CASE REPORT

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Patient diagnosed with mantle cell lymphoma with tumour lysis syndrome – Case Report and literature review

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Abstract

Mantle cell lymphoma (MCL) is an aggressive, rare form of non-Hodgkin lymphoma (NHL). This lymphoma is characterized by the expansion of mature B cells which spread in the bone marrow, blood, lymphatic tissues and extranodal sites. Due to limited treatment options, it is one of the most complex neoplastic diseases of the lymphoid system. The typical age of onset is 60–70 years. Occasionally, tumour lysis syndrome (TLS) can occur due to the cancer cells breaking-down too quickly. The sudden, intense breakdown of the cancer cells releases large amounts of potassium, purines and phosphates. In the clinical case described by the authors, the patient was diagnosed with MCL in the generalized CS III stage. The patient additionally developed TLS. Previously, the patient had been treated with rituximab at the Department of Haematooncology, and due to respiratory and renal failure, was subsequently admitted to the Intensive Care Unit (ICU) of the University Hospital in Lublin.

Key words

tumour lysis syndrome, rituximab, mantle cell lymphoma

INTRODUCTION

Mantle cell lymphoma is a rare malignancy [1] which originates from B cells. The classic subtype of this lymphoma is positive for the t(11,14) translocation and SOX11 expression, and is characterized as a mature B cell tumour [1, 2]. The presence of the t(11,14) translocation juxtaposes the *CCDN1* gene with the immunoglobulin heavy chain locus, leading to cyclin D over-expression [3]. MCL is characterized by a relapsing and remitting course considering current treatment strategies [4, 5]. With each successive line of therapy, remission shortens [4, 5]. The standardized incidence rate is 2–3/10000, which accounts for 5–10% of new non-Hodgkin lymphoma cases [2]. Patients suffering from MCL usually live for years but have numerous relapses [6]. Overall, 5-year relative survival is about 50%, and can reach from 75% in patients younger than 50 years to about 36% in patients who are 75 and older [6]. The Mantle Cell International Prognostic Index (MIPI) helps assess the prognosis [6]. Significant pathological variables important in determining the prognosis are cell morphology, which can be evaluated using a light microscope, the presence of the *TP53* gene mutation, and the rate of proliferation of cancer cells [6].

The initial treatment of patients depends on many factors. Attention is paid primarily to the patient's condition and eligibility for stem cell transplantation [6]. Patients who qualify for transplantation are usually treated aggressively with rituximab and high-dose cytarabine [6]. Elderly or younger patients not eligible for transplantation usually receive bendamustine with rituximab [6]. In addition, patients in both groups receive additional rituximab as maintenance therapy [6].

Aggressive treatment can bring positive results in long-term remission in some patients. Although it can also have a negative impact causing the patient TLS. It is an acute, directly life-threatening syndrome of metabolic disorders due to the rapid breakdown of cancer cells. Most cases occur in the first days of cytotoxic chemotherapy, used because of a tumour that is characterized by high proliferative activity and high chemosensitivity. It can also occur after the use of anti-cancer drugs or molecularly-targeted drugs [7]. Cytoreductive treatment causes the massive release of granules into the bloodstream, manifested by hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and uremia leading to muscle weakness and paralysis, sensory disturbances, impaired consciousness, cardiac arrhythmias, and convulsions [7]. Subsequently, patients can develop kidney failure, multiple organ failure, and sudden death.

The aim of the study is to present a literature review based on the clinical case of a patient with mantle cell lymphoma who also developed tumour lysis syndrome.

CASE REPORT

A 76-year-old patient diagnosed with mantle cell lymphoma, with a history of arterial hypertension, hyperlipidemia, atherosclerosis, and Chronic Obstructive Pulmonary Disease (COPD), was admitted to the Haematooncology Department of the University Hospital for cytoreductive treatment with rituximab.

