ANURIA SECONDARY TO HOT WEATHER-INDUCED HYPERURICAEMIA: DIAGNOSIS AND MANAGEMENT

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Ann Saudi Med 2003;23(5):283-290

Background: There is little information on the management of anuria secondary to severe volume depletion or as a rare manifestation of heat stroke in areas of the world with very hot summers. We present our experience with hot weather-induced hyperuricaemia in Kuwait.
Patients and Methods: Patients presenting to our urology unit as an emergency during the hot summer months of April to October (average temperature 40-55°C) were suspected of having hot weather-induced anuria secondary to hyperuricemia if they had a history of working in the sun for 6 to 8 hours per day and a progressive decrease in urine output to complete anuria. The diagnosis was confirmed by demonstration of elevated serum creatinine and uric acid, ultrasound findings of normal kidneys, ureters, and bladder (KUB) or mild to moderate hydronephrosis, but no features of chronic renal disease and little or no urine in the bladder. Management consisted of emergency cystoscopy, retrograde pyelogram, ureterorenoscopy (URS), and 'J' stents followed by rehydration, oral allopurinol and urinary alkalinization.
Results: Twenty-nine patients (27 males and 2 females, mean age, 44.52±8.3 years) satisfied the diagnostic criteria for anuria secondary to hot weather-induced hyperuricaemia. Twenty-eight (97%) patients worked outdoors on construction sites. Six patients had small radiopaque calculi on plain KUB X-ray. During cytoscopy and URS, uric acid crystals were encountered in all patients in the ureters and bladder. Recovery of renal function was complete in 23/29 (79.3%) patients, while 4/29 (13.8%) had partial recovery and 2/29 (6.9%) had no renal recovery.
Conclusion: Hot weather-induced anuria secondary to hyperuricaemia is a complication of severe dehydration. Effective treatment will result in successful resolution of this rare but reversible cause of acute renal failure in about 80% of cases. Ancillary treatment methods like haemodialysis or the use of PCN can be safely avoided in the majority of the patients. However, rehydration alone may be insufficient treatment in these patients.

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Accepted for publication
March 2003

Key words: hot weather, anuria, hyperuricaemia, uric acid nephropathy, 'J' stents.

Uric acid is the end product of catabolism of nucleic acid and purines in humans. Although the majority of mammals catabolize purines to the soluble end product allantoin, some humans excrete the less soluble urate because they lack the enzyme uricase. Several factors influence the renal handling of urate. Physiologically, the major factors that modulate urate excretion are tubular fluid pH, tubular fluid flow rate and renal plasma flow. Hyperuricaemia develops because of over-production or impaired renal excretion of uric acid. Over-production of uric acid occurs because of a secondary increase in purine synthesis due to certain enzyme deficiencies, increased or rapid turnover of tissue nucleic acid (as in myeloproliferative disorders, carcinomatosis and chronic haemolytic anaemia).[1-4] Impaired renal excretion of uric acid occurs when there is reduction in fractional urate clearance (e.g. in hypertension, sickle cell anaemia, increased organic acids as in exercise), or reduction in glomerular filtration (e.g. volume depletion, nephrogenic diabetes insipidus) or reduction in functional renal mass (e.g., chronic renal failure).[3] Acute uric acid nephropathy is a disorder in which there is an abrupt deterioration in renal function due to deposition of urate and uric acid crystals within the kidney substance and the collecting system at concentrations exceeding super saturation. Precipitating factors include infections, dehydration, and fever, in each of the above-mentioned states.[5]

Patients with hyperuricaemia may develop three types of renal lesions. The first type is progressive renal insufficiency in which monosodium urate crystals deposit in the interstitial parenchyma. The second type is uric acid nephrolithiasis in which uric acid precipitates under appropriate conditions. The third type is the less well-recognized acute uric acid nephropathy in which uric acid crystals can obstruct the collecting system and the patient can present in acute renal failure.[6] Whereas the literature

contains a number of papers describing the management of acute uric acid nephropathy in conditions such as in lympho- or myeloproliferative disorders or during cytotoxic drug usage.[4-7] There is little information on the management of this potentially life threatening condition in patients presenting with anuria secondary to severe volume depletion or as a rare manifestation of heat stroke in areas of the world with very hot summers. We present our experience in managing this clinical entity in Kuwait, a country in the Arabian desert where average temperatures in the summer months of April to October are between 40 and 55^{0}C.

