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Case Report

An Abstruse Case of Refractory Hypokalemia- A Cabalistic Diagnosis

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ABSTRACT:
Every physician comes across several diagnostic challenges while managing cases with electrolyte imbalances. Abiraterone acetate is the chemotherapeutic agent used in the treatment of Castration-resistant prostate cancer (CRPC). We report a diagnostic challenge faced due to persistent hypokalemia in a patient with prostate cancer. An elderly male who is a known case of type 2 diabetes mellitus, Castration resistant carcinoma prostate, on chemotherapy was admitted with electrolyte imbalance, bilateral lower limb cellulitis and Acute kidney injury. Even after prompt treatment, his hypokalemia persisted. Upon further workup, he was diagnosed to have syndrome of apparent mineralocorticoid excess (SAME) and was treated and discharged with low dose steroids upon which his potassium was corrected to normal. Treatment of such cases with low dose prednisone lowers the ACTH levels and in turn, reduce the mineralocorticoid related complications like hypokalemia in mCRPC patients treated with Abiraterone acetate.

Key words: Refractory Hypokalemia, Syndrome of Apparent Mineralocorticoid Excess, mCRPC, Abiraterone acetate, ACTH.

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INTRODUCTION

Every physician comes across several diagnostic challenges while managing cases with electrolyte imbalances. It is not uncommon to find patients with persistent hypokalemia in clinical practice. Hypokalemia is present when the serum potassium level is below the normal value (<3.5mEq/L). The common causes of hypokalemia are transcellular shift and loss of body potassium. The transcellular shift occurs due to drugs like beta-agonists, insulin, alkalosis while diuretics, hypomagnesemia, diarrhoea etc cause potassium depletion. Abiraterone acetate is the chemotherapeutic agent used in the treatment of Castration-resistant prostate cancer (CRPC). We report a diagnostic challenge faced due to persistent hypokalemia in a patient with prostate cancer.

CASE PRESENTATION:

An elderly diabetic male was admitted in our hospital with bilateral lower limb cellulitis & constipation. On examination, he was dehydrated, delirious and had hypotension (BP 80/50mmHg). Per rectal examination revealed hard stool/ fecolith. His past medical history was significant for Metastatic Castration-Resistant Prostate Cancer (CRPC) diagnosed 2 years back with Gleason score 5+5 and bone scan showed extensive bone metastasis. He had received degarelix injection but as his serial Prostate-Specific Antigen (PSA) was raising the oncologist started Abiraterone acetate 1000mg with prednisolone 5mg. His Serum testosterone level was 8.4ng/ml in Feb 2019. He had undergone bilateral orchidectomy in September 2019 and his recent PSA was 66.03ng/ml. Upon arrival to our hospital, initial laboratory workup showed high random blood glucose 226mg/dL, raised creatinine(1.6mg/dL), hypernatremia (158mEq) hypokalemia (2.2mEq), mild liver dysfunction (AST130 IU/L ALT 56 IU/L s.albumin 3g/dL) severe metabolic alkalosis with respiratory alkalosis (pH 7.619 HCO3 40.3 pCO2 39.2) while urine examination revealed pyuria, albuminuria (4+) and bacteriuria. Prompt inotropic support and potassium correction was initiated. Abiraterone acetate was

stopped however prednisolone 5mg was continued. Urine culture and blood culture showed K.Pneumoniae and was treated as per the culture sensitivity report. Ultrasonography abdomen showed bilateral hydroureteronephrosis with bilateral grade 1 renal parenchymal changes. Within 5 days of treatment, his Serum creatinine improved (1.11mg/dL) but he had persistent hypokalemia while the serum magnesium level was normal. Further endocrinological workup showed the following findings. His 8 AM Serum cortisol was 5.7µg/dL, PO4- 1.7 S.calcium 8 (corrected Calcium 8.8mg/dL) urine spot sodium was 70 mEq/L and urine spot potassium was 21.1 mEq/L. Serum aldosterone and renin levels were normal. Spironolactone 50mg tablet was added. The dose of prednisolone was increased from 5mg/day to 10mg/day and hydrocortisone 100mg twice daily was added. His potassium came to normal (4.3mEq/L).

