In healthy population, uric acid comprises the major component of 10-20% of renal stones. Extreme hyperuricaemia is seen in cancer patients with tumour lysis syndrome (TLS) which is classically associated with haematological malignancies with rapid tumour growth rates such as acute lymphoid leukaemia and high grade lymphomas. Primary myelofibrosis (Agnogenic myeloid metaplasia-AMM) is a chronic myeloproliferative disease characterized by splenomegaly, a leukoerythroblastic blood picture, teardrop poikilocytosis and varying degrees of marrow fibrosis. Due to the increased extramedullary haematopoiesis, hyperuricemia may occur. However, TLS in patients with AMM is, according to the available literature, described just in one patient. In this paper we present a case of a 47-year-old male patient who was admitted to the hospital with symptoms of fatigue and small amount of urine, and clinical signs of plethora and enlarged spleen. The laboratory findings showed leuko-and erythrocytosis, increased levels of urea-BUN (32 mmol/l) and creatinine (766 mmol/l) as well as uric acid (920 mmol/l). The immediate abdominal ultrasound confirmed extreme splenomegaly, but also showed bilateral hydronephrosis of grade II-III with two stones in proximal part of right ureter and one in proximal part of left ureter as well as empty bladder. Stones were not seen on plain film. Since the patient was in complete anuria, with further rapid elevation of BUN and creatinine levels, bilateral ureteral stents were applied together with extensive hydration, urine alkalinization and administration of allopurinol which resulted in the complete recovery of kidney function. The bone marrow biopsy was also performed and histopathological diagnosis was: Hypercellular phase of AMM.

Key words: uric acid stones, ureteral obstruction, tumour lysis syndrome, myelofibrosis

INTRODUCTION

The formation of stones in urinary tract affects 5-10% of the population in Europe and North America1. In healthy population, uric acid comprises the major component of 10-20% of renal stones. Increase in frequency is seen in regions with hot weather such as Australia - about 17%. The majority of uric acid (urate) stones occur in men - 75%, with a peak frequency between 60 and 65 years of age. Uric acid is formed by the activity of xantine oxidase (XO) and is an end-product of the metabolism of endogenous (60%) and exogenous protein and purine nucleotides2. Uric acid has proinflammatory and proliferative effects on vascular smooth muscle and it has been found to inhibit both basal and vascular endothelial growth factor-induced nitric oxide production in endothelial cells3. Endothelial dysfunction represents a predominant early feature of atherosclerosis, diabetes, hypertension and heart failure and makes this population prone to cardiovascular complications and microthrombus formation4. The increase in uric acid is seen in numerous conditions - in patients with chronic diarrhoea syndrome and gouty diathesis that occurs in response to precipitation of monosodium urate monohydrate crystals in various tissues followed by an inflammatory response4, in healthy individuals with the high dietary intake of foods rich in nucleoprotein (meat, liver, kidney, legumes)2, and can be induced by drugs such as salicylate, chlorotiazide, pyrazinamid, angiotensin II, epinephrine and norepinephrine5.

Extreme hyperuricaemia is seen in cancer patients with tumour lysis syndrome (TLS) which occurs in the setting of rapid cell turnover or cellular death6 leading to a subsequent release of cellular breakdown products sufficient to overwhelm the excretory mechanism and the body’s normal functional capacity7. The urates most commonly found in urinary calculi are the ammonium hydrogen urate which is frequently accompanied by magnesium ammonium phosphate hexahydrate (struvite) and calcium oxalate oxalate monohydrate
Crystals of uric acid are precipitated when supersaturation with uric acid is high.

The important factors are high excretion of urate, a small urine volume and a low urinary pH. Infrared spectroscopy has been successfully used for stone composition analysis, but when the stone could not be analyzed, the correct conclusion can be made following this algorithm:

- Uric acid stones are radiolucent on a plain abdominal film and radio-opaque on CT
- Urinary pH is usually low
- Serum or plasma uric acid is high
- Stone fragments rapidly dissolve in tromethamine solution
- The urine sediment becomes orange or red-brown

The treatment options in patients with uric acid stones is pharmacological (XO inhibitors), but in the cases of the ureteric stones with large diameter (i.e. more than 7mm), with the high risk of pyonephrosis or urosepsis, when an adequate pain relief cannot be achieved or in the very rare cases of bilateral ureteral obstructon, the active stone removal is indicated.

