1130-0108/2009/101/4/288-294
REVISTA ESPAÑOLA DE ENFERMEDADES DIGESTIVAS

REV ESP ENFERM DIG (Madrid)
Vol. 101. N.° 4, pp. 288-294, 2009

CLINICAL NOTE

Acute spontaneous tumor lysis syndrome in a patient with Crohn's disease taking immunosuppressants

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ABSTRACT

Acute tumour lysis syndrome (TLS) is a catastrophic complication of the treatment of certain neoplastic disorders. It most commonly occurs in association with hematologic malignancies and appears a few hours to a few days after initiation of specific chemotherapy, as the result from the release of intracellular components into the bloodstream due to abrupt malignant cell death. Acute spontaneous TLS is rare, and it has been described in leukemia and lymphoma and in some patients with solid tumors prior to institution of therapy. The syndrome is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and acute oliguric or anuric renal failure due to uric acid precipitation within the tubules (acute uric acid nephropathy) and to calcium phosphate deposition in the renal parenchyma and vessels.

We report a case of acute spontaneous TLS in a patient with Crohn's disease treated with immunosuppressive drugs, who developed a plasmocytoma, in which serum uric acid concentration attained exceptionally high levels (44 mg/dL). The patient underwent acute oliguric renal failure, which required treatment with hyperhydration, urine alkalinization, urate oxidase and hemodialysis, with a fatal evolution.

In conclusion, the present case report has several peculiarities: that of being one of the rare examples of spontaneous TLS, that of showing an exceptionally severe hyperuricemia, probably the highest ever reported in the literature, and that of the possible increased risk of tumours in patients with Crohn's disease taking immunosuppressives and/or TNF antagonists.

Key words: Tumour lysis syndrome. Spontaneous. Acute renal failure. Hyperuricemia. Immunosuppressive therapy. Infliximab. Crohn's disease.

Received: 05-12-08.
Accepted: 02-01-09.

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Froilán Torres C, Castro Carbajo P, Pajares Villarroya R, Plaza Santos R, Gómez Senent S, Martín Arranz MD, Adán Merino L, Martín Arranz E, Manceñido Marcos N, Peces R, Benito López D. Acute spontaneous tumor lysis syndrome in a patient with Crohn's disease taking immunosuppressants. Rev Esp Enferm Dig 2009; 101: 288-294.

INTRODUCTION

Tumor lysis syndrome (TLS) is an urgent oncological condition characterized by electrolytic and metabolic alterations that appear as a result of the release of a huge volume of intracellular substances because of a rapid destruction of tumor cells (1-5). It develops more frequently in patients with malignant hematological neoplasia following the beginning of chemotherapy. It is less frequently associated with solid tumors. Very rarely, the spontaneous necrosis of a malignant neoplasm, where cytostatic treatment is not given, determines the appearance of this condition; however, there are few cases described in the literature. We report the case of a patient with Crohn's disease on immunosuppressants who developed spontaneous tumor lysis syndrome as presentation of a high-grade plasmocytoma that was eventually diagnosed by means of necropsy. This case is of particular interest due to: a) the exceptional "spontaneous" nature of this tumor lysis syndrome, which occurred without chemotherapy; b) the fact that the patient presented with extreme hyperuricemia, probably the highest level reported in the literature; and c) the current controversy surrounding therapy with immunosuppressants and/or biological agents in inflammatory bowel disease, and its being linked to the development of certain tumors.

CASE REPORT

A 50-year-old man with Crohn's disease, ileal inflammation and complex perianal fistulae who was on immunosuppressants was admitted to our institution suffering from fever, perianal suppuration and diarrhea for 1 week. The patient had been receiving ongoing treatment with salicylates and azathioprine (2.5 mg/kg/day, adjusted according to TPMT levels) for 2 years, and had been given 6 doses of infliximab, as part of a biological treatment program that was discontinued 6 months prior to the current admission for work-related reasons.