Patients and Methods

This was a prospective study, over a 42-month period (April 1998 to October 2001). Patients presenting as an emergency to our urology unit during the hot summer months of each year, with hot weather related anuria, were included in the study. Inclusion criteria were a history at presentation of minimal or no urine production in the preceding 12 to 36 hours in the summer months, laboratory finding of high serum creatinine and hyperuricaemia. Patients often appeared toxic, dehydrated, and restless. Most patients were manual workers, mostly in the construction industry, working outside for 6 to 8 hours in the hot summer months in Kuwait with average outside temperatures varying between 40^{0}C and 55^{0}C. Patients were excluded if they had lympho- or myeloproliferative disorders, were receiving any form of chemotherapy or had other known causes of hyperuricaemia, e.g., previous history of gout, polycythaemia, morbidly obese patients or alcoholics.

Physical examination confirmed dehydration and a confusional state. Small quantities of dark concentrated urine were obtained following urethral catheterization. Plain X-ray of KUB showed small radiopaque calculi in some patients. Ultrasound of the KUB showed various grades of obstructed ureters and kidneys, but no large urine volume in the bladder and no features suggestive of chronic renal disease. The mainstay of diagnosis in these patients in addition to the above features was the finding of high serum uric acid (>400 µmol/L; normal 200-400 µmol/L), high serum creatinine (>150 µmol/L; normal 80-120 µmol/L), or slightly elevated or normal serum potassium with mild derangement, or near normal levels of other electrolytes.

Our management strategy consisted of (a) either emergency cystoscopy, retrograde pyelogram, ureterorenoscopy (URS), flushing of uric acid crystals from the ureters followed by insertion of 'J' stents, occasional Dormia basket for extraction of small uric acid stones and urethral catheterization, or (b) if the patient was unfit for general anaesthesia, or if retrograde 'J' stenting failed, then a percutaneous nephrostomy (PCN) tube was inserted. Other ancillary treatment procedures included adequate hydration using I.V. fluids, oral allopurinol tablets, use of sodium bicarbonate or one-sixth molar lactate to alkalinize the urine and treatment of concurrent renal or ureteric calculi using lithotripsy. Tiny crystals obtained from the ureters and bladder were sent for biochemical analysis. Patients who did not improve on the above regimen within 48 to 72 hours were subjected to haemodialysis. A progressive rise in serum creatinine and hyperkalaemia were specific indications for haemodialysis.

Our criteria for successful resolution of anuria consisted of rapid improvement in sensorium, adequate hourly urine output (>50 mL/hr) within 12 hours of 'J' stenting, and a gradual normalization of serum electrolytes, creatinine, urea and uric acid levels on the above treatment protocol. The degree of renal function recovery was classified as complete recovery if serum creatinine fell below 120 µmol/L, or partial recovery if it was between 120 and 250 µmol/L, and no improvement if serum creatinine stabilized above 250 µmol/L. In addition, creatinine clearance was measured in patients with partial or no renal function recovery on a regular basis to establish any changes in renal function recovery with time.

Results

Between April 1998 and October 2001 (42 months), 29 patients (27 males and 2 females), with mean age of 44.52 years (SD±8.3) satisfied the above diagnostic criteria of anuria secondary to hot weather induced hyperuricaemia. All patients presented with anuria either alone (n=3; 10.3%) patients or associated with different degrees of loin pain, nausea, vomiting and varying degrees of dehydration (n=26; 89.7%) patients. Twenty-eight (97%) patients were manual workers working mostly outdoors on construction sites.

