CASE REPORT

Acute tubular necrosis (ATN) presenting with an unusually prolonged period of marked polyuria heralded by an abrupt oliguric phase

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SUMMARY

A 50-year-old African-American man presented with acute tubular necrosis (ATN) secondary to hypotension from non-typhoid Salmonella gastroenteritis and bacteraemia. The oliguric phase lasted only 24 h followed by prolonged polyuria for 20 days, with urine output in excess of 16 L/day at maximum. As indexed in PubMed this is only the second published case of this nature since 1974, in which an abrupt oliguric phase of 24 h or less heralded prolonged polyuria in ATN. The diagnosis is challenging as fractional excretion of sodium early in the clinical course and rapid normalisation of serum creatinine with intravenous fluids (IVF) may point towards prerenal azotaemia resulting in a premature discharge from hospital. Patients with an abrupt oliguric phase may suffer a secondary renal insult from the profound fluid loss that is to follow and may need inpatient monitoring with supplemental IVF to prevent deleterious outcomes.

BACKGROUND

Acute tubular necrosis (ATN) is the second most common cause of acute kidney injury (AKI) in the hospital setting after prerenal azotaemia. It commonly occurs in three clinical stages (initiation, maintenance and recovery) and is associated with polyuria in the recovery phase. The duration of both the oliguric (maintenance) and the diuretic phase of ATN is unpredictable, lasting from days to weeks, with the average durations of oliguria and diuresis being 11.8 and 12 days, respectively.[1] Further, the urine output (UOP) rarely exceeds 7–8 L in 24 h. This case report examines the role of a short oliguric phase (24 h or less) in the potentiation of prolonged, marked polyuria in the recovery phase. The early recognition of AKI in such high-risk patients with Gram-negative septicaemia or other hypoperfused states is imperative. Intravenous fluids (IVF) hydration to match ongoing losses early in the course of renal injury can prevent a secondary renal insult and offset progression to chronic renal failure or dialysis dependence.

CASE PRESENTATION

A 50-year-old African-American male truck driver presented with 5 days of nausea, vomiting and non-bloody diarrhoea. His medical history was remarkable for dyslipidaemia, hypertension and hypothyroidism status post-thyroidectomy for Graves' disease. He was unable to tolerate solids or liquids and became increasing lethargic over this time. He also noted that he had not passed any urine on the day he presented to hospital. His urine was non-bloody, non-frothy and dark yellow on the day prior. He had no history of significant alcohol use, cigarette smoking or illegal drug use. He was in a monogamous relationship. Both of his parents had type 2 diabetes mellitus with no other significant family history. His only medication was levothyroxine 0.25 µg daily but he had poor compliance and follow-up owing to lack of insurance. There were no sick contacts or travel history. He ate a beef hamburger prior to the onset of symptoms. On examination, the patient appeared lethargic but was in no gross cardiorespiratory distress. He was tachycardic, non-oedematous and had delayed capillary refill. He was febrile to touch with a maximum recorded temperature of 102.5°F (39.2°C). His only other significant finding was the presence of hyperactive bowel sounds.

INVESTIGATIONS

In view of depressed UOP and elevated serum creatinine on presentation, a renal ultrasound was performed and this excluded obstructive uropathy with normal-sized kidneys (approximately 11 cm). Urinalysis and microscopy at presentation revealed protein 70 mg/dL, trace leucocytes, negative nitrite and moderate blood with 10 red cells/high-power field, one hyaline cast and two squamous epithelial cells. No red or white cell casts were seen. pH was 5.0 with specific gravity of 1.011. Glycated haemoglobin (HbA1c) confirmed de novo diabetes at a value of 7.3%. His serum thyroid-stimulating hormone (TSH) was elevated at 38.8 µIU/mL. His complete blood count on admission revealed 6500/mm^3 white cells, 17.5 g/dL haemoglobin concentration (with haematocrit of 50.8) and 265 000/mm^3 platelets. The urine sodium and creatinine concentrations on admission day 1 were measured at 15 mmol/L and 211 mg/dL, respectively, which gave a calculated fractional excretion of sodium (Fe Na) of 0.3%. Serum creatine kinase (CK) was elevated at 3830 U/L. The trend of relevant values for renal function panel results while inpatient are seen in table 1.

DIFFERENTIAL DIAGNOSIS

In a patient presenting with nausea and vomiting with clinical signs of dehydration with elevated serum creatinine, the leading differential was AKI secondary to prerenal azotaemia. This was

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Table 1 Values for serum Crea, serum Na, Osm Calc, total intake (both oral and intravenous over 24 h) and UOP as they varied with the LOS