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The patient was diagnosed with mantle cell lymphoma in the generalized stage CS III with the involvement of lymph nodes, bone marrow, blood, gastrointestinal tract and spleen. On physical examination, the presence of enlarged cervical, axillary and inguinal lymph nodes was palpable, and hepatosplenomegaly was also found. In addition, lymph nodes in the abdominal cavity were also palpable. Lymphocytosis was present in laboratory tests. The patient reported the following clinical symptoms: weakness, shortness of breath, night sweats, low-grade fever for about three months, during that time he lost about five kilograms of body weight.

On the first day after administration of rituximab, the patient's consciousness deteriorated and respiratory and renal failure developed. Laboratory tests showed TLS features: hyperkalemia (7.63 mmol/l), hyperuricemia (12.2 mg/dl), creatinine (2.25 mg/dl). In addition, the patient's renal failure worsened. Oliguria was present and very concentrated urine – eGFR 39. The baseline lactate dehydrogenase (LDH) value was 518 IU/L; tumour volume – 400 ml.

The patient was diagnosed with tumour lysis syndrome. The patient received the following TLS prophylaxis: rasburicase with allopurinol (reduced dose due to eGFR 39); empirical antibiotic therapy according to eGFR – piperacillin with tazobactam was used. In order to lower the level of potassium, the patient was given furosemide, salbutamol in the evening, glucose 5% and insulin and calcium chloride 10% were added. The patient was intubated, mechanically ventilated, and transferred to the ICU.

In the ward, the patient was sedated with fentanyl and propofol. Mechanical ventilation was introduced with Synchronized Intermittent Mandatory Ventilation, Pressure Regulated Volume Control (SIMV-PRVC), a fraction of inspired oxygen (FiO2) of 60%, tidal volume (TV) of 500 ml, and frequency (f) 25/min. The circulatory system was haemodynamically monitored and required a continuous infusion of norepinephrine. Dialysis access was established, and continuous renal replacement therapy (CRRT) with calcium-citrate anticoagulation was started.

For the next four days, the ICU patient remained in a very severe condition and needed both respiratory and circulatory system support. Due to anuria and peripheral oedema, CRRT was continued. On the fifth day, the patient was still in a very serious condition. In the morning, sedation was turned-off. The patient was noted to be markedly agitated, but unable to make logical contact. An attempt at spontaneous breathing was unsuccessful.

The patient continued to be mechanically ventilated, initially with Pressure Support Ventilation (PSV) and then with PRVC, FiO2 35%, TV 500 ml, f 20–26/min. The circulatory system remained inefficient and required an infusion of norepinephrine. Anuria and massive peripheral oedema persisted. The patient's condition remained unchanged on the sixth, seventh, and eighth days. Despite the applied treatment, his condition deteriorated, and multi-organ failure increased. On the ninth day, the patient's condition was severe. Based on the haematological consultation conducted that day, he was disqualified from further treatment for the underlying disease. As a consequence of an increasing multiple organ failure, the patient died.

DISCUSSION

Four morphological variants of MCL are known: leukemic nodal, classic, blastoid, and pleomorphic. Blastoid and pleomorphic forms are more aggressive and have a worse prognosis. The prognostic index (MIPI) differentiates patients into groups depending on age, performance status assessed according to the Eastern Cooperative Oncology Group (ECOG), LDH, white blood cell count, and Ki67 protein [8, 9]. In addition, the detection of *TP53* mutation at the time of diagnosis results in a poor response to intensive chemotherapy, and is associated with poor prognosis [8, 10].

MCL may have very different clinical manifestations [11]. Most patients (almost 70–80%) have an aggressive form of the disease manifested by lymphadenopathy or extranodal disease at an advanced stage. However, the disease can be much milder, for example, it may be asymptomatic lymphocytosis or non-volume lymph node/extranodal illness [11]. In less than half of patients, b-symptoms adversely affect prognoses, such as unintentional weight loss, fever, and night sweats. Patients can present with symptoms of a distended abdomen due to hepatosplenomegaly. Lymph nodes and spleen are often involved. Then Waldeyer's ring, bone marrow, and peripheral blood become involved. Patients may also present with symptoms suggestive of extranodal involvement of the gastrointestinal tract, lungs, and/or central nervous system and orbit. When selecting the appropriate treatment for the patient, age, general fitness status, and comorbidities are considered [8].

