Incidental hyperkalemia: An unusual and unexpected case of severe hyperkalemia in an otherwise stable post–liver transplant recipient

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Abstract

Hyperkalemia is a potentially life–threatening electrolyte abnormality. We describe a case of severe hyperkalemia secondary to the combination of immunosuppressant, antibiotic, and antifungal therapy in a liver transplant patient. A 68–year–old man in stable condition was found to have a serum potassium level of 7.9 mmol/L one year after an orthotopic liver transplant. Other causes of hyperkalemia were ruled out and his hyperkalemia resolved with conventional therapy and adjustment of his medications. With an increasing number of post–liver transplant patients in British Columbia, similar clinical situations may become more frequent. This case illustrates the importance of regular monitoring of this patient population.

Background

The concentration gradient of potassium across cellular membranes is crucial in the regulation of the resting membrane potential of excitable cells. Deviations from the normal range can result in significant cardiac, neuromuscular, and metabolic manifestations. Hyperkalemia, generally defined as serum concentration of potassium greater than 5.0mmol/L, is a common clinical issue.[1] The potential causes of hyperkalemia are numerous, but can be broadly grouped into the following categories: increased exogenous intake, increased cellular release, and reduced urinary excretion; medications can contribute to the latter two.[1-2] Here we present a case of hyperkalemia in a stable post–liver transplant recipient taking a combination of medications that contributed to decreased potassium excretion.

Case

A 68–year–old male of Indo–Canadian background presented to the emergency department after a routine laboratory test reported a serum potassium level of 7.9mmol/L.

Eleven months earlier, he had received an orthotopic liver transplant for decompensated liver cirrhosis secondary to primary sclerosing cholangitis. Prior to his transplant, a computed tomography scan of his abdomen incidentally showed a 3cm opacity in the left lower lobe of the lung. Analysis of bronchoalveolar lavage confirmed cryptococcal infection. After consultation with the infectious diseases service, the patient was started on high–dose fluconazole therapy at 400mg daily, which was to be continued for one–year post transplant. About nine months after his transplant, the patient developed bilateral shoulder pain and swelling in the extremities. He was seen by the rheumatology service, and a 10mg daily dose of prednisone was started for preliminarily diagnosed psoriatic arthropathy. Other medications taken by the patient included tacrolimus 1.5mg twice daily (BID) and mycophenolate mofetil 500mg BID for maintenance immunosuppression. The patient was taking trimethoprim/sulfamethoxazol (TMP-SMX) 160/800mg three times per week for *Pneumocystis carinii* pneumonia prophylaxis post–transplant, but this had been discontinued a few weeks prior to presentation.

His past medical history also included long–standing ulcerative colitis, for which he took mesalamine, variceal bleeding due to portal hypertension, proton pump inhibitor therapy, and benign prostatic hypertrophy, for which he underwent a transurethral resection of prostate procedure three months post–transplant.

Post–transplantation, the patient underwent regular outpatient blood tests for monitoring of medication levels and attended regular appointments with both the solid organ transplant and the infectious disease services. Of note, there had been a history of mild intermittent hyperkalemia, not exceeding 6.0mmol/L, last documented nine months prior to presentation.

When the patient arrived at the emergency department, he was experiencing no symptoms of hyperkalemia, such as chest pain, palpitations, nausea, parasthesias, or fatigue.[1] His physical examination was unremarkable and an urgent ECG did not show features consistent with hyperkalemia, such as flattened P waves, QRS widening, peaked T waves, or conduction blocks.[1] Admission bloodwork was also significant for an increase of creatinine level of 126μmol/L (eGFR 50mL/min) from the patient's baseline of around 80-100μmol/L. Arterial blood gas showed pH of 7.36, close to the lower limit of normal, pCO2 of 33mmHg, and HCO3- of 18mmol/L. His complete blood count was unremarkable, liver function tests were normal, and tacrolimus level was at 6.5μg/L (therapeutic range 4.0-8.0μg/L). Urine electrolyte values were collected around five hours after admission and initial management and therefore were omitted here.

The patient was promptly given calcium gluconate for cardiac protection. Insulin was given with complimentary 50% dextrose to shift potassium into intracellular space. Sodium polystyrene sulfonate (Kayexalate) was given for binding of intestinal potassium. In addition, normal saline was given intravenously to correct his acute kidney injury. Repeat bloodwork showed return of potassium and creatinine to normal levels within the next 24 hours. He remained normokalemic overnight and his creatinine level normalized to around 100μmol/L.