A physical examination revealed the patient to be in poor condition generally, with fever (39 ºC), low blood pressure (BP 80/40 mmHg), tachycardia (104 bpm), and tachypnea (22 rpm). A "mass effect" could be noted in the right iliac fossa, with heightened consistency, and a fistulous orifice was visible in the left gluteus, over an area that was indurated, erythematous, hot, and painful. Emergency tests revealed anemia (Hb 7.9 g/dl, Hct 29%), renal failure (serum creatinine, 4 mg/dl), and high levels of acute phase reactants (C-reactive protein, 127; platelets, 424,000/μL). Based on a diagnosis of probable sepsis and multifactorial renal failure (salicylates, dehydration...), serum therapy was commenced and broad-spectrum antibiotics administered. In the 24 hours that followed the patient became confused and agitated, and his renal function deteriorated further, with metabolic and hydroelectrolytic alterations (urea 68 mmol/L, creatinine 6.9 mg/dl, sodium 138 mmol/L, potassium 6 mmol/L, total calcium 7.5 mmol/L, inorganic phosphorous 5.1 mmol/L, LDH 17.481 U/L, urate 44 mg/dl). These results led to a Doppler ultrasound scan of the kidney. The organ appeared regular in the scan, which was interpreted as renal failure of aggravated multifactorial origin due to the precipitation of uric acid crystals. Hyperhydration treatment was begun, with urine alkalinization and hemodialysis. Allopurinol and rasburicase were administered, leading to a marked decrease in urate levels (urate 1.8 mg/dl). However, in light of the progressive worsening of the clinical and general state of the patient, an abdominopelvic CT scan was conducted (Fig. 1), which showed a retroperitoneal mass measuring 13 x 10 cm, and a lesion in the right flank measuring 15 x 8.6 cm, which appeared to correspond to a mass with a fixed ileum and a thickened wall. An underlying neoplasia could not be ruled out. The scan also revealed multiple adenopathies in the mesenteric, iliac, and inguinal chains, as well as a left perirectal lesion, probably linked to a previous abscess and perianal fistula. This latter lesion was the only radiological finding, which was diagnosed two months prior to the current episode, in a magnetic resonance scan of the abdomen and pelvis conducted as part of the ongoing perianal disease monitoring.

