Tumor lysis syndrome (TLS) is a potentially fatal complication of anti-cancer therapy that is usually seen in patients with bulky, rapidly proliferating, treatment-sensitive tumors such as hematological malignancies, but it rarely occurs in a variety of solid tumors such as colorectal carcinoma. Combination chemotherapy with infusional 5-fluorouracil/leucovorin and irinotecan has been recently accepted as the first treatment option for metastatic colorectal cancer. We present a case of tumor lysis syndrome in a patient with metastatic colon carcinoma that occurred 72 hrs after the initial course of a combination chemotherapy with irinotecan and 5-fluorouracil/leucovorin. Despite the immediate treatment with aggressive hydration by a sodium bicarbonate infusion, followed by forced diuresis and uricolytic therapy, he died of a sudden cardiac arrest complicated by acute renal failure. Our case indicates that administration of 5-fluorouracil/leucovorin and irinotecan for bulky tumors of colorectal origin with a rapid doubling time may induce an acute tumor lysis syndrome, which necessitates frequent laboratory monitoring and a close follow-up of the patient as well as prompt initiation of appropriate therapeutic measures.

Key words: 5-fluorouracil/leucovorin, colon cancer, irinotecan, tumor lysis syndrome.

Introduction

Tumor lysis syndrome (TLS) is a potentially fatal complication of anti-cancer therapy that is usually seen in patients with bulky, rapidly proliferating, treatment-sensitive tumors. It is due to massive necrosis of neoplastic cells, sometimes occurring spontaneously but more often after chemotherapy and radiotherapy, as well as hormone therapy or biological response modifiers plus immunotherapy. The release of intracellular ions and metabolic by-products into the blood stream causes the biochemical and clinical hallmarks of the syndrome. Most cases of TLS have been reported after treatment for hematological malignancies, and it rarely occurs in a variety of solid tumors such as small cell lung cancer. To our knowledge, TLS in colorectal cancer is so rare that only one case has been reported in the literature.

We report a case of TLS in a patient with metastatic colon carcinoma that occurred after an initial course of a combination chemotherapy with irinotecan (CPT-11) and 5-fluorouracil/leucovorin (5-FU/LV).

Case report

A 66-year-old man with a diagnosis of prostate cancer was hospitalized in the Hematology/Oncology Service with a complaint of fatigue. His medical history revealed that he had been diagnosed as having prostate adenocarcinoma (T1cN0 M0) (Gleason 3 + 4: 7) by a transrectal fine-needle biopsy and had received prostate irradiation (66 Gy) 2 years before. After radiotherapy, he was no longer under clinical follow-up.

Upon admission to the hospital, the vital parameters were normal. His physical examination was only remarkable for a hepatomegaly without tenderness. The complete blood count showed a mild anemia (hemoglobin, 9.2 g/dL) with microcytosis and hypochromia (mean cell volume, 69.0 dL; mean cell hemoglobin, 19.8 pg; mean cell hemoglobin concentration, 24.5 g/dL). The serum iron parameters were consistent with an iron deficiency anemia. The blood chemistry showed a mild increase in lactate dehydrogenase (LDH) and hypoalbuminemia (Table 1). Serum PSA level was normal. The carcinoembryonic antigen level was high (3785 ng/mL; upper limit of normal, 4). An esophagogastroduodenoscopy revealed erosive gastritis and healing erosive lesions in the prepyloric region, where multiple biopsies were obtained. A colonoscopic examination was remarkable for a tumor mass, 4 x 5 cm in diameter, giving the impression of an external infiltration of the sigmoid colon. It was 18 cm distant from the anal sphincter. Multiple biopsies were obtained (Figure 1). Owing to the patient’s intolerance to the colonoscopy, it was impossible
to go forward anymore. The histopathological analysis of the biopsy showed an adenocarcinoma of the sigmoid colon with irregular glandular or cribriform structures. The cells had extensive eosinophilic cytoplasms with hyperchromatic nucleoli (Figure 2). Immunohistochemical study of the biopsy with PSA done for the differential analysis of prostate cancer was negative. The diagnosis of a colon cancer was made.

Computerized tomography scans of the chest and abdomen revealed bilateral metastatic nodules in the lungs and multiple metastatic nodules in the liver, with the greatest dimension of $10 \times 10$ cm, with two tumor foci at the cecum and rectosigmoid colon, respectively. He also had peritonitis carcinomatosa. The bladder and prostate were both normal. A bone scan was remarkable for multiple areas of increased activity consistent with metastases.

The patient received 5-FU (400 mg/m$^2$ by bolus infusion and 600 mg/m$^2$ by continuous infusion) preceded by LV (200 mg/m$^2$ by 2-h infusion on days 1 + 2) as well as CPT-11 (180 mg/m$^2$ by 1.5-h infusion on day 1), every 2 weeks. He tolerated the chemotherapy well until 72 hrs after treatment, when his urinary output began to decrease (700 cc/24 hrs). The laboratory parameters obtained in this period showed, besides the previously observed abnormalities, an important worsening of renal functions, hyperuricemia, hyperphosphatemia and hypocalcemia. The LDH level had increased (Table 1). Peripheral blood smears revealed hypochromia and anisopoikilocytosis of red blood cells. Corrected reticulocyte count was 1.2%. Thus, hemolytic anemia was excluded. The coagulation profile was normal. The urine was acid with a pH of 4.5 and spot urine Na level was 18 mmol/L, suggesting a renal cause for the renal failure. Arterial blood gas analysis showed metabolic acidosis (pH 7.14, pCO$_2$ 44 mm Hg, pO$_2$ 40 mm Hg, HCO$_3$ 12).