Twenty-five (86.2%) patients were admitted during the summer seasons. The remaining 4 (13.8%) patients were admitted during the other months of the year (2 in November and 2 in March). Twenty (69%) patients had bilateral kidneys while 9 (31%) patients had solitary kidneys. The few milliliters of urine collected by urethral catheters showed acidic urine and the presence of uric acid crystals in all the patients. All patients had elevated serum creatinine (mean±SD, 488±32 µmol/L; normal 80-120 µmol/L) and serum uric acid (570+60 µmol/L; normal 200-400 µmol/L). The serum potassium was above normal in 12 (41.4%) patients; the mean serum potassium in the 12 patients was 5.9 (SD±2.3) (normal 3.5-5.3 µmol/L).

Plain KUB X-ray showed tiny radiopaque calculi in the pelvis or ureter in 5 (17.2%) patients. The calculi were big enough to cause obstruction in only 3 (10.3%) patients. Ultrasound of KUB revealed near-empty bladders, different degrees of pelvi-calyceal dilatation, or mild to moderate hydronephrosis and kidney stones in 5 (17.2%) patients. Two of 3 patients with significant ureteric calculus had mild to moderate hydronephrosis on ultrasound of KUB. No patient had bilateral radiopaque ureteric calculi.

TABLE 1. Recovery of renal function after intervention in patients with acute renal failure secondary to hyperuricaemia depending on whether patients had bilateral or solitary kidneys.

No. of kidneys	No. of patients	Degree of renal function recovery* Full n	Full %	Partial n	Partial %	None n	None %
Bilateral	20	17	85	2	10	1	5
Unilateral	9	6	66.7	2	22.2	1	11.1
Total	29	23	79.3	4	13.8	2	6.9

**Classification of renal function recovery depended on post treatment serum creatinine, if serum creatinine is: <120 umol/L=full recovery; >120<250 umol/L=partial recovery; >250 umol/L=no recovery.*

TABLE 2. The effect of the presence of systemic diseases on renal function recovery.

Systemic Disease*	No. of patients	Degree of renal function recovery* Full n	Full %	Partial n	Partial %	None n	None %
Absent	17	16	94.1	0	01	1	5.9
Present	12	7	58.3	4	33.3	1†	3.5

**Systemic diseases include diabetes mellitus, hypertension or a combination of the 2 diseases; †serum uric acid also remained high in this patient.*

Of the 29 patients, 26 (89.7%) had emergency endoscopic procedures as indicated above. One (3.5%) patient required haemodialysis and 2 (7%) patients underwent primary PCN tube insertion due to a critical electrolyte imbalance that made them unfit for general anaesthesia. Retrograde pyelogram performed in 26 (89.7%) patients revealed filling defects due to ureteric stones in only 6 (20.7%) patients. URS was attempted in 26 (89.7%) patients. Ureteric stones were extracted in 4 (13.8%) patients and the stones were pushed back into the renal pelvis in 2 (6.9%) patients. At endoscopy, numerous fine yellowish shining crystals were seen flowing down into the urinary bladder and a very concentrated urine containing fine debris was seen in all patients. 'J' stents were successfully inserted in 24 (82.80%) patients. Two (6.9%) patients could not be stented due to technical difficulties. These 2 (6.9%) patients had a PCN tube inserted successfully.

Twenty-three (79.3%) patients had complete recovery of renal function within 7 days of initiating treatment. Four (13.8%) patients had partial recovery over a period of 18 to 24 days, but there was no improvement in two (6.9%) patients 4 weeks after initiating treatment (Table 1). Of the six (20.7%) patients who did not recover completely, only one (3.5%) did not have concurrent general systemic disease, one (3.5%) had diabetes mellitus and the remaining 4 (13.8%) patients had both diabetes mellitus and hypertension (Table 2). In addition, two (6.9%) of these 6 (20.7%) patients had solitary kidneys. One of the two patients who had no improvement in renal function had a single kidney, diabetes mellitus and hypertension.