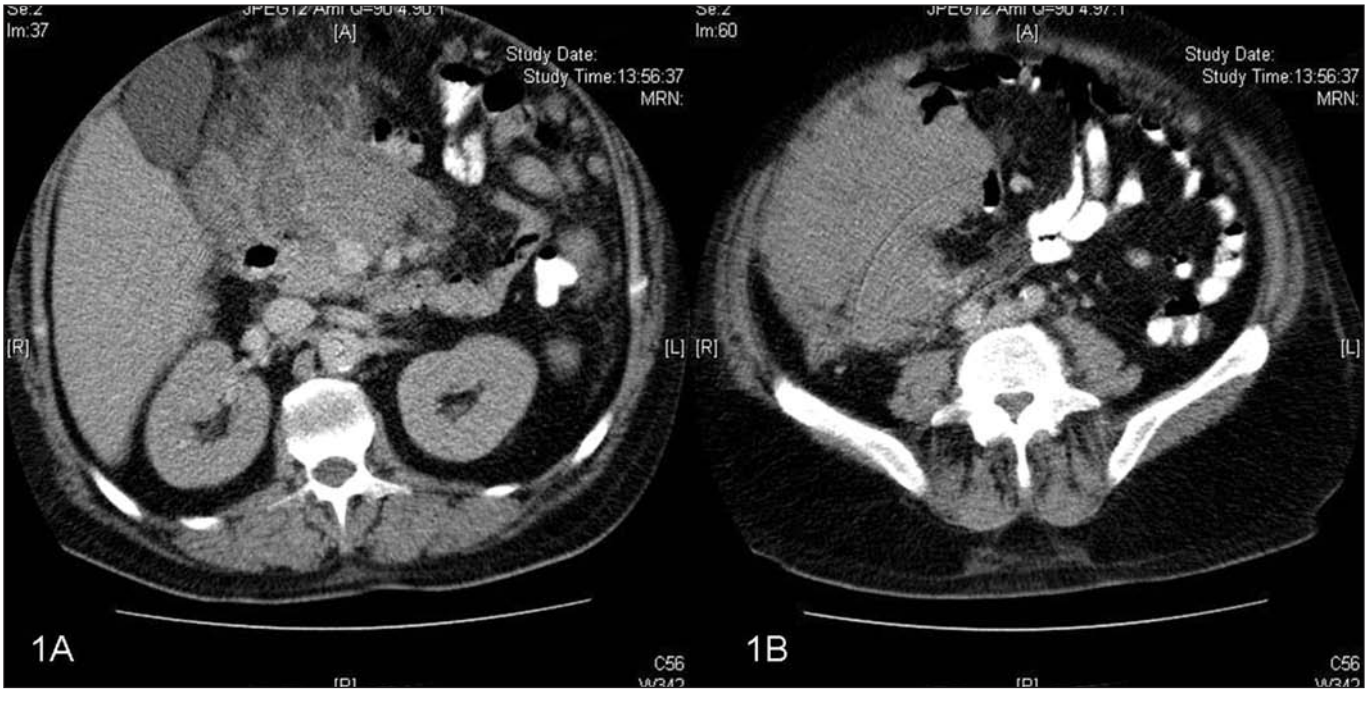

Fig. 1. Abdominopelvic CT scan: A. Retroperitoneal mass measuring 13 x 10 cm, with no clear plane of separation between the head and the body of the pancreas. B. In the right flank a lesion that may correspond to a mass with fixed ileum and thickened wall, with a maximum diameter of 15 x 8.6 cm, may be seen.

TAC abdomino-pélvico: A. Masa retroperitoneal, de 13 x 10 cm sin claro plano de separación con cabeza y cuerpo pancreático. B. En flanco derecho, lesión que pudiera corresponder a un conglomerado de asas fijas con pared engrosada, de diámetro máximo de 15 x 8,6 cm, sin poder descartar neoplasia subyacente.

In spite of the supporting treatment the patient continued to have fever, confusion, progressive dyspnea, and anuria, and died three days after admission. The definitive diagnosis was obtained by means of a necropsy: plasmoblastic plasmocytoma with predominance of light lambda-type chains infiltrating the terminal ileum, the root of the mesentery, the abdominal lymph nodes, and the bone marrow (Figs. 2 and 3).

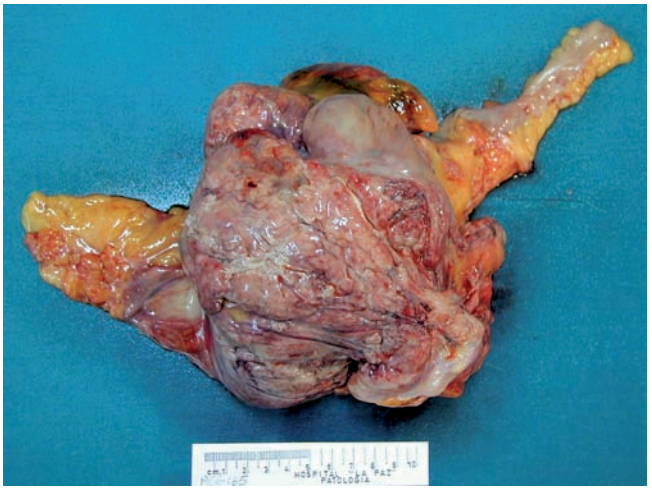

Fig. 2. Necropsy results: tumoral mass with mamelonated edges infiltrating the terminal ileum.
Pieza de necropsia: masa tumoral de bordes mamelonados que infiltra íleon terminal y ciego.

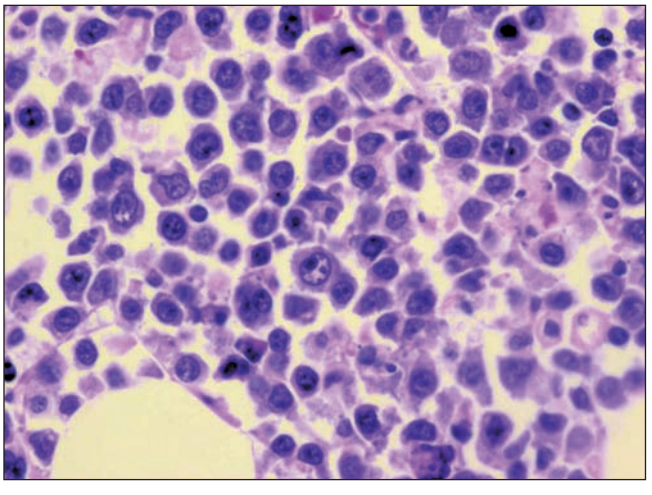

Fig. 3. Histological image of a high-level plasmacytoma: medium and large cells with plasmacytoid characteristics, and a basophilic, hyperchromatic nucleus with large nucleoli.
Imagen histológica del plasmocitoma de alto grado: células de mediano y gran tamaño de hábito plasmocitoide, con núcleo basófilo, hipercromático y gran nucléolo.

