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The Case | Metabolic alkalosis in a patient with cystic fibrosis

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Table 1 | Blood and urinary blood tests

	Blood tests									Arterial blood tests				Urine					
	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Bicarbonate (mmol/l)	BUN (mg/dl)	Crea (mg/dl)	Corrected calcium (mg/dl)	Magnesium (mg/dl)	Phosphate (mg/dl)	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)	Bicarbonate (mmol/l)	pH	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	FeMg (%)	TTKG
Normal range	136–146	3.5–5.5	97–105	23–30	7–20	0.5–0.9	8.7–10.2	1.5–2.3	2.5–4.3	7.35–7.45	32–45	72–104	21–28						
Day 0	137	3.6	97	35	13	0.6	9	2.4	3.2	7.35	70	134	38						
Day 7	136	2.7	83	43	4	0.4	8.4	1.1	1.1	7.57	59	111	54.2	7	157	17	174		4.33
Day 10	129	2.5	73	39	6	0.4	6.5	0.5	1.6	7.58	51	73	47.7	7.5	119	75	191	57	17.2
Day 14	136	2.9	79	45	3	0.4	7.6	1.6	2.7	7.55	61	47	53.8	7	121	30	150	68	10.3

Abbreviations: BUN, blood urea nitrogen; Crea, creatinine; TTKG, transtubular potassium gradient.
Day 7: Onset of the metabolic alkalosis and other electrolytes disturbances.
Day 10: 3 days after intravenous repletion of potassium, calcium, magnesium, and phosphorus.
Day 14: Patient was on spironolactone for 2 days.

A 21-year-old woman with cystic fibrosis (CF) with recurrent admissions for CF exacerbations, diabetes mellitus, and allergic bronchopulmonary aspergillosis was hospitalized with shortness of breath and hemoptysis. During her course, she required intubation and was treated with several antibiotics including polymyxin and inhaled tobramycin on admission, then rifampin and intravenous (IV) tobramycin (dose of 7 mg/kg daily) beginning on hospital day 3. The tobramycin troughs ranged between <0.2 and 0.4.

Initially, she had a chronic respiratory acidosis with normal serum electrolytes and creatinine. On day 7, she developed profound hypokalemia, hypomagnesemia, hypocalcemia, and metabolic alkalosis (Table 1), which persisted for 2 weeks despite aggressive electrolyte repletion with oral and IV potassium chloride, IV magnesium sulfate (640 mg/h), and IV calcium gluconate (400 mg/h).

During the intensive care unit stay, the patient did not receive any loop diuretics and her serum creatinine was stable. The patient serum glucose levels were initially intermittently high but the electrolytes disturbances persisted even after her hyperglycemia was controlled on an IV insulin (mostly below 250 mg/dl).

Additional evaluation showed serum parathyroid concentration of 17 pg/ml (10–65 pg/ml), inappropriately low for the level of hypocalcemia. The 24-h urine calcium was 440 mg/24 h. The urinalysis was negative for glucosuria and proteinuria. The fractional excretion of urate was 7.8% (normal: 6–20%); the fractional excretion of phosphorus was 10.25% (normal: 5–20%).

What is your diagnosis?

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The Diagnosis | Bartter-like syndrome

Table 2 | Blood and urinary blood tests (IV tobramycin started on day 3 and stopped on day 12, and inhaled tobramycin stopped on day 19)

