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A Rare Presentation of Multiple Endocrine Neoplasia With Concurrent Aldosterone-Producing Adrenal Adenoma

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ABSTRACT

Background: Multiple endocrine neoplasia type 1 (MEN1) is a disorder characterized by the occurrence of tumours in two or more endocrine glands of a patient. Coexistence of different endocrine tumors warrants additional screening for multiple endocrine neoplasia syndromes, especially in patients with adrenal apparent adenoma.

Case presentation: We present the case of a 52-year-old male was admitted to Army Specialty Medical Center because of neck pain that had persisted for 4 months and aggravated muscle pain for 3 days. After admission, the patient showed hypertension and hypokalemia. The plasma aldosterone levels increased, and the renin levels decreased. Adrenal contrast-enhanced CT showed a nodule shadow on the left external branch of the adrenal gland, suggesting the possibility of adrenal adenoma. Other imaging examination suggested that the patient had thyroid nodules, parathyroid nodules, pituitary microadenomasm. The adrenal vein sampling (AVS) results indicated dominant secretion from the left adrenal gland. The patient was diagnosed as: 1. Primary aldosteronism-induced hypertension; 2. multiple endocrine neoplasia; 3. rhabdomyolysis; 4. hyperlipidemia; 5. fatty liver disease; 6. lumbar disc herniation; 7. fascia inflammation of the lower back. The Whole-exome sequencing of the peripheral blood from the patient showed the heterozygous variant of the genes CACNA1D and MYH8.

The patient was performed left adrenal resection surgery in the Urology Department. Postoperative pathological specimen examination suggested a (left adrenal tumor) cortical adenoma. He achieved complete biochemical success and partial clinical success.

Conclusions: Our findings confirm the need for careful genetic analysis of patients with MEN1 and establish a likely pathogenic role for the new heterozygous variant of the genes CACNA1D and MYH8, at least in the rare subset of MEN1 associated with primary aldosteronism.

INTRODUCTION

Multiple endocrine neoplasia (MEN) is a group of syndromes with a genetic predisposition to the appearance of endocrine tumors, and shows autosomal dominant transmission, mainly involving the parathyroid gland, pancreatic islets and pituitary gland. It is a rare disease, with an estimated prevalence of one in 30000 individuals and a high penetrance and an equal sex distribution Ventura et al. (2019).

The types of MEN mainly include MEN-1, MEN-2, and MEN-4, depending on the specific endocrine glands affected and the involved gene mutations.

While most patients diagnosed with MEN inherit the condition as an autosomal dominant trait, sporadic cases can occur even without family history. Adrenal lesions have been reported in about 36-73% of MEN1 patients, while the majority of adrenal tumours have been reported as non-hyperfunctioning Ventura et al. (2019).

The objective of the present study was to report on a MEN1 case characterized by primary aldosteronism, with particular concern on the possible predisposing genetic defects.

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Keywords: primary aldosteronism; multiple endocrine neoplasia; hypokalemia.

CASE PRESENTATION

A 52-year-old male was admitted to Army Specialty Medical Center because of neck pain that had persisted for 4 months and aggravated muscle pain for 3 days. The patient began experiencing neck pain, muscle stiffness, limited mobility, and lower limb fatigue 4 months prior. Cervical spine MRI in our outpatient department indicated the following: 1. Degenerative changes in the cervical spine: Cervical disc herniation from 3/4 to 6/7; and 2. a Schemer's nodule that had formed at the lower edge of the cervical vertebral body. An outpatient doctor diagnosed neck muscle strain, which improved significantly, and the patient was treated symptomatically with drugs such as etoposide. Three days prior, the patient experienced muscle pain and fatigue in the proximal left upper arm, which worsened after activity. Two days prior, the patient experienced worsening pain in the left upper arm and muscle pain in the proximal right upper arm. One day prior, the patient experienced lower back pain and aggravated traction pain while walking.

Past history The patient had a history of gout without regular uric acid lowering treatment.

Family history None.

