Case Report

RHABDOMYOLYSIS IN PRIMARY ALDOSTERONISM: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Objective: Primary aldosteronism is one of the most common causes of secondary hepertension. We present here a case of primary aldosteronism in a 38-year-old Chinese male with a 6-year history of uncontrolled hypertension that evaded diagnosis until an attack of rhabdomyolysis due to profound hypokalemia. We also present the results of a comprehensive review of the current literature.

Methods: We describe the presentation and symptoms of the patient and review the relevant literature. A thorough literature search disclosed 15 further cases of rhabdomyolysis due to undiagnosed primary aldosteronism reported between 1978 and 2013. We summarized the clinical features, treatments, and outcomes of those cases.

Results: Many of the cases presented with previous hint of primary aldosteronism, yet they evaded diagnosis. Three of these patients developed acute renal failure. All patients survived, and many of them were restored to normal blood pressure and normal serum potassium levels after adrenal surgical interventions.

Conclusion: Primary aldosteronism can lead to severe acute consequences of rhabdomyolysis via hypokalemia. It is important to alert physicians to the need for hyperaldosteronism workup when a rhabdomyolysis patient is found to be hypokalemic. **(AACE Clinical Case Rep. 2015;1:e21-e27)**

Abbreviations:
ARR = aldosterone to renin ratio; **AVS** = adrenal venous sampling; **CPK** = creatinine phosphokinase; **CT** = computed tomography; **PA** = primary aldosteronism; **PAC** = plasma aldosterone concentration; **PRA** = plasma renin activity

INTRODUCTION

Primary aldosteronism (PA), a well-known cause of secondary hypertension, is characterized by excessive aldosterone and suppressed plasma renin activity. PA is generally regarded as a latent and chronic condition. Typical clinical presentations are uncontrolled hypertension, hypokalemia, and metabolic alkalosis. However, acute or even life-threatening complications can occur in patients with untreated PA.

In this article, we report the case of a 38-year-old Chinese male with a history of poorly controlled "essential" hypertension. He was misdiagnosed as 'hemolytic' at a local primary hospital, with symptoms of vomiting, myalgia, and dark urine and was finally found to have PA, which caused the hypokalemic rhabdomyolysis. Thus, a rare event chain encompassing PA, hypokalemia, and rhabdomyolysis was verified. A review of the current literature focusing on rhabdomyolysis was also conducted and the results are summarized.

CASE REPORT

A 38-year-old male with a diagnosis of "essential" hypertension for 6 years was admitted to a primary local

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hospital because of a sudden onset of painful limbs, vomiting, and dark urine. Physical examination and laboratory results included moderate fever (38.4°C), decreased muscle strength, profound hypokalemia (potassium, 1.4 mmol/L), significant enzyme abnormalities (aspartate transaminase, 850 U/L; alanine transaminase, 307 U/L; creatinine phosphokinase [CPK], >10,000 U/L; lactate dehydrogenase, 4,293 U/L), positive urine protein, negative urine red blood cells, urine occult blood (+++), and increased indirect bilirubin (19.7 mmol/L). Metoprolol was stopped. After vigorous hydration and intravenous potassium supplementation, the patient's urine color and muscle strength returned to normal, and he was then referred to the hematology department of our hospital with a diagnosis of "acute hemolysis and liver damage of unknown reason."

Upon admission to our hospital, a more detailed history was obtained. Uncontrolled hypertension, with a blood pressure of 130 to 160/80 to 110 mm Hg on metoprolol 95 mg/day and felodipine 10 mg/day, and a 3-year history of recurrent and self-relievable weakness and slight soreness of the limb muscles were revealed. No herbal treatment, licorice, or lipid-lowering agents (including statins) was ever used before. Physical examination showed that blood pressure was 165/102 mm Hg, the waist-to-hip ratio was 0.85, the body mass index was 22.8 kg/m^2, and his muscle strength was normal. The results of primary laboratory measurements are listed in Table 1. These measurements indicated hypokalemia, elevated enzymes, and normal thyroid hormone levels. Based on the patient's history of early onset and uncontrolled hypertension along with the absence of metabolic syndrome, long-term muscular weakness and hypokalemia with high tolerance to hypokalemia (minimal symptoms with a potassium concentration of 2.8 mmol/L at admission), PA was strongly suspected.