Through these findings, TLS was diagnosed. He was immediately treated with aggressive hydration by a sodium bicarbonate infusion, followed by forced diuresis and uricolytic therapy. Further work-up revealed slight changes in laboratory parameters in favor of an aggravation of TLS despite early initiation of appropriate therapeutic measures (Table 1). The patient was to be treated with hemodialysis for acute renal failure, but he died of a sudden cardiac arrest.

**Discussion**

TLS is a life-threatening, serious clinical complication of anticancer therapy. It sometimes occurs spontaneously. It is due to the release of intracellular ions and metabolic by-products into the blood stream as a result of massive necrosis of neoplastic cells.

The classic features of TLS (azotemia, hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia) occur during the treatment of rapidly proliferating, sensitive and bulky tumors$^1$. TLS is often observed in patients with hematopoietic malignancies but it has been rarely reported in solid tumors such as small cell lung cancer$^{2,3}$. Interestingly, several patients with TLS pre-
sented with tumors that generally respond very slowly to chemotherapy, such as breast and ovarian carcinoma.

One case of TLS was described in a patient as a treatment complication of a metastatic colorectal cancer with CPT-11 in 1995 by Boisseau et al.7 In this case report, a 42-year-old female with a colon adenocarcinoma of Dukes' C stage relapsed after six weeks with perirectal disease and multiple liver metastases. She received palliative pelvic irradiation (60 Gy) and chemotherapy with continuous infusion of 5-FU over 15 days. At the beginning of the treatment, laboratory values revealed hyperuricemia, hyperkalemia, and hyperphosphatemia. After two courses of chemotherapy consisting of 5-FU, owing to metastatic progression in the liver, it was decided to treat the patient with CPT-11 (300 mg/m²). At day 8, she was admitted for a profound general deterioration with severe metabolic anomalies consisting of hyperuricemia, hyperkalemia, hyperphosphatemia with hypocalcemia and acute renal failure. Despite forced diuresis, urine alkalization and uricolytic therapy, the patient died 48 hrs later due to renal failure with anuria. This case was the first report of TLS secondary to colon cancer or CPT-11 use. In this case, the TLS was spontaneous and was present before beginning the treatment. It was aggravated by CPT-11.

The difference from our patient (who also had a large tumor mass) was the fact that no sign of TLS was present before the chemotherapy. LDH was high in the beginning, but it can be considered a non-specific finding which occurs frequently in tumors of a large volume, especially in liver metastases. The TLS occurred 72 hrs after systemic chemotherapy and resulted in acute renal failure.

In both cases, the TLS resulted in the death of the patient. In many hematological malignancies, TLS is a well-known adverse event. It is part of the natural history of the disease and has a lower mortality rate because of the appropriate measures, which permit recovery of TLS without sequelae such as renal damage, taken in the beginning of treatment. In solid tumors, it indicates the presence of a large tumor mass with an aggressive behavior, and it can be considered as a poor prognostic factor. The mortality rate for patients with a solid tumor and with TLS appears to be higher than that reported for TLS following treatment of hematological malignancies, perhaps because of the greater use of prophylactic measures and increased awareness of possible complications during the treatment of such malignancies. So, solid tumor patients at the risk of TLS with fast growing and bulky tumors, and also who have the preexisting risk factors including azotemia, elevated serum LDH level and hyperuricemia, can be candidates to receive preventive measures such as hydration prior to the treatment, alkalization of the urine and allopurinol. Urate oxidase (rasburicase) is beginning to replace allopurinol as a more effective way to reduce hyperuricemia and thereby the risk of TLS.

5-FU is an anti-metabolite that inhibits thymidylate synthase activity. At the same time, it can directly affect cell DNA and RNA. It is considered as a phase-specific agent, and this fact favors its use in continuous infusion instead of bolus administration. Its main side effects are mucositis, diarrhea, hand-foot syndrome and myelosuppression. CPT-11 is a new cytotoxic agent and a water-soluble, semisynthetic derivative of a plant alkaloid called camptothecin that inhibits the DNA enzyme topoisomerase I. CPT-11 is mainly metabolized in the liver, and only up to 10-20% of its extraction is through the kidneys. SN-38, the active metabolite of irinotecan, is mainly excreted in the bile, and renal toxicity due to CPT-11 has never been reported except for the aforementioned case. The principle adverse events of CPT-11 are dose-dependent neutropenia and delayed diarrhea of a secretory mechanism. None of the well-known side effects of CPT-11 and 5-FU were observed in our patient.

These two cases illustrate that administration of CPT-11 for fast growing and bulky carcinomas of colorectal origin may induce an acute TLS, which requires frequent laboratory monitoring and a close follow-up of the patient, as well as the preventive measures taken before beginning the treatment.

References