Detective Nephron

Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Budding nephrologist L.O. Henle is now accompanied by a new budding nephrologist who calls himself Dr. Aldo.

Henle A case for you, sir!

The detective sits facing the window, awaiting the arrival of his new students.

Nephron (*curious*): Finally, something that might put an end to this utter boredom.

Henle It's a case of hyperkalemia.

Nephron (*smiling*): Ah, yes. Electrolyte disorders. The best part of nephrology! Nevertheless, no patient will thank you for fixing their acidosis.

Aldo This is an 81-year-old man with a serum potassium level of 7.5 mmol/L.

Nephron (*interrupting*): I don't need any of that information…. Oh, new fella! Dr. Aldo, welcome to nephrology. And you have a potassium case? Great!

Aldo Yes! Fits well with my name.

Henle Yes, Dr. Nephron, we did repeat the serum potassium level, and it's actually 8 mmol/L; and yes, you are right—the creatinine is normal at 0.6 mg/dL, with an estimated GFR of 85 mL/min.

Nephron Hyperkalemia with acute kidney injury is boring. But hyperkalemia with normal renal function is a treat for the nephrologist!

Henle (*whispering to Aldo*): I told you he is a bit strange.

Nephron How do we categorize the causes of hyperkalemia?

Aldo Too much intake?

Nephron Increasing potassium intake alone is not a common cause of hyperkalemia unless it is paired with decreased renal potassium excretion. In patients with low GFR or hypoaldosteronism, moderate increases in potassium intake can be an important contributor to the development of hyperkalemia, but otherwise it's rare.

Henle Shifting?

Nephron (*laughing*): Shifting where?

Pause.

Henle (*happy*): Out of the cells?

Nephron Are you going to stop after each answer and not complete your thoughts?

Aldo Insulin deficiency and hypertonicity can do it. Insulin promotes potassium entry into the cells. So, insulin deficiency and associated hyperglycemia can lead to hyperkalemia. The increase in plasma tonicity results in osmotic water movement from the cells into the extracellular fluid. This is accompanied by potassium movement out of the cells. Increased β-2-adrenergic activity drives potassium into the cells and lowers the serum potassium. So, β-blockers can actually lead to hyperkalemia. This patient has neither elevated blood glucose nor insulin deficiency, nor is he taking any β-blockers.

Henle (*showing off*): Acidosis can also lead to hyperkalemia. In patients with metabolic acidosis, such as lactic acidosis or ketoacidosis, excess hydrogen ions move inside the cells, which leads to potassium movement into the extracellular fluid, a transcellular shift that is obligated in part by the need to maintain electroneutrality. But this patient's laboratory results show no signs of acidosis.

Nephron (*angry*): That is not accurate. Organic acidosis such as lactic acidosis or ketoacidosis does not cause as much hyperkalemia as inorganic acidosis…

Henle (*interrupting Nephron*): … but I have seen a lot of patients with diabetic ketoacidosis that then had hyperkalemia …

Nephron (*interrupting Henle*): Aldo just said it! Diabetic ketoacidosis causes hyperkalemia because of the associated insulin deficiency and hypertonicity, not because of the acidemia.

Henle (*embarrassed*): Oh! My bad.

Henle But I think the most common cause of hyperkalemia is decreased renal excretion.

Nephron Please continue.

Aldo (*jumping in*): Renal potassium excretion primarily occurs in the principal cells in the segments that follow the early distal convoluted tubule: the late distal convoluted tubule, the connecting tubule, and the collecting duct.

Nephron Three major factors are required for adequate potassium secretion at these sites: adequate aldosterone secretion, appropriate response to aldosterone, and adequate distal sodium and water delivery.

Henle (*shocked*): So basically, what I was trying to say is that the main causes of reduced loss of potassium in the urine are reduced ALDO secretion, reduced response to ALDO, reduced distal sodium delivery in hypotension, and acute kidney injury.

Aldo (*interrupting*): Thanks for the shout-out!

Nephron Good work, team.

Henle Basically, our patient has normal renal function, good blood pressure control, and good urine output, and I doubt he has a hypo-ALDO state. He is taking no medications. He has a normal serum bicarbonate level, suggesting no signs of any form of distal renal tubular acidosis. He also is not taking any heparin or potassium-sparing diuretics.

Aldo (*confident*): You know that his white blood cell count is 796,000 per cubic millimeter, and he carries a diagnosis of chronic lymphocytic leukemia (CLL). Subsequently, he was given intravenous calcium chloride, dextrose, insulin, and resins. A 12-lead electrocardiogram (ECG) did not reveal any changes.

Nephron I love it! Love it! I love it when you guys hide important information from me!

Henle A repeated serum potassium level after the initial treatments revealed an increase to 9.8 mmol/L. A repeated ECG did not show any new

changes, and the patient continued to be asymptomatic.

Nephron So, you are telling me that this patient might have pseudohyperkalemia?

Aldo (*puzzled*): Great! But how do we prove it is pseudohyperkalemia?