DISCUSSION:

As the patient presented with severe symptoms, treatment was initiated before complete evaluation. During his hospital stay, the patient was treated with high-dose oral and intravenous potassium supplements and a diet enriched with potassium; his serum potassium ranged between 2.2 mEq/L and 2.8 mEq/L. The causes of hypokalemia, in this case, was approached systematically wherein the dietary causes and possibility of redistribution of potassium was excluded by taking meticulous history. Also in the former case, potassium should have returned to normal after intravenous correction. The possibility of familial hypokalemic periodic paralysis and thyrotoxic periodic paralysis is not possible as there is no obvious paralysis and thyroid function tests were normal. There was a possibility of the following diagnosis because of metabolic alkalosis- Primary hyperaldosteronism and other familial hyperaldosteronism, Cushing syndrome, renin secreting tumour, Liddle syndrome, renal artery stenosis and syndrome of apparent mineralocorticoid excess. Another possible mechanism of hypokalemia may be due to concurrent use of furosemide diuretic, however, in our case, the patient was not on any diuretic. As there was no hypertension with 8 AM cortisol being low and normal levels of Plasma renin and serum aldosterone, we ruled out Cushing syndrome, primary hyperaldosteronism and renin secreting tumours. Thus we conclude that the hypokalemia was due to syndrome of apparent mineralocorticoid excess (SAME) and the possible aetiology being abiraterone acetate.

Cortisol exhibits circadian rhythm in its secretion wherein there is the lowest level at midnight and peak level after waking and slowly return to their nadir. Serum cortisol level is regulated by negative feedback on the hypothalamic-pituitary-adrenal axis. Low cortisol stimulates paraventricular nucleus of the hypothalamus to release corticotropin-releasing hormone(CRH) which triggers anterior pituitary to release adrenocorticotrophic hormone (ACTH), thus increasing cortisol from adrenals. Up to a fivefold increase in ACTH causes hypokalemia, fluid retention, and hypertension as a consequence of deoxycorticosterone excess. Abiraterone acetate is a potent, selective and irreversible inhibitor of CYP17A1, a microsomal enzyme with 17 alpha-hydroxylase and C 17,20 lyase activities that are required for androgen biosynthesis via both classic and backdoor pathway[1, 2]. Normally, under the influence of ACTH, 17 alpha-hydroxylase catalyses the conversion of pregnenolone into 17OH-pregnenolone which is then acted upon by C17,20 lyase to form DHEA. DHEA is then converted to testosterone. Thus abiraterone reduces the serum androgens and cortisol by inhibiting two key enzymes in the pathway. We can see that androgen biosynthesis requires both the enzymes whereas cortisol synthesis requires only 17 α hydroxylase activity. In studies of mCRPC patients, abiraterone reduced serum cortisol to near the lower limit of the normal range [3] and increased ACTH from a median of 17 pg/mL (range: ,9–50 pg/mL) to a median of 124 pg/mL(range: 46–370pg/mL) [2].

Abiraterone acetate (1,000 mg) coadministered with prednisone (5 mg twice daily) was compared with placebo plus prednisone in patients with mCRPC in two phase III, multinational, double-blind, randomized, placebo-controlled trials. StudyCOU-AA-301 comprised 1,195 patients with mCRPC who had progressed after docetaxel treatment [3,4], and study COU-AA-302 involved 1,088 patients with mCRPC who had not received chemotherapy and who did not have clinically significant cancer-related symptoms (i.e., asymptomatic or minimally symptomatic patients)[5]. Both studies evaluated treatment effects on survival and disease progression, showing clinically meaningful and significant benefits in favour of abiraterone acetate plus prednisone [5,6]. Based on the results from these studies, abiraterone acetate in combination with prednisone was approved for the treatment of patients with mCRPC.

In syndrome of apparent mineralocorticoid excess [SAME], cortisol acts as a potent mineralocorticoid. Suppression of plasma cortisol with dexamethasone results in natriuresis, potassium retention and reduction in blood pressure. [7] In congenital form of SAME, there is deficiency of the enzyme 11 beta-hydroxysteroid dehydrogenase which converts cortisol and cortisone. Acquired causes for SAME are excess ingestion of liquorice, carbenoxolone and drugs inhibit the enzyme and results in persistent hypokalemia. In such patients cortisol binds to mineralocorticoid receptors resulting in SAME.

Our patient was already on long term prednisolone which can cause HPA axis suppression inducing secondary adrenal insufficiency. Thus the hypokalemia and hypotension in our case can be explained by inhibition of CYP17 by abiraterone

acetate and secondary adrenal insufficiency, a case of Syndrome of Apparent Mineralocorticoid Excess (SAME). Hypokalemia due to SAME might be well known among the oncology brethren however for the rest of the medical fraternity though not abstruse, it is a cabalistic diagnosis.