LOS (days)	Serum Crea (mg/dL)	Serum Na (mg/dL)	Osm Calc (mOsm/kg)	Total intake* (L)	UOP (L/24 h)
1	4.64	131	280	2.51	0.48
2	5.70	130	283	2.45	3.15
3	7.42	127	290	2.64	4.14
4	5.73	131	292	3.76	4.55
5	4.56	134	293	5.15	7.15
6	3.50	136	290	3.15	6.25
7	2.91	139	290	4.98	5.25
8	2.44	139	286	4.28	6.45
9	2.20	138	283	3.75	7.45
10	2.11	142	289	5.75	7.55
11	1.97	140	284	5.61	8.53
12	1.90	141	284	6.22	10.15
13	*1.73*	*142*	*285*	*4.56*	*10.50*
14	1.89	144	288	9.50	11.65
15	1.74	142	284	8.75	12.75
16	1.64	141	283	10.51	16.25
17	1.57	138	277	6.65	10.75
18	1.57	140	281	8.21	9.85
19	1.49	141	282	4.53	5.11
20	*1.52*	*137*	*275*	*3.21*	*3.62*
21	*1.51*	*139*	*279*	*2.85*	*3.12*
22	*1.64*	*138*	*280*	*2.41*	*2.60*

Italicised data represents days when no intravenous fluid was given.
*This data represents documentation as noted in the nursing and electronic medical record. The patient was advised to consume fluids *ad lib* and this may result in an underestimation of total daily fluid intake.
Crea, creatinine; LOS, length of stay; Na, sodium; Osm Calc, calculated osmolality; UOP, urine output.

consistent with Fe Na <1% measured at presentation. However, this does not explain the polyuria that followed, and given the hypotension on admission, ischaemic ATN was considered the primary aetiology. In cases of postischaemic ATN where urine electrolytes are measured early in the disease course, the Fe Na may be falsely low.[2] These patients are either making the transition from prerenal disease to postischaemic ATN or remain ischaemic with established ATN. In the latter scenario, most of the UOP may be coming from a small number of functional nephrons. A low Fe Na in the setting of continued ischaemia is appropriate and attainable since tubular function remains intact in these nephrons. Further, urine biochemistry has been shown to be unreliable in ATN secondary to septic AKI[3 4] and in animal models of Gram-negative septic AKI.[5] This is in keeping with the patient's presentation of Salmonellosis.

The association between Salmonella non-typhi and rhabdomyolysis as a precipitant of AKI has been well described in the literature.[6] However, this was largely excluded by a serum CK that trended to normal in less than 3 days with a peak value of 3830 U/L at presentation in the setting of poorly controlled hypothyroidism, which can typically cause an elevated CK of 2000 U/L or greater.[7] Urinalysis revealed no myoglobinuria and there was neither a history of muscle weakness or cramps nor red-brown urine. The clinical presentation of hypotension, oliguria (UOP of <500 mL in 24 h) and polyuria (UOP >3 L in 24 h), despite the absence of pathological examination, is most compatible with ATN.

Endocrine aetiologies of polyuria were also considered. The patient's newly diagnosed, asymptomatic diabetes was associated with HbA1c was only mildly elevated at 7.3% with inpatient glucometer readings averaging <150 mg/dL. It was unlikely that hyperglycaemia-induced osmotic diuresis was the cause of this patient's polyuria. While inpatient, the patient received levothyroxine at a maintenance dose of 75 µg daily. Thyrotoxicosis in animal models has been shown to downregulate aquaporin receptors resulting in polyuria.[8] The correction of his hypothyroid state may have enabled him to better excrete a solute-free water load[9] but does not explain the marked polyuria that ensued rather abruptly after less than 24 h of oliguria. Diabetes insipidus (DI), while implicated in polyuria, was unlikely since there was no history of psychiatric illness or medications that could implicate nephrogenic DI such as lithium, forscarnet or cidofovir. Central DI may present with abrupt polyuria but Head CT was negative for any acute infarct, pituitary anomaly or hypoxic brain injury.

TREATMENT

The patient completed 14 days of intravenous ceftriaxone while inpatient with bacterial clearance confirmed with negative blood cultures prior to discharge. De novo diabetes was managed with a low-dose insulin sliding scale and the American Diabetes Association (ADA) diet. Maintenance normal saline at a rate of 150–200 cc/h was administered with intermittent boluses to match ongoing losses. The patient was encouraged to drink fluids *ad lib*. In view of lethargy on presentation and elevated TSH, levothyroxine was given at a replacement dose of 75 µg daily.

OUTCOME AND FOLLOW-UP

The patient established a new baseline serum creatinine in the range 1.49–1.64 mg/dL in the past 3 days of admission with UOP under 3 L in 24 h. He was discharged to follow-up at free clinics in the area while awaiting insurance approval. He was counselled on a low salt, diabetic diet with advice to check his renal function panel once he had an established general practitioner. The decision to start an ACE inhibitor and metformin was deferred to his new physician. A 6-month postdischarge follow-up phone call was made and the patient voiced no acute symptoms. He was compliant with a statin for dyslipidaemia and levothyroxine at his discharge dosage. He was once again advised to establish follow-up and to have his blood pressure and renal function checked at a charity clinic in the interim.