**CASE REPORT**

A 47-years-old male patient was admitted to the hospital with the symptoms of fatigue, dyspnea on exertion, night sweats, nausea, muscle weakness, back pain and a small amount of urine. At the time of admission patient reported that he had had hard physical exertions for several days in high air temperature before the admission, and a 6-months history of hypertension treated with angiotenzin-converting enzyme (ACE) inhibitor and thiazide diuretic with normal laboratory findings done one month prior to the admission.

The physical examination demonstrated plethora, the thong was covered with white layer due to dehydration, and the admission vitals were: body temperature of 36.6°C, blood pressure of 140/90mmHg and heart rate of 90 beats/min. The electrocardiogram was unremarkable. He was without palpable cervical, armpit or inguinal lymphadenopathy. A liver edge was palpable on the right costal margin, but the spleen tip extended 12cm below the left costal margin.

The admission laboratory findings showed leukocytosis (WBC 11.8x10^9/l), increased haemoglobin (Hb 169 g/l) and haematocrit (Hct 0.53) with microcytosis (MCV 78.6 fl) and normal platelet count (Plt 311x10^9/l). The blood smear revealed immature forms of white blood cells with proportion of blasts less than 5%, several nucleated red blood cells, aniso-poikilocytosis with tear-drop cells. The liver function tests and the coagulation screening tests: thrombin time (TT), prothrombin time -PT (INR) and activated partial thromboplastin time (aPTT), as well as D dimer were within the normal ranges.

The levels of urea-BUN and creatinine were elevated (BUN-32 mmol/l, creatinine -766 mmol/l) as well as uric acid (920 mmol/l), lactate dehydrogenase (LDH) (1756 IU/l), and potassium (5.8mmol/l) while sodium, calcium and phosphate levels were normal.

The arterial blood gases showed pH 7.40, pO2 70mmHg and oxygen saturation 92%. The chest x-ray showed no active pulmonary disease.

The immediate abdominal ultrasound confirmed splenomegaly which maximal diameter exceeded ranges of the screen, but also showed bilateral hydrenephrosis of grade II-III with two stones in proximal part of right ureter and one in proximal part of left ureter as well as empty bladder (Figures 1, 2).

The stones were not seen on plain film. We concluded that bilateral obstructive uric acid calculus existed in the patient. As the patient was in complete anuria, with further rapid elevation of BUN and creatinine levels, the urgent cystoscopy was performed. As there were no pathological features found in the bladder, bilateral ureteral stents were applied. The first urinalysis performed immediately after kidney desobstruction revealed low pH 5.5, and the mass of amorphous urate crystals, bacteria and erythrocytes in its sediment which turned orange in room air.

Extensive intravenous hydration (150ml/h), urinary alkalization with intravenous 0.45% sodium bicarbonate solution and administration of allopurinol (300mg/day) by mouth followed the stents application. The applied therapy resulted in the constant decrease of the parameters of renal function, so the haemodialysis was not performed.

Four days later, values of BUN and creatinine turned to normal values together with normal diuresis. The urethral stents were removed. The computed tomography of abdomen displayed the extreme splenomegaly with cranio-caudal diameter 25cm, and the complete resolution of hydrenephrosis (Figure 3).

Then, the bone marrow biopsy was performed and histopathological diagnosis revealed the existence of chronic myeloproliferative disorder - Agnogenic myeloid metaplasia -AMM (Primary myelofibrosis) in hypercellulary phase.
Hyperuricaemia is one of the major signs or tumour lysis syndrome (TLS). TLS is a life-threatening condition characterized by massive and rapid destruction of tumour cells that leads to consecutive release of intracellular substances and their metabolites and further severe impairment of heart, kidney, muscle, brain and other organs. The cardinal signs of TLS are electrolyte abnormalities and renal failure. TLS is a direct result of chemotherapy, immunotherapy or radiotherapy. It is classically associated with acute lymphoid leukaemia, Burkitt’s and other high grade lymphomas i.e. haematological malignancies with high tumour growth fraction and rapid tumour growth rates, but TLS is also seen in some solid tumours. Increased purine metabolism leads to hyperuricaemia. Uric acid is normally filtrated by the glomerulus, partially reabsorbed in proximal tubuli and secreted in distal renal tubuli of the kidney. The rate of urate clearance is highly dependent on the glomerular filtrate flow rate. When dehydration is present, the glomerular filtrate flow rate is very low which may lead to subsequent ureteral obstruction. Urate nephropathy develops as a result of the acid conditions and the formation of urate crystals in the renal tubules and collecting ducts. It is seen that in low urine pH (about 5.0) uric acid is 13 times less soluble than it is at pH 7.0. According to the widely accepted classification system proposed by Razis et al. TLS can be divided into three grades depending on serum creatinine, potassium, phosphate and uric acid levels. TLS grade II (creatinine more than 2x upper limits of normal, potassium higher than 5.5 mmol/l) existed in our patient.