	Blood tests									Arterial blood tests				Urine					
	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Bicarbonate (mmol/l)	BUN (mg/dl)	Crea (mg/dl)	Corrected calcium (mg/dl)	Magnesium (mg/dl)	Phosphate (mg/dl)	pH	pCO_2 (mmHg)	pO_2 (mmHg)	Bicarbonate (mmol/l)	pH	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	FeMg (%)	TTKG
Normal range	136–146	3.5–5.5	97–105	23–30	7–20	0.5–0.9	8.7–10.2	1.5–2.3	2.5–4.3	7.35–7.45	32–45	72–104	21–28						
Day 14	136	2.9	79	45	3	0.4	7.6	1.6	2.7	7.55	61	47	53.8	7	121	30	150	68	10.3
Day 20	132	2.4	72	52	5	0.4	8.7	2.1	3.2	7.49	76	122	58	6.5	21	21	51	15	10.6
Day 25	135	4.9	83	40	8	0.5	9.6	1.1	5.1	7.45	63	80	44	8.5	10	44	57		
Day 47	133	4.3	86	36	17	0.5	9.7	1.5	4.3										

Abbreviations: BUN, blood urea nitrogen; Crea, creatinine; IV, intravenous; TTKG, transtubular potassium gradient.
Day 14: Patient was on spironolactone for 2 days.
Day 20: Amiloride 10 mg daily added to spironolactone 100 mg twice daily.
Day 25: Patient did not require electrolyte repletion except for per os magnesium.
Day 47: Discharged from the hospital.

Serum and urinary electrolytes showed a metabolic alkalosis with hypocalcemia, hypokalemia, and hypomagnesemia associated with hyperchloruria, hypercalciuria, high transtubular potassium gradient, and hypermagnesuria. The presentation is consistent with a diagnosis of Bartter-like syndrome secondary to aminoglycosides. The patient had no evidence of proximal tubulopathy (no glucosuria, normal fractional excretion of urate, and phosphate).

Aminoglycosides have excellent renal parenchymal penetration and can induce nephrotoxicity through two differents mechanisms: (1) megalin-induced endocytosis of the drugs leading to lysosomal rupture and proximal tubular cellular necrosis or (2) activation of the calcium-sensing receptors (CaSR) mostly following chronic therapy with low concentrations. The CaSR is localized in different parts of the nephron including the cortical thick ascending limb. The CaSR seems to be stimulated by aminoglycoside antibiotics (neomycin, gentamicin, and tobramycin) through a phosphatidylinositol 4,5 bisphosphate phospholipase C (PIP2-PLC)–dependent pathway, leading to an increase in the intracellular calcium, and inturn to a Bartter-like tubulopathy.[1] Other tubular dysfunctions described with aminoglycoside include Fanconi-like syndrome and distal renal tubular acidosis. Aminoglycoside antibiotics, which are polyvalent cationic molecules, stimulate the CaSR, leading to a decrease in NKCC2 luminal expression, which reduces the luminal positive driving force resulting in calciuria and magnesiuria.

Gentamicin infusion induces an increase in urinary excretion of magnesium and calcium in both neonates and healthy adults; these effects are transient.[2] In a rat model, gentamicin-induced urinary excretion of sodium, potassium, calcium, and magnesium was accompanied by upregulation of the CaSR and decrease in expression of Na^+-K^+-$2Cl^-$ cotransporter. The clinical picture is compatible with type 5 Bartter-like syndrome.[3]

Several case reports of aminoglycoside-induced Bartter-like syndrome were previously reported. The cumulative aminoglycoside dosage was variable between these patients (total gentamicin dose ranging between 0.04 g and 20 g). The recovery period ranged from 7 to 210 days.[3]

In this case, IV tobramycin was discontinued on day 12. The requirements for electrolytes repletion persisted even after the patient was started on spironolactone 200 mg twice daily and amiloride 10 mg daily. By day 25, the patient no longer required continuous IV electrolyte repletion and was able to maintain normal serum electrolyte levels, with the exception of magnesium (Table 2). She was discharged with normal serum electrolytes on magnesium oxide 1200 mg every 6 h, and amiloride 10 mg once daily.

The literature to date has reported associations between gentamicin/amikacin and Bartter-like syndrome. To our knowledge, this is the first reported association with tobramycin. We believe that exposure to such high doses of tobramycin occurred given the high metabolism of aminoglycosides in this cystic fibrosis patient.

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