With our treatment regimen, 28 of 29 (97%) patients had normal serum uric acid within two weeks of initiating treatment. The uric acid level remained high in one of the two patients whose renal function did not improve and who required haemodialysis. Seven (24%) patients had lithotripsy for significant renal or ureteric calculi. Chemical analysis of the extracted stones/crystals revealed uric acid crystals in all patients.

Discussion

Acute uric acid nephropathy is an obstructive nephropathy characterized by deposition of uric acid crystals in the collecting tubules. There are two main explanations for renal failure secondary to acute hyperuricemia—the intra-renal precipitation of crystals and ureteral obstruction.[1,8] Intrarenal precipitation of uric acid was first described by Bedrna and Polcak (1929).[9] They postulated that precipitation occurs spontaneously due to increased cell turnover or as a complication of chemotherapy leading to rapid cell destruction, as seen in leukemias and lymphomas. This type of renal failure is characterized by acute onset of hyperuricaemia, which might lead to diffuse intrarenal precipitation of crystals and subsequent anuria. These causes of hyperuricaemia appear to be more common in Europe and America,[1] but are very rare in our experience in the Arabian Gulf. This may be due to smaller numbers of patients with cancer in our community on an age-adjusted basis compared to Europe and America.

In our series, of 29 patients with acute onset anuria, the association with ureteric colic in most patients indicated some degree of ureteral obstruction. It would appear that moderate hyperuricaemia allows more time for actual stone formation or uric acid crystal aggregation, which may be enhanced by hyperacidic urine and oliguria induced by dehydration.[1,6]

In our series, no patients had either malignancy or a history of being on chemotherapy. However, there were 4 patients with hypertension, 2 with diabetes mellitus and 6 patients had both diseases. These systemic diseases or their complications may be associated with hyperuricaemia. All the patients with acute renal failure were mostly manual workers who admitted to working outdoors for 6 to 8 hours per day in the hot summer months of Kuwait. Only one patient was an office worker. He too admitted to prolonged exposure to hot weather prior to presentation to us.

Our experience indicates that acute renal failure due to hyperuricaemia secondary to volume depletion is a treatable condition, and physicians working in the Arabian Gulf or other

desert regions of the world should be aware of this presentation of heat-related illness during the summer months. In view of recently reported global warming even temperate regions of the world may not be exempt, and during unusually warm or hot summers, physicians should have a high index of suspicion for this condition.

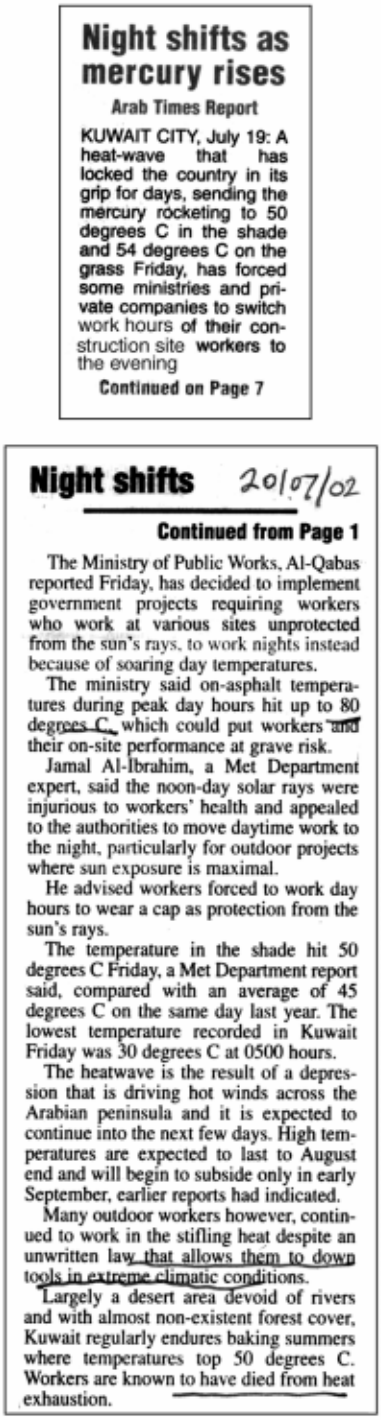
Our management strategy appears justified because in all patients with this disorder, cystoscopy and URS revealed the presence of uric acid crystals in urine in the bladder and ureter. These crystals were obviously causing some degree of obstruction of the ureter. However, since the patients were also volume depleted, there may not have been significant dilatation of the PCS or hydronephrosis. Treating the patients by rehydration alone (as is advocated for patients with acute uric acid nephropathy due to malignancies or following chemotherapy) may not be applicable to patients with acute uric acid nephropathy secondary to hyperuricaemia where there are uric acid crystals in the collecting system and ureters causing physical obstruction. Rehydration alone may not get rid of uric acid crystals and may lead to complete obstruction of the ureters.[10,11] Our experience also indicates that patients with certain pre-existing systemic diseases like diabetes mellitus or hypertension or those with single kidneys, deserve more aggressive treatment to achieve complete recovery of renal function.