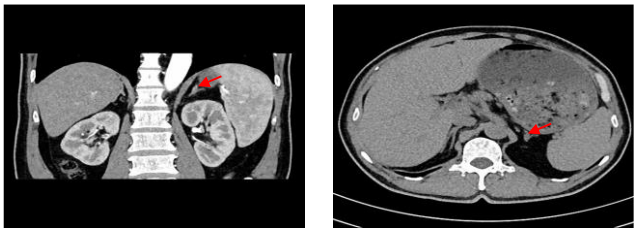
Routine laboratory tests During hospitalization, the serum K+ concentration fluctuated between 1.84 and 3.14 mmol/L. When the serum K+ concentration was 3.14 mmol/L, the 24-hour urine potassium concentration was 19.27 mmol/24 hours, and the red blood cell sedimentation rate was 20.0 mm/h. The myocardial enzyme spectrum was as follows: creatine kinase 3631 U/L and creatine kinase isoenzyme-MB 30.7 U/L. Blood lipids were as follows: triglyceride was 3.97 mmol/L; low-density lipoprotein cholesterol was 2.4 mmol/L; and high-density lipoprotein cholesterol was 0.91 mmol/L His liver function was as follows: total bilirubin 24.2 μmol/L, indirect bilirubin 20.1 μmol/L, and aspartate aminotransferase 55.8 U/L. His inorganic ion levels were as follows: total calcium, 1.98 mmol/L and inorganic phosphorus, 0.65 mmol/L. The urine microalbuminuria concentration was 85 mg/L, and the urine microalbuminuria/creatinine ratio was 93.69 mg/g. (Table 1). There were no significant abnormalities in thyroid function; prolactin, parathyroid hormone, or male hormone levels; the growth hormone levels; renal function; coagulation; and blood test results were normal.

Adrenal endocrine hormone and function testing the cortisol and ACTH hormone rhythms were both normal. According to both the upright and supine RAAS hormone measurements, the aldosterone levels increased (33 ng/dl (upright) and 37.2 ng/dl (supine)), and the renin levels decreased (< 0.5 mU/L) (Table 2).

A low-dose dexamethasone suppression test showed complete inhibition (Table 3). Based on the comparison of the results after saline load test and before test, the blood pressure was 149/95 vs. 152/98 mmHg; aldosterone was 75.9 vs. 53.5 ng/dl; and renin was <0.5 vs. <0.5 mU/L. The serum potassium levels were 3.12 vs. 2.98 mmol/L (Table 4). These findings indicated that saline loading did not reduce the patient's aldosterone levels.

Imaging examination Adrenal contrast-enhanced CT showed a nodule shadow on the left external branch of the adrenal gland, suggesting the possibility of adrenal adenoma (Figure 1).

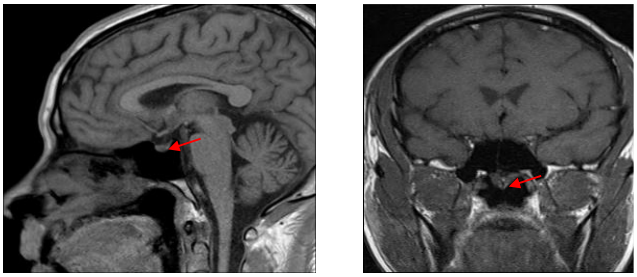
Figure 1: Adrenal contrast-enhanced CT.



Note: adrenal contrast-enhanced CT showed a nodule shadow on the left external branch of the adrenal gland, suggesting the possibility of adrenal adenoma.

Pituitary magnetic resonance imaging (MRI) revealed an abnormal signal in the pituitary gland, suggesting a pituitary microadenoma (Figure 2).

Figure 2: Pituitary MR image.



Note: An abnormal signal in the pituitary gland was considered a pituitary microadenoma.

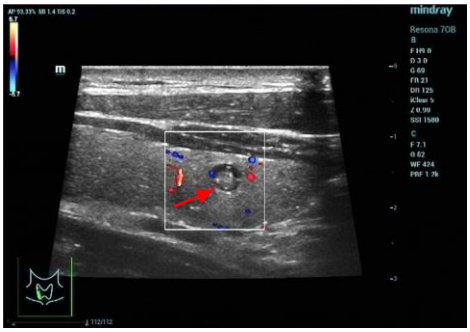
Parathyroid ultrasound revealed that the morphology of the right parathyroid gland was enlarged, and the echo was decreased, suggesting an adenoma or a cyst (Figure 3). Thyroid ultrasound revealed a cystic solid echogenic nodule in the right lobe of the thyroid (inclined toward the TI-RADS 3 type) and a cystic echogenic nodule in the left lobe of the thyroid (inclined toward the TI-RADS 2 type) (Figure 4). Cervical spine MRI indicated the following: 1. degenerative changes in the cervical spine and cervical disc herniation from 3/4 to 6/7. 2. A Shermer's nodule had formed at the lower edge of the cervical vertebral body. Electrocardiogram examination