The patient was then transferred to the endocrinology department and placed on felodipine 10 mg/day. High-normal plasma aldosterone concentration (PAC) and suppressed plasma renin activity (PRA) were found when the potassium concentration was 2.98 mmol/L, leading to a positive aldosterone to renin ratio (ARR) of 130 (Table 1). A captopril challenge test conducted for confirmation further affirmed the diagnosis of PA. During the captopril test, the patient's PRA and PAC were 0.24 ng/mL/hour and 10 ng/dL before the test and 0.02 ng/mL/hour and12 ng/dL after the test, respectively, indicating that his PRA was still suppressed and that his PAC had not declined. An adrenal computed tomography (CT) scan was then performed and revealed a normal left adrenal grand and a soft-tissue dense right adrenal mass measuring 1.0 cm in diameter, with homogeneous enhancement (Fig. 1). The patient refused to undergo adrenal venous sampling (AVS), although his endocrinologists strongly recommended this for subtype classification. Considering the patient's early onset hypertension, positive ARR and confirmatory test results, CT scan results, and the patient's unwillingness to undergo AVS, the patient was referred for laparoscopic surgery to remove the right adrenal tumor (Fig. 2) on the suspected diagnosis of 'aldosterone-producing adenoma'. The resected mass showed a typical golden-yellow appearance, and the results of histologic analysis were consistent with adrenal adenoma (Fig. 2).

Immediately after surgery, the patient's ARR dropped to 16.7 (Table 1). However, his blood pressure remained high (160 to 180/60 to 70 mmHg). The patient was discharged on the seventh day after surgery, with normal potassium level and blood pressure of 140/80 mm Hg on nifedipine 60 mg/day. One month later, the patient returned to the outpatient clinic with normal serum potassium level and a stable blood pressure of 130/70 mm Hg on nifedipine 30 mg/day.

Literature Review

Using PubMed Central (including MEDLINE), EMBASE, and Google Scholar, a thorough internet-based search of the English-language literature was conducted using the key words "rhabdomyolysis," "hypokalemia," "primary aldosteronism," and "Conn's syndrome," for articles published between 1978 and 2013. A total of 15 other cases of rhabdomyolysis due to undiagnosed PA were found. Pertinent secondary references were also retrieved and reviewed. As there was no consensus on the level of CPK for the diagnosis of rhabdomyolysis, we considered a level equal or greater than 1,500 U/L as the criterion. A total of 15 cases of PA complicated by hypokalemic rhabdomyolysis were identified (1-14). Clinical features, diagnosis data, and treatment and outcomes of all cases are summarized in Table 2.

DISCUSSION

Rhabdomyolysis is the abrupt degradation or resolution of myocytes and occurs when the sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump in the sarcolemma and/or the calcium exchanger (i.e., Ca^{2+}-ATPase pump) becomes dysfunctional, causing an increase in cellular permeability to sodium, excess intracellular calcium, and then activation of intracellular proteolytic enzymes that destroy the muscle cells. Rhabdomyolysis is a clinical emergency because it has the potential to lead to acute renal failure when the myoglobin released plugs renal tubules. The common and well known causes of rhabdomyolysis include excessive physical exertion, trauma, alcoholism, certain drugs (such as statins), and certain genetic disorders. When a patient presents to a physician with typical presentations of myalgia with the obvious predisposing factors listed above, the physician should promptly consider rhabdomyolysis as the diagnosis after measurement of CPK level. However, under condition in which clinical

Table 1
Laboratory Data on Admission

Item	Value	Reference Range
CBC		
RBC (/L)	4.35×10^{12}	$(4.3\text{-}5.8) \times 10^{12}$
HGB (g/L)	129	130-175
WBC (/L)	9.74×10^{9}	$(3.5\text{-}9.5) \times 10^{9}$
PLT (/L)	303×10^{9}	$(100\text{-}350) \times 10^{9}$
Serum Laboratory Tests		
AST (U/L)	715	15-40
ALT (U/L)	569	3-35
CPK (U/L)	2,974	24-184
CK-MB (U/L)	92	0-24
LDH (U/L)	1,104	71-231
ALB (g/L)	38.8	36.0-51.0
TBIL (μmol/L) DBIL (μmol/L)	10.73 3.5	4.0-23.9 0-6.8
ALP (U/L)	64.0	35-125
GGT (U/L)	15.0	10-60
BUN (mmol/L)	2.03	2.4-8.2
CREAT (μmol/L)	86	31.8-116
Random glucose (mmol/L)	7.46	6.1-7.8
UA (μmol/L)	136.8	90-420
K (mmol/L)	2.8	3.5-5.3
Na (mmol/L)	145.6	137-147
CO_2 (mmol/L)	26.3	20.2-29.2
Urinalysis		
RBC	(–)	(–)
Occult blood	+++	(–)
pH	7.0	5.4-8.4
Gravity	1.010	1.003-1.030
Urobilinogen (μmol/L)	3.2	3.2-16
Thyroid Tests		
FT_3 (pmol/L)	5.6	3.5-6.5
FT_4 (pmol/L)	21.19	11.5-22.7
TSH (μIU/mL)	2.415	0.55-4.78
PRA (ng/mL/h)		
Before operation	0.1	0.05-0.79
After operation	0.12	0.05-0.79
PAC (ng/dL)		
Before operation	13	5.9-17.4
After operation	2	5.9-17.4
ARR (ng/dL per ng/mL/h)		
Before operation	130	
After operation	16.7	