Chemical analysis of the extracted stones revealed pure uric acid crystals. Many of the fine crystals seen during the endoscopic procedures proved to be uric acid crystals by microscopic examination. However, the presence or absence of uric acid crystals in the urine alone does not appear to be a reliable test for diagnosing acute uric acid nephropathy.[8]

Complete recovery of renal function was evident in 23 patients (86%), and partial recovery was evident in 5 patients (11%) of whom 3 had both diabetes mellitus and hypertension; only one had diabetes mellitus. There was no significant improvement in one patient (4%) who had diabetes mellitus and hypertension. These results suggest that most of the renal units of those who did not have complete recovery (6 patients, 14%) had been insulted to some degree by the underlying systemic diseases, and they might have had asymptomatic hyperuricaemia. That is, they were suffering from both renal and obstruction effects.

Haemodialysis may be mandatory in cases of intrarenal obstruction to clear up the uric acid crystals and to prevent permanent renal insufficiency.[12] Haemodialysis was indicated only in one of our patients due to severe electrolyte imbalance. In the same patient, uric acid levels remained high.

The management of acute uric acid nephropathy secondary to leukemia or lymphoma or other myeloproliferative conditions is quite different from that secondary to heat stroke. In the former, the complication can be anticipated and preventive measures like the use of



Night shifts as mercury rises

Arab Times Report

KUWAIT CITY, July 19: A heat-wave that has locked the country in its grip for days, sending the mercury rocketing to 50 degrees C in the shade and 54 degrees C on the grass Friday, has forced some ministries and private companies to switch work hours of their construction site workers to the evening

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Night shifts 20/07/02

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The Ministry of Public Works, Al-Qabas reported Friday, has decided to implement government projects requiring workers who work at various sites unprotected from the sun's rays, to work nights instead because of soaring day temperatures.

The ministry said on-asphalt temperatures during peak day hours hit up to 80 degrees C, which could put workers and their on-site performance at grave risk.

Jamal Al-Ibrahim, a Met Department expert, said the noon-day solar rays were injurious to workers' health and appealed to the authorities to move daytime work to the night, particularly for outdoor projects where sun exposure is maximal.

He advised workers forced to work day hours to wear a cap as protection from the sun's rays.

The temperature in the shade hit 50 degrees C Friday, a Met Department report said, compared with an average of 45 degrees C on the same day last year. The lowest temperature recorded in Kuwait Friday was 30 degrees C at 0500 hours.

The heatwave is the result of a depression that is driving hot winds across the Arabian peninsula and it is expected to continue into the next few days. High temperatures are expected to last to August end and will begin to subside only in early September, earlier reports had indicated.

Many outdoor workers however, continued to work in the stifling heat despite an unwritten law that allows them to down tools in extreme climatic conditions.

Largely a desert area devoid of rivers and with almost non-existent forest cover, Kuwait regularly endures baking summers where temperatures top 50 degrees C. Workers are known to have died from heat exhaustion.