In young patients qualified for transplantation, induction chemotherapy is used as a first-line treatment, followed by haematopoietic stem cell transplantation [8]. As a maintenance treatment, patients are given rituximab for three years. There is no single specific substance regimen for induction chemotherapy. Particular schemes differ depending on the medical practice and the institution; however, it was conventionally assumed that the regimen should contain cytarabine [8]. In patients not qualified for intensive chemotherapy, less toxic agents, such as bendamustine/rituximab, are used. In the case of disease recurrence or progression, ibrutinib, lenalidomide, bortezomib, or venetoclax can be used as monotherapy.

Modern medicine also enables transplants to be carried out in patients. Autologous transplantation, also called high-dose chemotherapy, is supported by the transplantation of own cells. While in allogeneic transplantation, the donor may be related to the patient or unrelated. The donor may differ genetically and in terms of blood groups from the recipient but must be compatible with the HLA system. Autologous transplantation is preferred in younger patients with MCL and allows more prolonged survival free of disease progression [12]. On the other hand, allogeneic transplantation can provide lasting remission in selected patients [8].

Based on minimal residual disease (MRD) status, there is a possibility to determine the predictive rate of survival [3]. It has been proven that if MRD is not detectable after immunochemotherapy in patients with MCL, it indicates a better response. However, prognostic factors are also associated with poor prognosis [3]. These include high-risk simplified MIPI (s-MIPI), blastoid morphology, *TP53* mutation, and Ki67 index [3]. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is calculated from age, ECOG performance status, lactate dehydrogenase level, and white blood cell count as a weighted sum of pre-treatment values. Here, the proliferation of tumour cells expressed as