Abbreviations: ALB = albumin; ALP = alkaline phosphatase; ALT = alanine transaminase; ARR = aldosterone to renin ratio; AST = aspartate transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CK-MB = creatine phosphokinase isoenzyme-MB; CPK = creatine phosphokinase; CREAT = creatinine; DBIL = direct bilirubin; FT_3 = free triiodothyronine; FT_4 = serum free thyroxine; GGT = glutamyltranspetidase; HGB = hemoglobin; LDH = lactate dehydrogenase; PAC = plasma aldosterone concentration; PLT = platelets; PRA = plasma renin activity; RBC = red blood cells; TBIL = total bilirubin; TSH = thyroid-stimulating hormone; UA = uric acid; WBC = white blood cells.

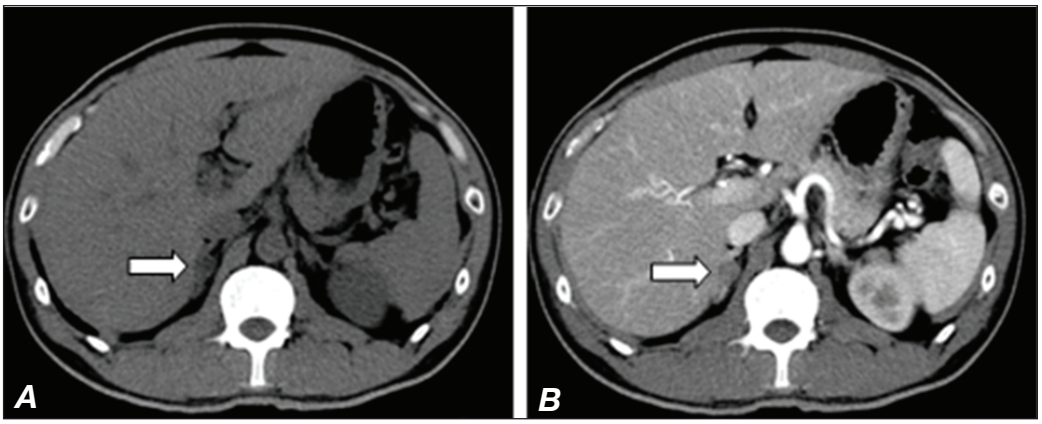

Fig. 1. Computed tomography: Nodular mass on the right adrenal gland (arrow in *A*) with honogenous enhancement (arrow in *B*).

manifestations of rhabdomyolysis are confounded by other symptoms or indications in the history are absent, the diagnosis could be missed.

Hypokalemia is a rare but well-established cause of rhabdomyolysis through derangement of Na/K-ATPase, which serves as the link between PA and rhabdomyolysis. The risk of PA causing rhabdomyolysis due to severe hypokalemia is relatively low, because not all patients with PA have low serum potassium concentrations. Several studies have shown that only a small proportion of patients (between 9 and 37%) are hypokalemic (15,16). Milder forms of myopathy resulting from hypokalemia, such as mild muscular weakness and extremity paresthesias, are much more commonly seen, especially in Chinese populations (17,18). Because of its relatively mild and the seeming lack of correlation with hypertension in the eyes of patients, myopathy from hypokalemia in PA is not always complained of to physicians or is interpreted as fatigue and overlooked by physicians. Fourteen of the 15 cases detailed in our literature review involved chronic muscular symptoms, but none were given due attention or inspection. In one case, the condition was diagnosed as transient ischemic attack without measurement of serum electrolytes (1). In the present case, the patient was prescribed

