Acquired polymyxin B-induced Bartter-like syndrome

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Abstract

Bartter-like syndrome (BLS) is a salt-wasting tubular disorder caused by a renal tubular defect in sodium reabsorption in the thick ascending limb of the loop of Henle (TAL) which triggers natriuresis, hypokalemia, and metabolic acidosis. This condition has been associated with certain diseases or medications.

We present the case of a 25-year-old man with osteomyelitis caused by VIM carbapenemase-producing *Pseudomonas aeruginosa* treated with polymyxin B (PB) and meropenem who, 16 days after beginning treatment, developed hypokalemia, hypomagnesemia, hypocalcemia, hypochloremic metabolic alkalosis and renal electrolyte losses, with normal kidney function. Polymyxin B-induced BLS was considered as a diagnosis of exclusion. Electrolyte correction was performed and, once treatment was suspended, the metabolic abnormalities improved. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.4229).**

Keywords: *Bartter syndrome, salt-wasting tubulopathy, hypokalemia; metabolic alkalosis*.

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Introduction

Bartter syndrome (BS) is a rare hereditary salt-losing tubulopathy with a low prevalence. There are cases of acquired tubulopathies, known as Bartter-like syndrome (BLS), caused by infections, autoimmune diseases or medications, which manifest with electrolyte depletion and metabolic alkalosis (1).

Polymyxin B (PB) and polymyxin E (colistin) have resurged as treatments for some infections caused by multidrug-resistant Gram-negative bacteria. However, their use has been limited by their side effects, especially neurotoxicity and nephrotoxicity. Their high nephrotoxic potential is dose-dependent and can be explained by their high rate of renal excretion, short half-life (4-6 hours), and complete elimination in 48 to 72 hours, which causes oxidative stress and necrosis of the tubular cells (2).

Below, we present a case of PB-induced BLS, a rare complication that should be considered.

Clinical case

This was a previously healthy male patient in his 20s with a history of a traumatic complex fracture of the left elbow that required external fixation. Eight months after removing the fixator, he developed an infection at the operative site. He was treated surgically, with a finding of osteomyelitis due to VIM carbapenemase-producing *Pseudomonas aeruginosa from the* metallo-beta-lactamase group. Given the anatomical site of the sample, the microorganism isolated, and the availability of medications in the institution, treatment was prescribed with PB, meropenem and vitamin C for six weeks, with subsequently negative cultures.

After 16 days of antibiotic treatment, the patient complained of two days of extremity paresthesias, coupled with dysphagia for solids. On assessment, his vital signs were as follows: blood pressure 123/65 mmHg, heart rate 59 bpm, respiratory rate 16 breaths per minute, temperature 36.2°C, O_2sat 97% on room air, blood glucose level 89 mg/dL and urine output within normal limits. On physical exam, he had distal tremors with positive Chvostek´s and Trousseau´s signs. The tests ordered showed persistent hypokalemia, hypochloremia, hypomagnesemia, hypocalcemia and metabolic alkalosis. An electrocardiogram showed sinus bradycardia and a corrected QT interval of 315 ms. The laboratory results are shown in Table 1, below.

In view of the serum and urinary electrolyte disorders, along with metabolic alkalosis, and after ruling out other etiologies, he was diagnosed with PB-induced BLS. He received intravenous potassium, calcium gluconate and magnesium sulfate replacement. Twenty-four hours after replacement, the patient´s symptoms and electrolyte abnormalities resolved completely; however, he experienced relapses during the antibiotic treatment. Since no other pharmacological options were available at the institution, he had to complete antibiotic treatment as an inpatient. He received oral potassium gluconate, calcium with vitamin D_3 and magnesium chloride capsules as maintenance therapy. On day 50, he finished treatment, with no further relapses and successful withdrawal of the replacement therapy (Figure 1).