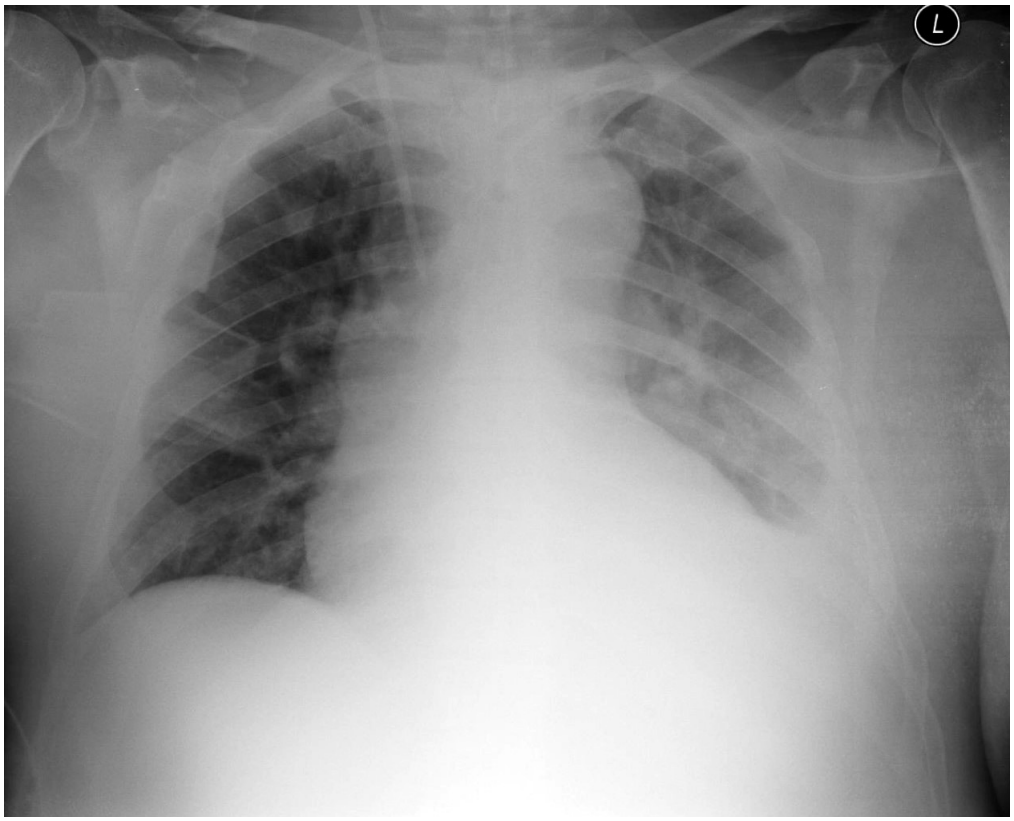

Figure 1. X-ray of the patient's lungs taken on the day of admission to the ICU. Visible thinning of the left lung area corresponds to the presence of free fluid in both pleural cavities. Spotty segmentally confluent shadows may correspond to inflammatory ones parenchymal densities in the perihilar regions of both lungs

the Ki67 index is added together with the MIPI score [3]. Based on the MIPI-b result, patients can be divided into three groups: low, moderate, and high risk [3]. However, patients are rarely classified as low-risk because they show results similar to those of the MIPI-b medium-risk cohorts [3].

The *TP53* gene mutation also has a high predictive value. The deletion occurs on the short arm of chromosome 17 containing the p53 gene. This aberration can be detected by *in-situ* fluorescence hybridization or single nucleotide polymorphism array analysis. The mutation in the *TP53* gene can be identified by next-generation sequencing or reverse transcription polymerase chain reaction. Limit values for *TP53* expression have been determined [3]. This was carried out by the European Mantle Cell Lymphoma Network (European MCL Network) by analyzing tissues from 365 patients using immunohistochemical techniques [3]. Based on this, expression in the range of 1% – 10% is defined as low [3], intermediate between 10% – 50%, and high when the expression is greater than 50% [3]. If possible, *TP53* mutation should be carried out both before the implementation of treatment and with each subsequent line of therapy, as it is a valuable source of information on the patient's prognosis [3].

Tumour lysis syndrome. TLS is one of the most common emergencies in oncological patients [13]. It occurs not only in oncological adults and children undergoing chemotherapy, but also can occur spontaneously [13]. TLS is more often recognized in patients suffering from haematological malignancies, for example, highly malignant lymphomas such as Burkitt's lymphoma or leukemias such as acute lymphocytic leukemia [14].

A tetrad of symptoms characterizes TLS: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia as a result of an excessive disintegration of proliferating cancer cells [15]. It most often occurs in the first week of cytotoxic chemotherapy of tumours with high proliferative activity and high chemosensitivity-[15]. In sporadic cases, it may occur spontaneously [16]. Excessive breakdown of nucleic acids and increased catabolism of purines cause hyperuricaemia, which may lead to acute renal failure with elevated urea and creatinine, anuria, and progressing oedemas. Increasing hyperkaliemia causes weakness, decreased muscle tone, and severe cardiac arrhythmia. Lack of appetite, nausea, and event tetany occurs due to hypocalcaemia. In a latent manifestation of TLS, purely laboratory abnormalities are observed. The frequency of its occurrence in oncological patients varies depending on the cancer and appears in more than 20% of haematologic cancers [16].

Typically, MCL is categorised into a low-risk group for TLS [16]. It is said that the incidence of clinical TLS is estimated at 3–7% in leukemia and 4–11% in lymphomas, overall [16], although there are some subtypes that have an incidence of up to 25% [16]. The overall incidence of TLS in adults undergoing therapy for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), which also includes MCL, is about 4.8% despite appropriate prophylaxis in 66% of these adult patients [16].