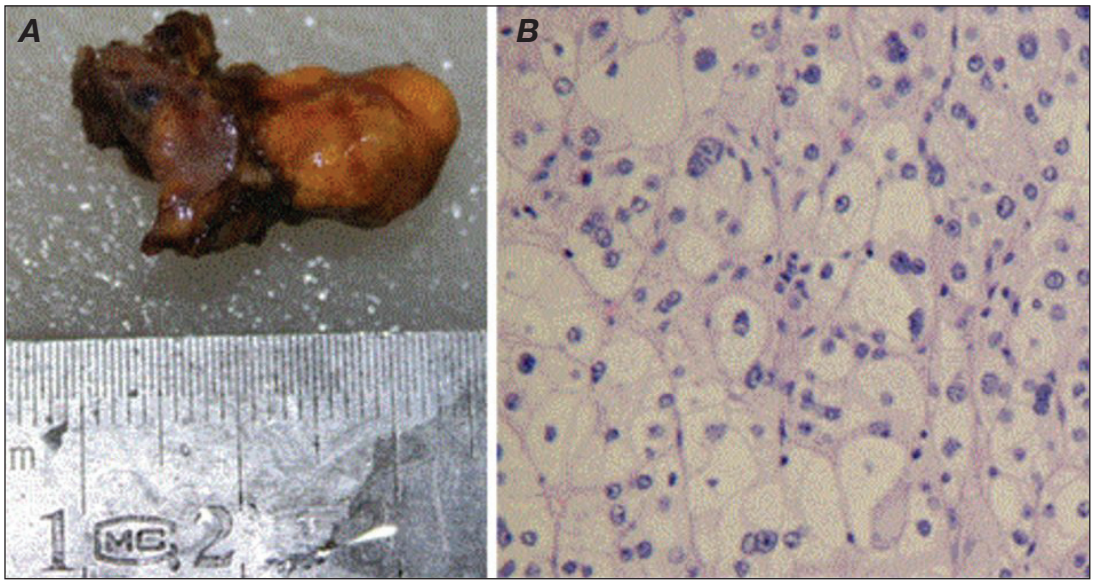

Fig. 2. *A)* Macroscopically: The mass is measured 1.5 × 1 × 0.8 cm at the largest diameters with some atrophic adrenal tissue at side. It is well-circumscribed and encapsulated with a typical golden yellow appearance. *B)* Microscopically: The tumor consists mainly of clear cell with abundant intracytoplasmic lipid droplets (vacuolated cytoplasm), low nucleocytoplasmic ratio, small rounded nuclei and indistinct nucleoli. These cells form cords and nests with relatively abundant vasculature or sinusoidal structures. Giant cells with mononuclear or multinuclear scatter around. Karyokinesis is not found.

Table 2
Summary of Clinical Features, Diagnosis Data, Treatment, and Outcomes of All Cases

Case (ref.)	Age (years)	Sex	History of hypertension	Anti-HTN drugs	BP at admission (mm Hg)	Muscular weakness	K+ (mmol/L)	Na (mmol/L)	CO_2 (mmol/L)	CK (U/L)	PAC (ng/dL)	ARR (ng/dL per ng/mL/h)	Confirmatory tests	AVS	Image investigation	Subtype
1 (1)	55	M	5 years	Amlodipine, Valsartan, HCT	138/68	Yes	1.4	152	38	15,760	26.6	>266	NA	Yes	CT	Adenoma
2 (2)	73	M	10 years	Amlodipine	140/80	Yes	1.6	NA	37	7,463	49.8	71.14	NA	NA	CT	Uniliteral hyperplasia
3 (3)	42	F	No	None	166/108	Yes	1.3	138	38.8	21,000	96.6	>241.5	Saline infusion	NA	CT	Adenoma
4 (4)	14	F	NA	None	160/120	No	1.7	145	Metabolic alkalosis	3,375	29.5	>147.5	NA	NA	CT, MR	Adenoma
5 (5)	28	F	No	None	174/111	Yes	1.8	143	30.3	12,147	19.8	141	NA	NA	CT	Adenoma
6 (6)	36	F	6 years	Atenolol, Chlorthalidone	152/108	Yes	2.2	NA	37	2,860	0.0174	>0.087	Saline infusion	NA	CT	Adenoma?
7 (7)	50	F	4 years	Amlodipine	180/70	Yes	1.95	NA	NA	9,546	62.2	NA	NA	NA	Ultrasound, CT	Nodular hyperplasia
8 (8)	45	F	4 years	Nitrendipine, Captopril	143/80	Yes	1.38	142.1	24.4	4,907	63.9	76.12	NA	NA	CT	Adenoma
9 (9)	44	F	NA	NA	NA	Yes	1.98	146	31.9	8,531	44.97	642.43	NA	NA	CT	Adenoma
10 (9)	42	F	2 years	Nifedipine, atenolol, losartan	160/100	Yes	2.0	145	38	11,347	22,600	113,00000	NA	NA	CT	Adenoma
11 (10)	44	F	3 years	ACEI, verapamil	160/90	Yes	1.2	137	NA	6,133	46	153.3	NA	NA	CT	Adenoma
12 (11)	30	F	5 years	Fosinopril, HCT, furosemide	170/100	Yes	1.3	146	30	1,751	97.1	NA	NA	NA	Ultrasound, CT	Adenoma
13 (12)	32	F	2 years	β-blocker, HCT	170/110	Yes	2.0	NA	NA	10,000	29	58	Saline infusion	NA	Scintigraphy	Adenoma
14 (13)	60	M	3 years	Metoprolol, methyldopa	185/100	Yes	1.4	144	NA	36,000	22	0.23	NA	NA	CT	NA
15 (14)	49	M	NA	HCT	150/100	Yes	2.5	142	19	12,030	90	300	Saline infusion	Yes	NA	Adenoma