Acute spontaneous TLS (STLS) occurs prior to the initiation of cytotoxic therapies. Cases of STLC are rare, and are reported in highly aggressive lymphoid malignancies especially in the course of prolonged fever episode prior to treatment as the theoretical cause. Only a few cases of STLS in other tumours - acute myeloid leukaemia and solid tumours - germ cell tumour and adenocarcinoma of the lung have been published. The preexisting renal insufficiency, elevated LDH, the use of potential nephrotoxic drugs and bulky disease are proposed as the additional risk factors for STLS.

In Medline literature search (January 1966 - January 2009) we have found one case report of STLS and urinary tract obstruction. But, in paper presented by Naeije G. et al. the obstructive uropathy was subsequent to neoplastic infiltration of the bladder, which was not present in our patient. Primary myelofibrosis (Agnogenic myeloid metaplasia-AMM) is a chronic myeloproliferative disease characterized by splenomegaly, a leukoerythroblastic blood picture, teardrop poikilocytosis, varying degrees of marrow fibrosis, and extramedullary hematopoiesis. AMM remains an incurable disease. A conservative approach to management is generally accepted and therapeutic intervention is reserved just for patients with symptoms. Due to the increased extramedullary hematopoiesis, hiperuricaemia may occurs. In performed Medline search we have found only one report of STLS in an elderly patient with 18-month history of transfusion dependent AMM and moderate renal insufficiency. In our patient there was no evidence of preexisting renal failure and no anaemia. He had elevated LDH levels and extreme splenomegaly. Patients with AMML, according to revised 2008 World Health Organization (WHO) classification system for adult Chronic myeloid neoplasms and Mayo Prognostic Scoring System for AMM - one point each for haemoglobin g/dl, leucocyte count or 30 x10^9/l, platelet count or 450 x10^9/l or monocyte count or 10 x10^9/l, can be divided into three categories. Our patient was in low risk category patients with AMML. Within this category of patients, the existence of splenomegaly and elevated LDH levels are indication for introduction of drug therapy (hydroxiurea, thalidomide or lenalidomide).
Furthemore, the dehydration due to hard physical exer-
tions for several days in high air temperature before the
admission, and a 6-months history of hyper tension treated
with ACE inhibitor and thiazide diuretic were additional
existing risk factors in our patient.
In our case, the differential diagnosis for acute renal fa-
ure included STLS, pre-renal azothemia due to dehydr-
ation, ACE inhibitor and thiazide cytotoxicity and urinary
tract abstraction. Since the renal function was completely
recovered after the application of urethral stents and in-
travenous hyperhydration, urine alkalinization and allopur-
inol administration we have concluded that the STLS due
to previously undiagnosed and untreated AMML, together
with coexistence of other risk factors was the cause of
acute renal failure and extreme hyperuricaemia which lea-
ded to bilateral uric acid stones ureteral obstruction.

SUMMARY

OBOSTRANA URETERALNA OPSTRUKCIJA ZBOG
HIPERURIKEMIJE UZROKOVANE PRIMARNOM MI-
JELOFIBROZOM

Mokračna kiselina je glavna komponenta u oko 10-20%
svih burežnih kamena. Dijagnoza uratna kalkuloze se
može postaviti na osnovu sledenja kriterijuma: uratni ka-
menci se ne vide na standardnom rendgenskom snimku,
ali se mogu videti ultrazvučnim ili CT pregledom, pH uri-
na je nizak, koncentracija mokračne kiseline u serumu je
visoka, fragmenti kamena se brzo rastvaraju u rastvoru
mokravne kiseline, ali se mogu videti ultrazvučnim ili CT
pregledom. Kamenci se ne vide na standardnom rendgen-
skom snimku, bio je postavljen na osnovu sledećih kri-
terijuma: uratni kamenci su zapačeni u uretere, in-
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