Detective Nephron

Detective Nephron, world-renowned for expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 57-year-old with a serum bicarbonate of 44 mmol/L.

Nephron (*excited*) Whoa! Finally...electrolytes stuff and possibly alkalemia.

Mac Trust me, you are going to enjoy this one!

Nephron Did you know that I get bored with low bicarbonate levels? High bicarbonate levels give me a rush, as the diagnosis is usually more interesting.

Mac Hmm...I can totally relate to that.

Pause

Mac She is in her 50s with a history of an unexplained rheumatologic disorder. The preliminary diagnosis is possible CREST syndrome. Her chief complaint is pain in her fingers and toes, worsening over the last few months. Two weeks ago, she had a black fingertip. Her blood pressure is 155/80 mm Hg and no edema on exam. Her fingers are cool to touch. She was given anticoagulation and calcium channel blockers. Blood cultures were negative.

Nephron Stop! Where is the electrolyte disorder? This is all good but....

Mac (*laughing out loud*) Since her admission, her serum bicarbonate levels have been in the 40- to 44-mmol/L range.

Nephron (*angry*) Oh, come on! And they noticed it on day 4? Why do we draw labs daily then?

Mac (*surprised*) I thought you love esoteric stuff. Well, they hydrated with normal saline for 2 days, and it did not change; stuck at 44. The ball's in your court now!

Nephron (*bored, rolling his eyes*) Metabolic alkalosis, a disorder that elevates the serum bicarbonate, can be seen with several disorders. Metabolic alkalosis consists of a generation phase and a maintenance phase. The generation phase refers to the initial event that causes the alkalosis. Metabolic alkalosis is generated either when hydrogen is lost or less commonly, when bicarbonate is gained. Once metabolic alkalosis occurs, the kidneys should be able to quickly correct it by excreting bicarbonate. However, there are factors that are present that do not allow the kidneys to do so; factors that "maintain" the alkalosis. We call this the maintenance phase. The main factors that maintain the alkalosis are low glomerular filtration rate, hypokalemia, hyperaldosteronism, and hypochloremia. In the past, hypovolemia was considered a factor—the so-called "contraction alkalosis"—but we know that experimentally, you can correct metabolic alkalosis by giving chloride without correcting the volume deficit. On the other side, you can correct the volume deficit without giving chloride, and the metabolic alkalosis persists. The issue is that we often lose fluids in the form of sodium chloride, so chloride is lost along with volume. When you give normal saline, you give volume, but you also give chloride. The proper term should be chloride-deficient metabolic alkalosis. Looks like they ruled it out. What is the serum creatinine?

Mac (*yawning*) Glad you asked. It has been in the 0.6- to 0.8-mg/dL range. She has normal kidney function, and hence, she should be able to excrete excess bicarbonate in the urine. She is not taking in any excess alkali (outpatient or inpatient). This alkalosis can only persist if there are maintenance factors.

Nephron (*winking*) Glad you are thinking what the kidney is thinking! So, if you think about generation phase, think in four buckets of how we can lose hydrogen: cellular shift, gastrointestinal (GI) losses, kidney losses, or less commonly, how we gain bicarbonate…usually due to external sources of bicarbonate.

Mac Her serum potassium level is 4.1 mmol/L and has been stable the last few days. No repletion was required. Yes, I know you will ask why hypokalemia causes metabolic alkalosis. To answer briefly, hypokalemia increases kidney ammoniagenesis and ammonium excretion, which can both generate and help to maintain the metabolic alkalosis. In addition, the loss of potassium will cause potassium to move from the intracellular space to the extracellular fluid. To maintain electroneutrality, the hydrogen ions will move inside the cells, which will lead to an increase in plasma bicarbonate levels.

Nephron (*laughing*) Well done, Mac. What about the GI losses?

Mac No vomiting; hydrogen loss can result from the loss of gastric secretions, such as vomiting, or less likely, from diarrhea in some patients. She had neither.

Nephron But wait! Why? Why? Why? Diarrhea? I thought that was causing normal anion gap metabolic acidosis.

Mac (*trying to remember*) Oh yes; you are correct. Diarrheal stool typically has a relatively high alkali concentration, and as a result, large-volume diarrhea typically generates metabolic acidosis but with rare disorders that increase GI chloride loss, such as congenital chloridorrhea, and in some patients with villous adenomas.

Nephron (*jumping in*) Oh...you are good!

Nephron (*to himself*) I actually do not miss Henle anymore. Wonder what he is up to these days.

Mac (*surprised*) Obviously! And by the way, normal calcium, ruling out calcium-alkali syndrome.

Silence

Mac Here are the rest of the lab data that may be helpful: normal white cell count, hemoglobin of 11.3 g/dL, and normal platelets. Serum sodium is 136 mmol/L, chloride is 105 mmol/L, and blood urea nitrogen is 7 mg/dL. As I mentioned earlier, serum total CO_2 is 44 mmol/L.