DISCUSSION

Bacteraemia secondary to Salmonella is relatively uncommon in immunocompetent patients.[10] This patient was noted to have elevated finger stick glucose on the morning of admission (fasting) and his body habitus was consistent with truncal obesity. An HbA1c of 7.3% confirmed the suspicion of diabetes (there was no history of polyuria, polydipsia, nocturia or weight loss), a well-known risk factor for Salmonellosis.[10] Diabetes is also a risk factor for pre-existing tubular injury that would predispose to a more severe presentation of ATN. The same applies to chronic hypertension. The patient in this case was diagnosed with hypertension 5 years earlier but was not on any medication for the past 3 years.

In 1974, Hsu *et al* described a case of marked polyuria in ATN secondary to hypotension from severe haemorrhage into the gastrointestinal tract seen in a 52-year-old Caucasian woman. Noteworthy is that this case noted a very short period of oliguria lasting only 24 h followed by marked prolonged polyuria (as high as 45 L in 24 h).[11] The underlying hypothesis

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in this case was that unusually prolonged and massive diuresis was explained by the short period of oliguria. The patient in this case was known to have congestive heart failure and pulmonary emboli. These are both risk factors to decreased renal perfusion and oxygen supply predisposing towards ischaemic injury from hypotension and ATN. In the present case, a similar presentation occurred since the patient only noted decreased UOP on the day of presentation to hospital and was oliguric for the first 20 h of admission. This was followed by an impressive 20 day period of polyuria. In both cases hypotension from haemorrhage, and in this case Gram-negative septicaemia, were the mediators of the initial renal insult.

This patient's body weight was 83.9 kg and an appropriate UOP would be approximately 2 L/day (1 mL/kg/h). His underlying diabetes was never symptomatic prior to admission (no nocturia, polyuria or polydipsia reported) and further his serum glucose never exceeded 250 mg/dL for the entire admission with most values in the range of 100–160 mg/dL. This made the differential of osmotic diuresis unlikely. The correction of his underlying hypothyroidism with levothyroxine may have enhanced excretion of a solute-free water load. However, this dosage is very unlikely to have overcorrected him into a hyperthyroid state that, in animal studies, is strongly associated with polyuria.[9]

As documented in table 1, there is a relatively rapid return of glomerular filtration rate (GFR; as estimated from the serum creatinine) to baseline compared with the normalisation of UOP. This was also noted by Hsu *et al* raising the importance of the duration of the oliguric period in protecting against fluid and electrolyte loss. Sodium excretion was monitored at that time and that manuscript was able to demonstrate a prominent natriuresis in addition to diuresis. No comment can be made on sodium excretion in the present case as urinary sodium was not routinely measured on a daily basis.

This relatively rapid restoration of GFR in the setting of a short oliguric phase appears to indicate that immature nephrons are faced with an insuperable filtrate and solute load. This defect in reabsorptive capacity was demonstrated grossly on Day 13 of admission when the patient was given a trial of no IVF and still had a UOP of >10 L with clinical signs of dehydration (thirst, prolonged capillary refill and orthostatism) the following day (see italicised portion of table 1). Water restriction testing by Hsu *et al* also suggested abnormal tubular reabsorptive function that would neither decrease UOP nor concentrate the urine appropriately. Studies have shown that although tubular regeneration initiates soon after ischaemic or nephrotoxic insults in ATN,[12 13] the functional maturation of tubules may lag even after structural maturation appears complete.[14 15]

The depressed renal cortical blood flow in the oliguric phase of ATN[16] spares the immature nephrons while cellular regeneration is taking place. It is reasonable to infer that an oliguric phase of the standard duration will essentially prevent marked fluid and electrolyte losses during the polyuric phase when the GFR has normalised. When this relationship between functional maturation of the nephron and return of the GFR is lost, as per the two cases mentioned, a marked diuretic phase can ensue. Further research into short oliguric phase ATN must be performed to confirm this hypothesis as the data on this subject is sparse at best.

In conclusion, it is important to recognise that ATN can present with a short oliguric phase. The underlying mechanism of this is not defined as, to date, this is only the second reported case on the subject. Urine biochemistry can mislead physicians into a diagnosis of prerenal azotaemia when urine samples are taken early in the disease course or in cases of septic ATN.[3–6] It is important that patients presenting in this manner are not prematurely discharged as secondary renal insults from ongoing fluid losses in the polyuric phase may lead to worsening renal function or dialysis dependence. There is no standardised consensus on safe hospital discharge for the patient with polyuria, but it is reasonable to suggest that a patient may be allowed home if oral intake can match ongoing urinary losses or if UOP is <3 L in 24 h.

Learning points

- In cases of septic acute tubular necrosis (ATN) or if urine samples are taken early in the course of ATN, urine biochemistry and fractional excretion of sodium may falsely be indicative of prerenal azotaemia.
- ATN is typically associated with an average oliguric phase of 11.8 days, but it is possible that the oliguric phase may last less than 24 h.
- In patients who present with such a short oliguric phase of ATN (especially 24 h or less), a prolonged period of marked polyuria may ensue.
- Physicians must be wary of this anomalous presentation as premature discharge prior to the resolution of polyuria can lead to secondary renal insults and worsening renal function.
- There is no established consensus on this subject but it is suggested that a patient who is recovering from polyuria may be safely discharged when oral intake matches ongoing urinary losses or if urine output is <3 L in 24 h.

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