The patient was discharged from hospital in stable condition. Since tacrolimus is associated with hyperkalemia (see discussion), the dosage was adjusted from 1.5mg to 0.5mg BID upon discharge. One week after discharge, outpatient bloodwork showed a mild increase in potassium levels once again, to 5.0mmol/L, requiring him

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to take a five–day dose of Kayexalate which returned his potassium to 4.0mmol/L. Once off Kayexalate, the patient's potassium levels returned to 5.3mmol/L. In consultation with the infectious diseases team, it was thought that fluconazole, perhaps in combination of his other immunosuppressive drugs, continued to contribute to hypoaldosteronism and decreased potassium excretion. Therefore, his fluconazole was stopped. Hyperkalemia has not recurred in this patient after this episode.

Discussion

Hyperkalemia is known to be associated with increased mortality and morbidity.[3] One nonfatal case of a potassium level of 14mmol/L has been previously reported, but it is generally accepted that serum levels greater than 6.0mmol/L require immediate management, especially if the rise in potassium occurred acutely.[1,4] Many factors can contribute to hyperkalemia. In this case, hyperkalemia was caused by reduced renal excretion associated with polypharmacy and a decline in GFR.

Decreased GFR of any cause, including acute or chronic renal failure or low effective circulating volume, leads to decreased sodium delivery to the distal nephron.[1,5] A decrease in sodium reabsorption by the selective epithelial sodium channels (ENaC) located on the apical surface of principle cells leads to a less favorable electrical gradient for the excretion of potassium into the lumen through the renal outer medullary potassium (ROMK) channels, also located on the apical surface.(Table 1).[2] Hypoaldosteronism of any cause also leads to decreased renal excretion of potassium, as the number of open ENaCs and the function of Na-K-ATPases are under the control of aldosterone.[1,2] Hypoaldosteronism can result from adrenal insufficiency, as in Addison's disease or from decreased production of aldosterone as a result of medications such as angiotensin-converting enzyme inhibitors (ACEi).[5] Alternatively, patients can be in a hyporeninemic hypoaldosterone state, such as type IV renal tubular acidosis.[1] Medications may also induce aldosterone resistance in the distal nephron.[5] Medications known to cause this side effect include potassium–sparing diuretics such as spironolactone, calcineurin inhibitors such as tacrolimus or cyclosporine, and antibiotics including TMP, among others.[5] Finally, dysfunction in the sites of renal potassium excretion, as seen in the various types of renal tubular acidosis, are known to present with metabolic acidosis and hyperkalemia.[2]

The patient in the present case had several risk factors for developing hyperkalemia. His GFR was low on presentation for unclear reasons. A reduction in extracellular fluid volume is a very common reason for a low GFR and reduces sodium delivery to the distal tubule, which in turn, limits potassium excretion. This effect may explain the reduction in the patient's potassium level after normal saline was given. Tacrolimus has been known to cause decreased GFR.[8] The mechanism behind this relationship has been postulated to be multifaceted, including direct injury to the endothelium and decreased production of prostaglandins and other vasodilators.[8-9] In addition, tacrolimus has also been shown to inhibit Na-K-ATPase, leading to decreased transepithelial potassium secretion, as well as cause renal tubular acidosis in the distal tubules.[8-9] Despite these known adverse effects, immunosuppression–induced hyperkalemia and acid–base imbalance is uncommon after liver transplant.[8] Indeed, only three such cases have been reported so far.[8,10-11] Another significant contributor to hyperkalemia in this case is likely the long–term use of TMP–SMX, even though it was discontinued just before presentation. TMP blocks the ENaCs much like potassium–sparing diuretics, effectively causing functional hypoaldosteronism.[1,12] TMP–SMX in standard dosage is fairly well tolerated, especially given the relatively short half–life (6-12 hours).[13] However, its use in patients with kidney injuries or who are taking medications including NSAIDs, ACE inhibitors, and calcineurin inhibitors warrants regular monitoring.[14] Fluconazole has also been reported to be associated with severe hyperkalemia in the pediatric population as well as reported to be associated with functional adrenal insufficiency, including mineralocorticoid insufficiency.[6-7] It is of note that active fungal infections are a contraindication to liver transplantation. However, in this patient's case, the cryptococcal lung infection pre–transplant was adequately treated and he was in the maintenance phase of treatment and monitored by the Infectious Diseases service.

Table 1 | Sites of Potassium Handling and Drug Activity in the Kidney
Sites of potassium handling and activity of drugs relevant to this case. K: Potassium; TAL: Thick Ascending Loop; DL: Distal Tubule; CCD: Cortical Collecting Duct; TMP-SMX: Trimethoprim/Sulfamethoxazol; SE: Side effect

Site	K Movement	Active drugs
TAL	Reabsorption	Loop Diuretics
DT	Excretion	Thiazide Diuretics
CCD (Principle Cells)	Excretion	K Sparing Diuretics TMP-SMX (SE)

In summary, this asymptomatic post–transplant patient presented with potentially life–threatening hyperkalemia. The cause was most likely multifactorial, including medications specific to the transplant process. With a growing population of post–liver transplant patients in B.C., it can be expected that this patient's clinical situation will be encountered again in the future.

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