Nephron (*shocked*) Ah! I have a diagnosis for you already! But first, we need to make sure there is no hypertension or primary hyperaldosteronism here.

Mac (*jumping in*) Any cause of primary and inappropriate hypersecretion of mineralocorticoids can lead to and maintain a metabolic alkalosis, which is generally accompanied by hypertension and hypokalemia, but she has no such findings. Her hypertension has been stable for years, and her potassium has never been low in the past. In addition, her bicarbonate levels in the last few visits to her doctor were normal but started rising more recently. She is also not on any diuretics that can do this. Metabolic alkalosis and hypokalemia are characteristic features of Bartter and Gitelman syndromes. These disorders are produced by genetic defects in ion transporters but doubt she has that suddenly at the age of 57. She is also hypertensive.

Nephron So let's get back with our case. This is a nice discussion so far.

Mac (*confidently*) FYI…her urine studies done initially showed urine sodium of 40 mmol/L and Cl of 49 mmol/L. Her urine chloride was not low. In addition, we got some additional labs, such as lipids; serum complements were all normal. Her anti-nuclear antibody and rheumatoid factor were elevated.

Nephron Hmmm…. Did you notice that her serum anion gap is negative? Because of the patient's benign clinical appearance and a negative serum anion gap, the possibility of a spurious result should be entertained, my friend.

Mac (*confused*) Good point!

Nephron (*interrupting*) Not just a good point; it's an excellent point! We keep talking about low and high bicarbonate, but no one does a venous blood gas these days. Why not?

A few hours later

Mac We got a venous blood gas with a pH of 7.42, PCO_2 of 37, PO_2 of 157, and bicarbonate of 23. Interestingly, a serum chemistry done using i-STAT showed a total CO_2 of 24, and a routine lab test showed a serum bicarbonate of 39 mmol/L.

Nephron Is this serum bicarbonate real? With the history of unexplained rheumatic disease, digit pain, and elevated rheumatoid factor, please obtain immunoglobulin (Ig) levels and a serum free light chain assay.

A few weeks later

Mac (*nodding*) Her IgM level came back as 1700 mg/dL (very elevated), and a bone marrow done confirmed a diagnosis of Waldenstrom macroglobulinemia (WM). I assume the hyperbicarbonatemia was spurious, and we should ignore it?

Nephron (*puzzled*) Paraproteins may cause abnormal laboratory findings in three ways: 1) through the disease process itself, 2) by interacting with the target of an assay, and 3) by creating spurious results because of their interference with the assay method. Paraproteins have been shown to cause interference with the assays of multiple laboratory tests, including blood counts, sodium, calcium, phosphorus, lipids, coagulation profiles, iron studies, blood urea nitrogen, creatinine, bilirubin, C-reactive protein, glucose, uric acid, lactate dehydrogenase, and alkaline phosphatase. Among the paraproteins, IgM is more often the culprit because of its high molecular weight.

Mac Is it dependent on the load of the paraprotein?

Nephron I am not sure. Both false-positive and false-negative results may occur. In general, the paraprotein interference is concentration dependent. Some of the techniques many have used to avoid spurious results include alternate lab assay methods; doing i-STAT and venous blood gas levels, as you did; or removal of the paraprotein load before laboratory analysis. It is possible that the interference might be precipitation related to the IgM protein and the serum sitting in that milieu for a longer time compared with the emergent sample done.

Mac (*jumping in*) Bicarbonate is not that common. For some of the other electrolytes, this is a major concern. One can see pseudo hypercalcemia, pseudo hyperphosphatemia, and pseudo hypophosphatemia with paraproteinemia. It is critical to recognize these spurious electrolyte disorders to avoid unnecessary interventions that can potentially lead to harmful side effects.

Nephron Go get this patient some chemotherapy!

Mac (*confused*) Yes; apparently, she is on a bendamustine-based therapy already.

A few weeks later

Nephron (*to himself*) Tough case for Mac, but she did a great job.

Mac You know, you were on target! The patient's subsequent outpatient laboratory findings were that after she began treatment for WM with bendamustine and rituximab, her serum IgM levels returned to the normal range, and the routine chemistry results also revealed a bicarbonate level within the normal range.

Nephron (*jumping in*) There we go again. From a simple lab abnormality, you made a systemic diagnosis!

Mac (*surprised*) I agree with you, and it is prudent to have a high clinical suspicion of abnormal laboratory values in the setting of paraproteins, as the machines are usually unable to detect interference on their own. As a result, we could reduce or prevent incorrect diagnoses, prolonged hospital stays, prescriptions of inappropriate treatment, and morbidity or mortality in our patients.

Nephron (*laughing*) There you go again. Fascinating diagnosis, and treatment was to do nothing. Do no harm first, my friend, do no harm! Let's have some NY-style coffee today. ■

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