DISCUSSION

TLS, described for the first time by Bedrna and Polcak in 1929, encompasses a range of hydroelectrolytic and metabolic alterations that are often associated with malignant tumors that have a high growth ratio and, as a result, they are highly responsive to cytotoxic medication. The typical form of presentation occurs in patients with hematological neoplasia, or, more rarely, with solid tumors in the first 5 days following chemotherapy onset (1-5). Very rarely, this condition is determined by the spontaneous necrosis of malignant neoplasias. Hyperuricemia, hyperpotassemia and hyperphosphatemia accompanied by hypocalcemia and acute renal insufficiency may occur individually or in combination, and may determine the term of the tumor lysis syndrome.

Spontaneous TLS is very rarely described in the medical literature (Medline 1960-2008, key words: tumor lysis syndrome, spontaneous). The first case was described in 1977 by Crittenden and Ackerman in a patient with disseminated gastrointestinal carcinoma (1). Since then, we have collected only 22 documented cases: 4 of these cases were associated with leukemia (6-8), 2 were linked to germinal cells (9), 8 were linked to solid tumors (5,10-15), and 8 to lymphoma (4,16-23).

Our case is a very good example of spontaneous TLS, because even if it fulfilled the listed electrolytic and metabolic criteria, apart from pertaining to a very high level of LDH and marked lactic acidosis, we were unable to find a link to one of the currently described triggers (1-3,17) (chemotherapy, glucocorticoids, radiotherapy, interferon, methotrexate, or tamoxifen).

The pathophysiology of this clinical case was complex. The degradation of a large number of cancer cells leads to the release of considerable quantities of potassium, phosphorous, and nucleic acid purines, which subsequently are metabolized into uric acid through the action of xanthane oxidase in the liver. When the amount of uric acid exceeds the filtration capacity of the kidneys, this leads to a precipitation of uric acid crystals in the renal tubules, leading to the onset of renal insufficiency. Hyperphosphatemia leads to a precipitation of calcium phosphate salts in the microvasculature and renal tubules, thus exacerbating renal function impairment. However, given the clinical transcendence of this condition, the most dangerous consequence of TLS is hyperpotassemia, which is secondary to the release of intracellular potassium (1-4,17). On the other hand, renal failure in itself diminishes the excretory capacity of all of the above metabolites, thereby leading to an increase in their blood levels and further aggravating the previous metabolic instability. As a result, the patient develops oliguria, hyperazotemia, severe cardiac arrhythmias, and neurological deterioration, all of which can result in death.

In the case in question, the patient was admitted with oligoanuric renal failure and extreme hyperuricemia as a precipitating factor (with the highest reading seen in the

relevant literature), presenting during the course of the condition with progressive neurological deterioration, resulting in a coma state twelve hours before death.

The ideal treatment for this syndrome is preventive, based on hydration, urine alkalinization, allopurinol, and renal function optimization prior to the beginning of chemotherapy (1-4,6,17,18,21-23). These universal measures are very important, but particularly in patients presenting with risk factors for the development of this syndrome, such as high levels of LDH (1,500 U/L), previous renal insufficiency, conditions affecting the bone marrow, and/or high sensitivity of the tumor to cytotoxic agents (17).

Once the onset of TLS has been diagnosed, rapid and intensive treatment may diminish mortality. The range of available treatment options includes hyperhydration to improve renal perfusion, rectification of electrolytic imbalances through the usual means, and allopurinol and rasburicase (recombinant urate oxidase) to reduce uric acid levels (1,2,17,24). Urine alkalinization with sodium bicarbonate is not recommended as a routine procedure, especially in the presence of hyperphosphataemia, since if the uric acid is made soluble, this also increases the risk of calcium phosphate precipitation (17). Hemodialysis (24) is reserved for cases in which the resolution of renal insufficiency is unlikely as a result of its clinical course, when hydroelectrolytic alterations threaten the life of the patient, or in cases where there is uncontrollable hypervolemia or hypertension.