Table 1. *Laboratory tests.*

Variable	Result	Reference	Variable	Result	Reference
Na^+ (mEq/L)	135	135 - 145	Mg^{2+}(mEq/L)	1	1.6 – 2.3
K^+ (mEq/L)	2.8	3.5 – 5.1	Ca^{2+} (mEq/L)	0.86	1.1 – 2.6
Cl^- (mEq/L)	93	98 – 107	$HCO3^+$ (mEq/L)	27.4	22 - 26
Urinary Na^+ (mEq/L)	55	0 - 20	Urinary dens. (mOsm/l)	1,010	1,005 - 1,025
Urinary K^+ (mEq/L)	40	0 – 20	Blood osm. (mOsm/l)	276	280-295
Urinary Cl^- (mEq/L)	57	20 – 40	Creatinine (mg/dl)	0.5	0.7-1.2
Urinary Ca^{2+} (mg/dl)	4.6	2 - 4.5	Urea nitrogen (mg/dl)	10	8 – 20
TTKG	4		Renin (IU/mL)	214	2.8 - 39.9
Albumin (g/dL)	4.4	3.5-4.5	Parathyroid hormone (pg/ml)	35	9-44
Aldosterone (pg/m)	101	29-161	TSH (mIU/L)	3.02	0.3-4.5
Urinalysis: pH 8, no signs of infection, +++ amorphous phosphates					
TTKG: transtubular potassium gradient, Dens.: density, Osm.: osmolarity.					

Discussion

Bartter syndrome is a hereditary disease characterized by a sodium reabsorption defect in the transtubular canals of the thick ascending limb of the loop of Henle (TAL), which causes natriuresis and water loss. Aldosterone-mediated sodium reabsorption is increased in the distal tubule, favoring K^+ and H^+ excretion with consequent hypokalemia and metabolic alkalosis. In addition, paracellular Ca^{2+} and Mg^{2+} reabsorption is altered, leading to hypocalcemia and hypomagnesemia. The acquired forms have similar biochemical characteristics (3). Bartter-like syndrome has been reported in association with tuberculosis infection, Sjögren´s syndrome, sarcoidosis, cystic fibrosis, bulimia, anorexia, and chronic diarrhea or as a side effect of certain medications like colistin (4), aminoglycosides (5), amphotericin B, antituberculosis drugs, cisplatin, cyclosporine, prostaglandins, diuretics, laxatives and heavy metals (6).

Bartter-like syndrome is a diagnosis of exclusion and should be suspected in all patients with persistent hypokalemia and metabolic alkalosis. Symptoms are attributed to electrolyte depletion and may manifest as paresthesias, cramps, tremors, altered consciousness, and even tetany or arrhythmias. The time of onset ranges from 3 to 18 days after beginning treatment (7,8). In the case presented, the paresthesias and dysphagia started on day 14, and electrolyte disturbances were documented as of day 16.

As a diagnosis of exclusion, other etiologies that could explain the signs and symptoms, such as parathyroid-related calcium disorders, primary aldosteronism, Cushing syndrome or apparent mineralocorticoid excess were ruled out (7). The elevated renin was explained by activation of the renin-angiotensin-aldosterone system secondary to subacute loss of sodium, chloride and water (8). Elevated urinary electrolytes confirmed the presence of a tubulopathy.

Hereditary BS results from a mutation of one of the TAL ion transport proteins, such as the Na^+-K^+-$2Cl^-$ cotransporter, ROMK, chloride channels (ClC-Kb and ClC-Ka), and barttin or MaGE-D2 (1). In BLS, there is no genetic substrate, and its onset, influenced by a noxa, is generally explained by increased renal tubule permeability, altered exchange pump function with lost positive electrical potential, activation of calcium-sensitive receptors, the onset of cellular edema and, finally, cell lysis (8).

Only one similar case associated with the use of PB was found in the literature review, described by Goldin et al. (9), which differed from ours in the presence of acute kidney injury. This poses the possibility of variable BLS presentations, understanding that its onset is due to a specific noxa and not genetic damage, which implies that not all patients will develop all of the signs and symptoms. This clinical variability could be explained by each person´s intrinsic substrate, in which risk factors like treatment duration and dose, coadministration with other nephrotoxic drugs (in this case, meropenem) and patient comorbidities are important (4).

Treatment consists of suspending the noxa and correcting fluid and electrolyte imbalances, either orally or intravenously, until normal serum levels are reached. The use of potassium sparing diuretics (spironolactone, eplerenone or amiloride) or nonsteroidal anti-inflammatories has been described (8). In some BLS cases, improvement in the tubulopathy may take several months to years. In our case, the patient´s electrolyte disorders resolved with replacement in the acute phase and maintenance therapy. Once the antibiotic was discontinued, electrolyte supplementation was able to be withdrawn.

In conclusion, BLS is a rare complication caused by certain medications. The reported PB-related cases are anecdotal and are more common with colistin. Therefore, all patients treated with polymyxins require strict electrolyte monitoring to detect any abnormalities early and thus reduce the risk of potentially fatal complications.