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARR = aldosterone to renin ratio; AVS = adrenal venous sampling; BP = blood pressure; CK = creatine kinase; CT = computed tomography; F = female; HCT = hydrochlorothiazide; HTN = hypertension; M = male; MR = magnetic resonance; NA = not available; PAC = plasma aldosterone concentration.

antihypertensive medications by his physician every 2 months for nearly 6 years, but the muscle symptoms were never considered.

Although PA is recognized as the most frequent cause of endocrine hypertension, it is not easy to diagnose and has a low degree of diagnostic suspicion. One important reason for missed diagnoses of PA in hypokalemia-induced rhabdomyolysis is that a wide variety of ailments could lead to this electrolyte abnormality, which masks the possible prime underlying condition, especially when the association between PA and rhabdomyolysis is not well recognized. Among the 15 reviewed cases, 11 patients had hypertension plus chronic muscular weakness. Nevertheless, none of these patients was subjected to further evaluation of their PA before the episode of rhabdomyolysis. Presumably, better application of the guidelines (19) would be helpful in diagnosing PA and preventing this acute complication. In the present case involving uncontrolled hypertension, the algorithm recommended by the Endocrine Society Clinical Practice Guidelines places a high value on the diagnosis of PA (19), but AVS was not performed.

Once diagnosed, treatment of PA is often straightforward, involving either removal of the aldosterone-secreting tumor or use of aldosterone antagonists. After these interventions, most of the pathologic changes caused by excessive aldosterone, including hypertension, hypokalemia, and metabolic alkalosis could revert to normal. Duration of hypertension has been reported by several studies as a negative predictor of outcome following unilateral adrenalectomy for aldosterone-producing adenomas (20), suggesting that delays in diagnosis may result in a poorer response to specific treatment once PA is finally diagnosed. The 6-year delay in PA diagnosis may have been the reason that our patient had to take antihypertension agents after adrenalectomy.

Several issues should be addressed in this case report. First, adopting the ARR to detect PA is accepted in order to avoid delays and allow the patient to proceed directly to confirmatory testing. However, it is known that continued medication or suboptimal conditions of testing may have impact on the ARR. Felodipine (a calcium-channel blocker) use in this patient with hypokalemia when measuring the PAC and PRA may decrease the ARR, which could lead to false-negative results. But, as we report here, the ARR in this case was still positive, strongly suggesting a diagnosis of PA. Second, as recommended in the Endocrine Society Clinical Practice Guidelines, patients with a positive ARR should undergo any of 4 confirmatory tests, including oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge in order to definitively confirm or exclude the diagnosis. Actually, all four of these confirmatory tests are in common use; there is currently insufficient direct evidence to recommend one over the others. It should be noted that confirmatory tests requiring oral or intravenous sodium loading should be administered with caution in patients with uncontrolled hypertension or congestive heart failure, which leads to adoption of the captopril challenge test in many clinical centers. Third, although AVS was not performed in this case in consideration of the patient's unwillingness and the solitary unilateral apparent adenoma on CT scan, it should be noted that AVS by an experienced radiologist is necessary for distinguishing between unilateral and bilateral adrenal disease.

CONCLUSION

The present and reviewed cases indicate that without proper diagnosis and treatment, chronic PA can result in severe acute consequences of rhabdomyolysis via hypokalemia. Based on the information presented in our review of the pertinent literature, we highlight the importance of obtaining a detailed history and the need for a hyperaldosteronism work-up when a rhabdomyolysis patient is found to be hypokalemic.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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