In our case, in spite of timely treatment (hemodialysis, hyperhydration, urine alkalinization) and the positive response of hyperuricemia to treatment with rasburicase (uric acid 1.8 mg/dl 48 hours after treatment onset), the extraordinary aggressiveness of the plasmoblastic plasmocytoma proved fatal 72 hours after admission.

Finally, it is appropriate to comment on the safety profile of the immunosuppressants and biological agents used in the treatment of inflammatory bowel disease. Although it is certain that the incidence of neoplasia, especially certain types of lymphoma, has increased in patients treated with azathioprine and/or biological agents, in standard clinical practice treatment benefits are considered to outweigh potential risks (25-27). Furthermore, although there is some controversy surrounding this issue, recent studies and the recommendations currently in place by Grupo Español de Trabajo de Crohn y Colitis Ulcerosa (GETECCU - Spanish Working Group on Crohn's Disease and Ulcerative Colitis), whereby infliximab is to be used (26), allow us to conclude that recommencing or continuing treatment with immunomodulators in patients who are candidates for treatment with biological agents is highly recommended.

Another peculiarity of our case is that, against the higher expected risk of neoplasia in relation to combined treatment with immunosuppressants and biological agents, the patient had voluntarily discontinued treatment with infliximab six months before the episode described herein, and as a result had since then only been receiving treatment with azathioprine.

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Síndrome de lisis tumoral "espontáneo" en paciente con enfermedad de Crohn tratado con inmunosupresores

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RESUMEN

El síndrome de lisis tumoral (SLT) es una complicación catastrófica del tratamiento de ciertas enfermedades neoplásicas. Si bien es más frecuente en pacientes con neoplasias hematológicas malignas tras el inicio de la quimioterapia, puede presentarse excepcionalmente, tras la necrosis espontánea de algunos tumores, en ausencia de tratamiento citostático. Clínicamente cursa con hiperuricemia, hiperfosfatemia, hipocalcemia, hiperpotasemia y fallo renal agudo.

Presentamos el caso de un paciente con enfermedad de Crohn en tratamiento inmunospresor, que desarrolló un síndrome de lisis tumoral espontáneo como debut de un plasmocitoma. Al ingreso, se objetivó un fracaso renal oligoanúrico que, a pesar de tratamiento precoz con hiperhidratación, alcalinización de la orina, urato-oxidasa y hemodiálisis, tuvo un desenlace fatal en 72 horas.

Este caso reviste un interés particular por lo excepcional de la naturaleza "espontánea" del síndrome de lisis tumoral en ausencia de quimioterapia, por presentarse con una hiperuricemia extrema, probablemente la más alta de las recogidas en la literatura, y por la controversia actual de la terapia con inmunosupresores y/o biológicos en la enfermedad inflamatoria intestinal y su relación con el desarrollo de determinados tumores.

Palabras clave: Síndrome de lisis tumoral. Espontáneo. Fracaso renal agudo. Hiperuricemia. Tratamiento inmunosupresor. Infliximab. Enfermedad de Crohn.

INTRODUCCIÓN

El síndrome de lisis tumoral (SLT) es una urgencia oncológica caracterizada por alteraciones electrolíticas y metabólicas que aparecen como consecuencia de la masiva liberación de sustancias intracelulares procedentes de una rápida destrucción de células tumorales (1-5). Se presenta más frecuentemente en pacientes con neoplasias hematológicas malignas, tras el inicio de la quimioterapia, siendo menos común su asociación con tumores sólidos. Excepcionalmente, la necrosis espontánea de una neoplasia maligna, en ausencia de tratamiento citostático, condiciona esta entidad y son muy pocos los casos recogidos en la literatura. A continuación, presentamos el caso de un paciente con enfermedad de Crohn en tratamiento inmunospresor, que desarrolló un síndrome de lisis tumoral espontáneo como debut de un plasmocitoma de alto grado, que se diagnosticó mediante necropsia. Este caso clínico reviste un interés particular por: a) lo excepcional de la naturaleza "espontánea" del síndrome de lisis tumoral en ausencia de quimioterapia; b) presentarse con una hiperuricemia extrema, probablemente la más alta de las recogidas en la literatura; y c) la contro-