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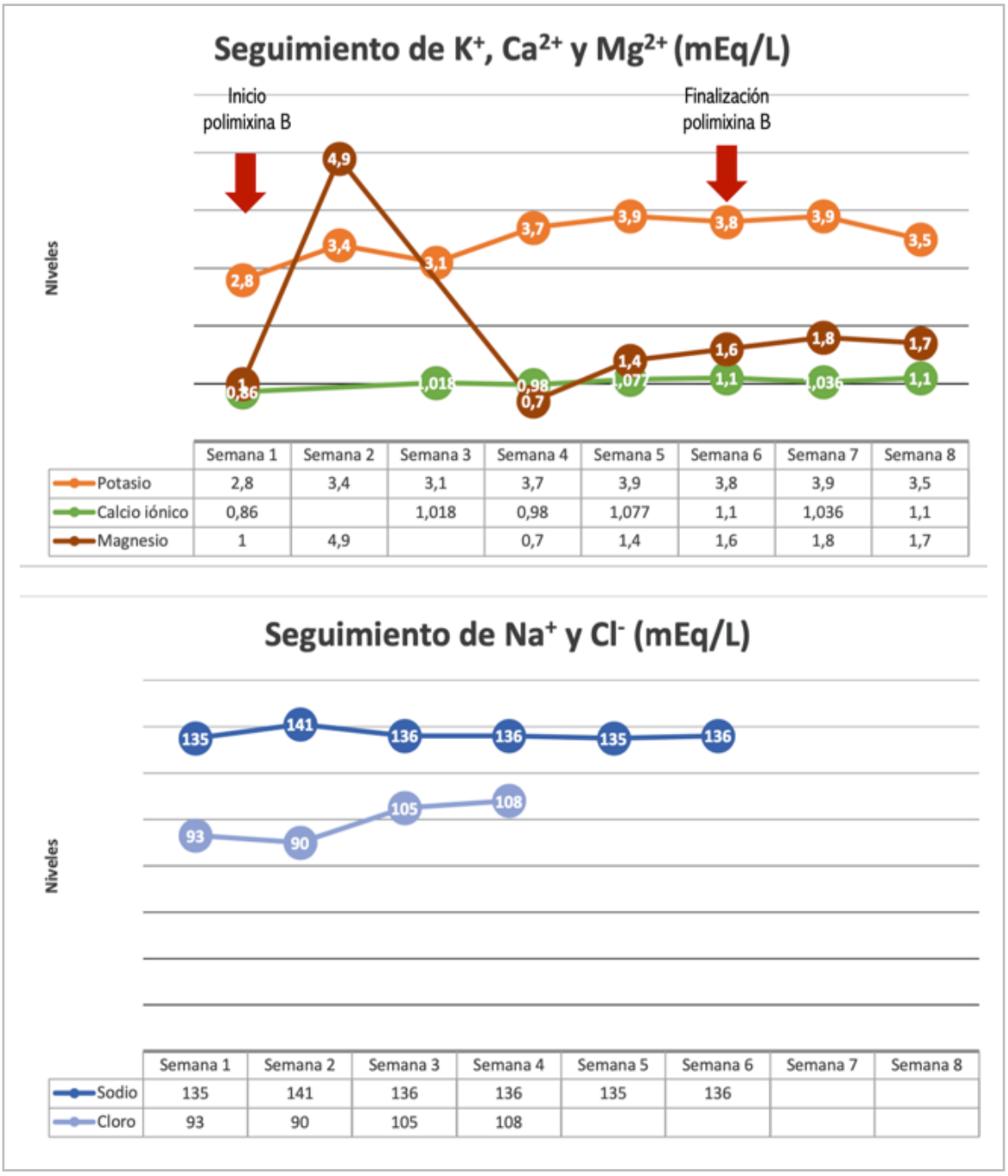

	Semana 1	Semana 2	Semana 3	Semana 4	Semana 5	Semana 6	Semana 7	Semana 8
Potasio	2,8	3,4	3,1	3,7	3,9	3,8	3,9	3,5
Calcio iónico	0,86		1,018	0,98	1,077	1,1	1,036	1,1
Magnesio	1	4,9		0,7	1,4	1,6	1,8	1,7

	Semana 1	Semana 2	Semana 3	Semana 4	Semana 5	Semana 6	Semana 7	Semana 8
Sodio	135	141	136	136	135	136		
Cloro	93	90	105	108				

Figure 1. *Electrolyte monitoring during and after treatment.w*

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