Figure 1. A clip from a local newspaper illustrating government policy in Kuwait regarding working outdoors by manual workers once the outside temperature is above 50°C.

allopurinol, urine alkalinization and hydration a few days before induction of chemotherapy can minimize the complication.[3] The latter presents as an acute emergency with anuria and preventive measures are not usually feasible. Moreover, urinary alkalinization using intravenous sodium bicarbonate or one-sixth molar lactate can take up to one week before any obstructing uric acid can be dissolved.[11] For patients with heat-related disorder and anuria, waiting for one week for the dissolution of ureteric uric acid crystals will not only increase the mortality rate, but will also increase morbidity rates like fluid overload since large volumes of molar lactate are required to dissolve uric acid calculi.[10,11]

As illustrated in the clip from one of the local newspapers in Kuwait (Figure 1), it is a policy of the Government of Kuwait for outdoor workers to "down tools" once the outdoor temperature is above 50°C. Furthermore, the government encourages employers to ask outdoor workers to work mostly in the cooler evening or nights (average temperature 30-40°C!). However, it would appear that most manual workers or some employers are not aware of this law or are unaware of the temperature to which they are exposed. Obviously, adhering to this law would reduce the incidence of this disorder in our part of the world.

Physicians working in hot regions of the world should have a high index of suspicion for hot weather-induced hyperuricaemia or acute uric acid nephropathy in a patient presenting with any combination of exposure to the sun, anuria, high serum creatinine and high uric acid. This potentially life-threatening clinical entity can be safely, effectively, rapidly and inexpensively managed by clearance of uric acid crystals and other debris from the ureter, followed by 'J' ureteric stenting, intravenous rehydration, the use of allopurinol and alkalinization of urine. Hemodialysis is rarely indicated in this condition. Complete recovery of renal function can be expected in about 80% of patients on the above regimen, even in the presence of underlying systemic diseases as long as the kidneys have not been functionally compromised. However, a partial or delayed response to treatment may occur in patients with compromised kidneys, due to diabetes, hypertension or infections. Whether early haemodialysis in such patients will produce rapid or enhanced recovery of renal function requires further study.

References

1. Al Sarraf D, Reese L. Management of acute renal failure due to marked hyperuricemia. *CMA Journal.* 1972;166-167.
2. Conger JD, Falk SA: Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. *J Clin Invest.* 1977; 59:786-793.
3. Conger JD: Acute uric acid nephropathy. *Med Clin North America* 1990;74 (4):859-871.
4. Steele TH. Hyperuricemic nephropathies. *Nephron*. 1999;81(Suppl. 1): 45-49.
5. Cameron JS, Moro F, Simmonds HA. Gout, uric acid and purine metabolism in paediatric nephrology. *Pediatr Nephrol.* 1993;7(1):105-118.
6. Kjellstrand CM, Campbell DC, Von Hartitzch B, Buselmeier TJ. Hyperuricaemic acute renal failure. *Arch Intern Med.* 1974; 133:349-359.
7. Pui CH, Jeha S, Irwin D, Camitta B. Recombiant urate oxidase (rasburicase) in the prevention and treatment of malignancy – associated hyperuricemia in paediatric and adult patients: results of compassionate – use trial. *Leukemia.* 2001;15(10):1055-1509.
8. Kelton J, Kelley WN, Holmes EW. A rapid method for the diagnosis of acute uric cid nephropathy. *Arch Intern Med.* 1978;138:612-615.
9. Bedrna J, Polcak J. Akuter harnleiterverschluss nach Bestrahlung chronischer leukemeim mit roentgenstrahlen. *Med Klin.* 1929;25: 1700-1701.
10. Lewis RW, Roth JK Jr, Polanco EJ, Roberts JA. Molar lactate in the management of uric acid renal obstruction. *J Urol* .1981;125:87-93.
11. Kursh ED, Resnick MI. Dissolution of uric acid calculi with systemic alkalinization. *J Urol.* 1984;132:86-87.
12. Allen AC. Acute lobular (membranoproliferative) glomerulonephritis with hyperuricaemia and obstructive uric acid nephropathy. *AJCP.* 1975; 65:109-120.