphocytes (mm^3)	1–3.9	630	460	140	163	170	–	140	90	1,500
Neutrophils (mm^3)	2–7.5	11,750	8,600	9,870	13,200	9,600	–	8,200	400	54,560
Hb (g/dL)	12.3–15.3	7.1	7.7	7.8	6.7	7.9	–	7.1	4.7	8.8
Hto (%)	36–45	23.4	26.4	27.6	22	25.3	–	24	12	30.9
Platelets (per µL)	150,000–450,000	946,000	749,000	892,000	717,000	606,000	–	249,000	48,000	151,000
CRP (mg/dL)	–	177	140	132	203	–	–	–	297	144
Albumin (g/dL)	0.5–2.2	3.65	–	–	–	–	–	–	–	–

BUN, Blood urea nitrogen; Cr, creatinine; P, phosphorus; UA, uric acid; K, potassium; Ca C, calcium corrected for albumin; Na, sodium; Cl, chlorine; LDH, lactate dehydrogenase; Hb, hemoglobin; Hto, hematocrit; CRP, c–reactive protein.

potassium >6 mEq/L, phosphate >4.5 mg/dL, as well as corrected calcium <7 mg/dL (ionized calcium <4.5 mg/dL or 1.12 mmol/L) (6), however, it is important to note that unlike the initial Cairo and Bishop's criteria, a 25% change in laboratory parameters may not be significant, unless they are already outside the normal range. Clinical TLS is defined by laboratory findings plus organ involvement (renal injury, cardiac arrhythmias, and seizures) or death, with renal involvement being the most common, the presence of symptomatic hypocalcemia should also be considered within these criteria (6,15).

Sarcomas represent about 1% of adult malignant neoplasms (16); TLS in a patient with ST, as reported in the present case, is an extremely rare event and have limited descriptions in the literature. Only 11 cases have been reported in patients with sarcoma until 2021; these are included in the review by Tsuchie *et al.* (8). Our case presents differential variables to previously reported cases, among the characteristics that stand out is the location in the lower limb that initially led to a supracondylar amputation and finally to a disarticulation of the limb, which implies a greater extension of the lesion, as well as progression with adrenal involvement, an aspect not evidenced in previous reports; in addition, the association with the prescription of Gemcitabine and Pazopanib. Similarly, the current case presented pulmonary and lymph node involvement, she is an adult patient like most previous cases, and his histological pattern is epithelial and fusiform.

It should be considered that the mortality rate of this syndrome in this type of tumor is substancial compared with that of those that are much more frequent (35% *vs.* 1.9% respectively) (17). In this case report, early identification

and initiation of therapy with rasburicase and hemodialysis allowed for metabolic correction and the continuation of chemotherapy and subsequent discharge without the need for renal replacement therapy. Other significant factors involved in ST are the presence of metastasis, including hepatic involvement, as well as altered renal function, elevated lactate dehydrogenase (LDH) levels and previous electrolyte disorders (7). We must consider that most of these risk factors previously described in the literature were present in our patient's case, notably the presence of extensive metastatic disease in the context of a sarcoma in progression with high cell proliferation refractory to anthracycline drug therapy, as well as a recent infectious process.

Chemotherapy with gemcitabine is a widely used therapeutic option in ST, and the description of TLS reported in the literature is rare; taking into account the occurrence of the event, in our case a reduction of 20% was considered for the second cycle of therapy in order to prevent a recurrence of the event, although the probability of its occurrence cannot be ruled out even if reduced doses of up to 50% are used as described in the literature (9,18). The same is the case with pazopanib, which was approved in 2012 for the management of this type of tumors, to date, two cases of TLS have been reported in tumors other than the one reported in this case (19).

Considering its low frequency, the limited data on TLS in patients with ST indicates that it is not recognized early. Measures to reduce the risk of its presentation, such as initiating prophylactic therapies, have not been not established; this impacts the course and outcome of the disease.

The present study has several strengths, among which the novelty of the case can be highlighted regarding the presence of tumor lysis in this type of patient and the relationship of the event with the prescribed cancer therapy, which makes this case a first line of scientific evidence, however, as a case report it has the limitation that it cannot be generalized beyond the context of the informed patient.

Conclusions

TLS is an oncologic emergency that is life-threatening which is best prevented rather than managed. Because this condition is very lethal, it is imperative that management be initiated early and performed by an interprofessional team. However, the few numbers of cases reported in the literature in patients diagnosed with soft tissue sarcoma could make this event goes unnoticed. Therefore, the risk of the event should be determined through early diagnosis and effective therapies should be initiated for saving the patient's life.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-111/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-111/coif) and report that this research has been funded by Dirección General de Investigaciones of Universidad Santiago de Cali under call No. 02-2023. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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