中文題目：難以解釋的高血鉀型代謝性酸中毒可以做為漿細胞惡病質疾病的臨床表徵-兩個相關病例的研究報告

英文題目：Unexplained hyperkalemic metabolic acidosis can be a manifestation of plasma cell dyscrasia: Two related case studies

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Introduction:

Plasma cell dyscrasia (PCD) is characterized by abnormal proliferation of monoclonal lymphoplasmacytic cells in bone marrow. Patients with PCD have a wide range of characteristics, including premalignant monoclonal gammopathy of undetermined significance (MGUS) and malignant multiple myeloma (MM), Waldenström's macroglobulinemia, AL amyloidosis or lymphoma. MM causes extensive expansion of abnormal monoclonal immunoglobulins in the body and may lead to hypercalcemia, renal failure, anemia and pathological bone fractures. Although PCD could be associated with renal proximal tubulopathy, the linkage between PCD and hyperkalemic metabolic acidosis (HKMA) remained elusive. Here, we reported two cases of unexplained HKMA, which closely associated with PCD characteristics of MGUS with IgG-kappa and MM with IgA-lambda dyscrasia, respectively.

Case presentation:

Case 1:

A 79 years old, non-diabetic, male patient had chronic kidney disease stage 5 and anemia (hemoglobin, 9.4 g/dL). The patient had recurrent hyperkalemia without taking any medications or Chinese herbs that may cause hyperkalemia. The patient had hypertension (144/67 mmHg) controlled by adalat OROS 30mg/day and doxazosin XL 4mg/day. Concurrently, the patient was prescribed with feburostat 80mg/day for gout treatment. Abdominal sonography displayed neither obstructive uropathy nor splenomegaly, except chronic renal parenchymal disease.

The laboratory test data showed hyperchloremic normal anion gap HKMA, inadequate urine acidification and low urine osmolal gap, which manifested abnormally impaired urine NH_4^+ secretion. During patient's hyperkalemia (serum K^+, 5.74-6.93 mEq/L), values of transtubular potassium gradient (TTKG) were between 2.1and 3.26 and the ratios of urine K^+/creatinine (UK^+/UCr) were between 3.16 and

6.68 mmol K^+/mmol creatinine. Normally, TTKG <7 and UK^+/UCr <20 mmol K^+/mmol creatinine during hyperkalemia indicated hypoaldosteronism. Contradictorily, the aldosterone level remained relatively high and gave rise to pseudohypoaldosteronism (PHA).

The hyperphosphaturia and β2-microglobulinuria revealed proximal tubulopathy. Additionally, serum immunofixation electrophoresis (SIFE) demonstrated monoclonal gammopathy of IgG-kappa. In 2-year follow-up studies, the serum free light chain ratios were within normal limits. The hematologic diagnosis was further confirmed the patient had typical characteristics of MGUS.

Case 2:

An 86 years old, non-diabetic, female patient had decreased appetite, diarrhea and blood pressure of 108/60 mmHg. She had taken methimazole (5 mg/day) for hyperthyroidism treatment. The patient had a prior surgery for right femoral intertrochanteric fracture 2 years ago. The thoracic and lumbar spine X-ray revealed multiple compression fractures at T10, T11, T12, L2, L3 and L5. The laboratory test results showed serum creatinine, calcium and CBC were all within normal ranges. Abdominal sonography displayed normal kidney size without obstructive uropathy.

However, unexplained HKMA had recurred to the patient. The patient had emergent hemodialysis once due to the recurrent, severe hyperkalemia (serum K^+, 9.8 mEq/L). Before clinical visit, the patient had minimal intake of dietary potassium and didn't take any medications or Chinese herbs that may cause hyperkalemia. The laboratory test results illustrated high anion gap HKMA and low urine osmolal gap, which indicated impaired urine NH_4^+ secretion. During patient's hyperkalemia (serum K^+, 6.0-7.0 mEq/L), low values of TTKG (0.48-1.73) and low ratios of UK^+/UCr (3.36-5.88 mmol K^+/mmol creatinine) were both found. While low values of TTKG pointed to hypoaldosteronism, the renin and aldosterone levels remained high. These results suggested a possible PHA.

The presentations of proximal tubulopathy including normoglycemic glucosuria and hypophosphatemic hyperphosphaturia, together with a reversed serum albumin/globulin ratio, all manifested the characteristics of PCD. The results of SIFE showed monoclonal gammopathy of IgA-lambda. The hematologist further confirmed diagnosis of MM, IgA-lambda, Durie-Salmon Stage IIIA. Unfortunately, despite four-month treatment with melphalan and prednisolone, the patient passed away due to sepsis.

Discussion:

We proposed six possible clinical indicators that link PHA and HKMA conditions to PCD in current case studies:

1. Dysfunctional K^+ secretion by crystalline depositions of monoclonal immunoglobulins in principle cells in cortical collecting duct (CCD). Abnormal expansion of monoclonal immunoglobulins can form crystalline deposition in the lumen and intracytoplasmic region of renal distal tubules and block K^+ secretion in principle cells in CCD, the primary response site of aldosterone. The action interferes aldosterone binding to its mineralocorticoid receptor (MR) or impairs Na^+ absorption via epithelial sodium channel (ENaC) while decrease K^+ secretion via renal outer medullary potassium channel (ROMK). Similarly, the effects mimic aldactone and amiloride, via aldosterone receptor blockade and voltage gated defect at ENaC, respectively, in PHA.
2. Defective H^+ secretion of H^+-ATPase in alpha-intercalated cell and in distal tubules. The bicarbonate loading test revealed 3.2% of fractional excretion of HCO_3^- with urine $PCO_2 < 40$ mmHg, while MM aggravated in Case#2. Both patients showed inadequate urine acidification, which indicated defective H^+ secretion by H^+-ATPase in distal tubules.
3. Abnormally impaired ammoniagenesis and decreased NH_3 and NH_4^+ production in proximal tubules. The urine pH 5.0 in Case#2 and low urine osmolal gap in both cases strongly implied impaired urine NH_4^+ secretion, which may be due to decreased NH_3 production. The reduction in NH_3 may stem from increased intracellular pH value in proximal tubules during hyperkalemia.
4. Reduced NH_4^+ contercurrent circulation, the key process of acid secretion in humans, in renal medulla during hyperkalemia. The unusual, high level of luminal K^+ competes with NH_4^+ binding to $Na^+K^+2Cl^-$ cotransporter (NKCC-2) of medullary thick ascending limb in the loop of Henle and blocks the contercurrent exchange of NH_4^+.
5. Decreased diffusion of NH_4^+ in medullary interstitium to distal medullary collecting duct (MCD).
6. Impaired acid secretion by reduction of NH_3 and NH_4^+ secretion in distal MCD.

Conclusion:

We present two related cases of possible mechanisms of K^+ secretion, NH_3 and NH_4^+ metabolism, and acid secretion in the renal tubules as clinical manifestations of PCD, caused by PHA and HKMA. Any unexplained HKMA with PHA in

combination with renal proximal tubulopathy may require further evaluations of possible diagnosis of PCD.

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