Nephron Let's end this confusion once and for all. He is not diabetic, nor does he have renal failure, and he has other normal laboratory results except for a crazy high white blood cell count and an alarming fatal potassium level, but he is laughing and talking in the examination room. Clearly, it is not real, and ECG repeated twice was normal. If this were real, he would have sine waves by now!

Henle Hmmm. Does CLL cause this degree of hyperkalemia?

Nephron The most common electrolyte disorder encountered in CLL patients is pseudohyperkalemia. An artifactually elevated serum potassium level or spurious hyperkalemia was first described with extreme leukocytosis (>600 × 109/L) in the 1970s and thereafter in several case reports.

Aldo (*jumping in*): I've heard about a large study. In over 300 patients with CLL listed in the Minnesota Tumor Registry between 1997 and 2014, the researchers found that the adjusted odds of hyperkalemia increased by 1.4 for every 10 × 109/L increase in white blood cell count. Below white blood cell counts of 50 × 109/L, the median estimated percentage of a patient's serum potassium being elevated was 1.7%, but it was considerably higher at 8.1% when the white blood cell count was ≥100 × 109/L. This is the first and only study to systematically look at serum and plasma potassium values in CLL patients, demonstrating that the results are related to pseudohyperkalemia.

Nephron (*shocked*): Usually, I don't like discussing random studies at this forum, but good for you. How do you remember that stuff? However, to our knowledge, there is no specific way to predict or correct the serum potassium value based on the white blood cell count.

Aldo The elevation in white blood cells causing pseudohyperkalemia is actually a rare cause. The three most common causes are mechanical trauma during venipuncture, hemolysis, and exercise-induced potassium movement out of muscle cells. When the platelet counts are very high (500,000/µL), as in thrombocytosis, measured serum potassium is elevated as potassium is released from the fragile platelets during clotting. However, in these cases, if the plasma potassium is checked (in a heparinized unclotted sample), the measured potassium will be normal because no clot formation occurred and no potassium was released. Elevation of blood platelet count by 1000 × 109/L can lead to an increase in 0.2 mmol/L in plasma potassium and 0.7 mmol/L in serum potassium. As a result, the potassium concentration is generally higher in serum than in plasma. Similarly, elevated potassium levels have been described in leukocytosis as well.

Nephron Dr. Aldo, you are on a roll!

Henle (*getting anxious and jealous*): How then does one get an accurate potassium result?

Aldo I would get a plasma potassium level. The definition of pseudohyperkalemia is a difference between serum and plasma potassium of more than 0.3 mmol/L.

Nephron keeps smiling.

A few hours later:

Aldo The plasma potassium is also elevated at 7 mmol/L. Now what? This must be real!

Nephron Are you sure?

Henle Routine serum analysis leads to high measured potassium levels resulting from release of potassium from the fragile leukemic cells during the clotting process. But in CLL, even the plasma levels of potassium are elevated. Severe leukocytosis leads to consumption of metabolic fuels that can impair Na-K ATPase activity, leading to release of potassium from a large number of white blood cells. Whereas in elevated platelet levels, serum and plasma levels can differentiate pseudohyperkalemia, elevated white blood cell–related pseudohyperkalemia might be not as straightforward to distinguish. Another interesting electrolyte disorder in CLL patients, though extremely rare, is reverse pseudohyperkalemia, where plasma potassium is higher than serum potassium. The mechanism is not well understood but can be due to increased sensitivity to heparin-mediated cell membrane damage during transport in pneumatic tubes, processing, or centrifugation in a hematologic malignancy.

Nephron Brilliant, Henle!

Aldo So, if plasma and serum potassium are both elevated, and we still think this is pseudohyperkalemia, should we get a whole blood potassium level from venous blood gas?

Nephron Let's try that.

A few hours later:

Aldo The venous blood gas potassium is also 7 mmol/L.

Henle (*with a smirk*): The time to collection and analysis of the blood sample can help eliminate some of these findings. Hence, blood gas levels are a good idea. Venous and arterial blood gas samples for potassium measurement can decrease the transit time to allow for more accurate potassium measurement. But we have to keep in mind that venous samples have more mechanical stressors compared with arterial blood draw techniques, making arterial draws more accurate.

Aldo (*angry*): Oh, well! Should we get an arterial blood gas, then?

Nephron Please get an arterial blood gas.

A few hours later:

Henle (*relieved*): The arterial blood gas potassium was 4.5 mmol/L.

The detective's eyes brighten.

Nephron Fascinating. Very well, then. And so, yet again, the nephrologists did it! Ask them to stop measuring the serum potassium and use the arterial blood gas potassium to check levels. Perhaps, do no harm—send the patient home! The exact mechanism of pseudohyperkalemia in extreme leukocytosis is not clear. However, the presence of pseudohyperkalemia should be strongly suspected with elevated potassium, the absence of clinical signs of hyperkalemia, absence of acid–base abnormalities, preserved kidney function, a normal ECG, and, in this case, the presence of extreme leukocytosis. Unlike thrombocytosis, plasma and serum potassium can both be misleading in elevated white blood cell counts. Arterial blood gas potassium might be the only accurate way to diagnose pseudohyperkalemia in such cases. Once again, great work, team, and let's get some New York–style coffee. I feel like having a banana today as well.

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