In the case of suspicion of TLS, careful observation of the patient and prompt treatment are very important. Treatment of this syndrome involves intravenous fluid infusion, diuresis with mannitol/furosemide, and urine alkalinization with sodium bicarbonate [16]. Allopurinol, febuxostat, and

rasburicase are also administered to reduce uric acid [16]. Renal replacement therapy is used for anuria associated with acute kidney injury (AKI) and to correct life-threatening electrolyte disturbances: [17, 18]. Despite proper treatment, mortality in the case of acute TLS is relatively high and can reach up to 51% [19]. According to statistics, patients with (AKI) showed significantly higher ICU, in-hospital, and six-month mortality than patients without AKI [16], respectively, 31%, 59%, and 66%.

The risk of TLS depends on two factors. First, the risk is related to the cancer itself. Tumour size and mass, multiple organ involvement, tumour proliferative potential, and chemosensitivity increase the risk of TLS [19]. Secondly, the risk of TLS depends on the patient's general condition, age, hydration status, kidney failure, presence of diabetes and heart disease [19]. Studies have shown that 1.08% of patients suffering from haematological malignancies and acute renal failure, developed TLS [19].

Treatment and prevention methods for TLS vary depending on the risk of TLS. When there is a low risk, no specific action is taken, the clinical situation is assessed and the patient is monitored [19]. At intermediate risk, the patient may be hydrated and treated with allopurinol (in paediatric patients, rasburicase may be considered). If there is hyperuricemia, this is treated it with rasburicase. At high risk of TLS, the patient is hydrate and rasburicase administered [19]. In the case of hyperkalaemia, it is recommended to suspend the supply of potassium, administer orally or rectally polystyrene sulfonate (cation exchanger) or calcium gluconate, which causes the return of potassium to the cell [19]. If this does not help, rapid-acting insulin with 25% glucose should be administered in a continuous infusion [19]. In the case of hyperphosphatemia, oral administration of aluminum hydroxide is recommended [19].

Laboratory criteria for the diagnosis of symptomatic TLS are uric acid >8 mg/dl or 25% increase from baseline, or potassium >6 mmol/l or 25% increase from baseline, or phosphate >2.1 mmol/L (children) >1.45 mmol/L adults or total calcium <1.75 mmol/L, or a decrease of 25% from baseline or creatinine >1.5 times the upper limit of normal for age [19].

Due to the serious consequences of delayed diagnosis of TLS, several predictors of TLS have been distinguished, such as renal dysfunction before admission, hyponatremia, metastases and/or large tumour mass, male gender, splenomegaly, and elevated creatinine, uric acid and/or lactate dehydrogenase before the start of treatment [16].

Table 1. Clinical chemistry test results on the day of ICU admission and during CRRT treatment

	Before ICU admission	First day of ICU stay	Third day of ICU stay
URIC ACID	6.20 mg/dl	2.50 mg/dl	-
INORGANIC PHOSPHATE	4.88 mmol/l	3.12 mmol/l	1.97 mmol/l
POTASSIUM	8.58 mmol/l	6.44 mmol/l	4.79 mmol/l
CREATININE	3.39 mg/dl	3.13 mg/dl	2.26 mg/dl
UREA	134. mg/dl	138.8 mg/dl	82.8 mg/dl
CALCIUM	1.94 mmol/l	1.720 mmol/l	2.42 mmol/l
pH	7.18	7.19	7.24
PaO_2	121 mmHg	83.3 mmHg	96.6 mmHg
LACTATE	0,8 mmol/l	1.0 mmol/l	0.8 mmol/l

ICU – Intensive Care Unit; CRRT–continuous renal replacement therapy

SUMMARY

Time is of the essence in any case of cancer. It is crucial to make a diagnosis quickly and take the appropriate course of treatment. Considering patients with haematological malignancies, one must consider the possibility of TLS, which, untreated or diagnosed too late, may result in the patient's death.

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