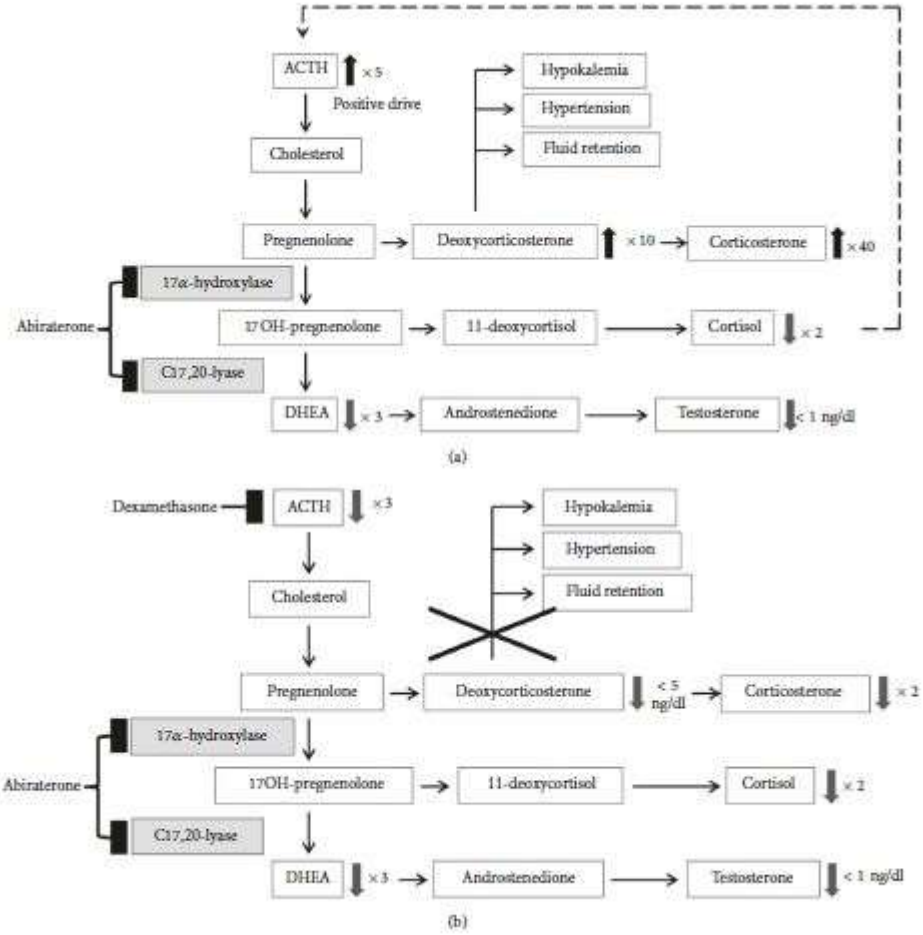

FIGURE 1: (a) Steroid biosynthesis pathway under abiraterone monotherapy. (b) steroid biosynthesis pathway under abiraterone plus dexamethasone. Inhibition of 17 alpha hydroxylase and C17 and 20-xylase result in a decrease of cortisol and a consequent increase in ACTH. Increased ACTH causes hypokalemia, fluid retention an hypertension as a consequence of deoxycorticosterone excess. Addition of dexamethasone 0.5mg/dl to adiraterone results in suppression of ACTH and a consequent decrease in deoxycorticosterone that prevents hypokalemia, fluid retention and hypertension.[2]

Source: Figure 3, Yamamoto Y, Akashi Y, Minami T, et al. Serious Hypokalemia Associated with Abiraterone Acetate in Patients with Castration-Resistant Prostate Cancer. *Case Rep Urol.* 2018;2018:1414395

CONCLUSION

Persistent hypokalemia always imposes diagnostic and therapeutic difficulties in patient care, especially elderly patients. Persistently low serum potassium inspite of adequate correction will raise the possibility of several specific etiological entities which needs to be promptly identified. Syndrome of apparent mineralocorticoid excess(SAME) is not an uncommon but under-reported entity in the medical world. Treatment of such cases with low dose prednisone lowers the ACTH levels and in turn, reduce the mineralocorticoid related complications like hypokalemia in mCRPC patients treated with Abiraterone acetate.

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