Table 1: Laboratory Data

Variable	Reference Range†	On Admission
Serum K+ (mmol/L)	3.5-5.3	3.14
24-hour urine potassium (mmol/24 hours)	35-100	19.27
Red blood cell sedimentation rate (mm/h)	27-34	20
Myocardial enzyme spectrum		
Creatine kinase (U/L)	50-310	3631
Creatine kinase isoenzyme-MB (U/L)	Jan-25	30.7
Blood lipids		
Triglyceride (mmol/L)	0.3-1.7	3.97
Low-density lipoprotein cholesterol (mmol/L)	1.55-3.12	2.4
High-density lipoprotein cholesterol (mmol/L)	1.16-1.42	0.91
Liver function		
Total bilirubin (umol/L)	1.7-23	24.2
Indirect bilirubin (umol/L)	0.00-16.2	20.1
Aspartate aminotransferase (U/L)	15-40	55.8
Inorganic ions		
Total calcium (mmol/L)	3.11-2.52	1.98
Inorganic phosphorus (mmol/L)	0.85-1.51	0.65
Urine Microalbuminuria (mg/L)	0.00-23.00	85
Urine Microalbuminuria/creatinine (mg/g)	0.00-30.00	93.69
Autoantibody		
Anti ScI-70 antibody	Negative	Positive (++)
Antinuclear antibody	Negative	Weakly positive
Urine osmolality (mOsm/L)	600-1000	290

†Reference values are affected by many variables, including patient population and laboratory methods used. The ranges used at Army Specialty Medical Center are for adults who were not pregnant and did not have medical conditions that could affect the results. Therefore, these methods may not be appropriate for all patients.

Figure 3: Parathyroid ultrasound

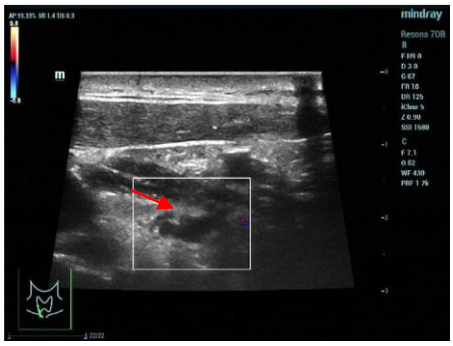


Note: The morphology of the right parathyroid gland was enlarged, and the echo was decreased, suggesting an adenoma or a cyst.

Table 2: Additional Laboratory Data.

Variable	Reference Range	On Admission
Cortisol rhythm		
8:00 (nmol/L)	185-624	279.73
16:00 (nmol/L)	185-624	199.78
0:00 (nmol/L)	<276	198.09
ACTH rhythm		
8:00 (pg/mL)	4.7-48.8	2.91
16:00 (pg/mL)	4.7-48.8	24.81
0:00 (pg/mL)	4.7-48.8	23.99
growth hormone		
8:00 (ng/mL)	0.003-0.971	0.02
16:00 (ng/mL)	0.003-0.971	0.01
0:00 (ng/mL)	0.003-0.971	0.1
Insulin growth factor (ng/mL)	46-230	124.1
RAAS hormone in supine position		
Aldosterone (ng/dl)	3.0-23.6	37.2
Renin (mU/L)	2.8-39.9	< 0.5
RAAS hormone in the upright position		
Aldosterone (ng/dl)	Mar-40	33
Renin (mU/L)	4.4-46.1	< 0.5

Figure 4: Thyroid ultrasound



Notes: A cystic solid echogenic nodule in the right lobe of the thyroid (inclined toward the TI-RADS 3 type) and a cystic echogenic nodule in the left lobe of the thyroid (inclined toward the TI-RADS 2 type) are shown.

Table 3: Low-dose dexamethasone suppression test

	Reference Range	Before test	After test
Plasma cortisol (nmol/L)	185-624	279.73	21.38
ACTH (pg/mL)	4.7-48.8	3.91	2.91

Table 4: Saline load inhibition test

	Before test	After test
Blood pressure （mmHg）	149/95	152/98
Aldosterone （ng/dl）	75.9	53.5
Renin （mU/L）	<0.5	<0.5
Serum potassium （mmol/L）	3.12	2.98

revealed sinus rhythm and ST-T changes. A chest X-ray showed no obvious abnormalities.

Genetic testing Whole-exome sequencing was performed on the peripheral blood of the patient (Figure 5), and the results indicated the presence of the pathogenic genes CACNA1D and MYH8. The heterozygous variant of CACNA1D; NM_000720.2:c.4750+18G>A. CACNA1D mutations were associated with developmental delay, elevated aldosterone levels and transient hypoglycemia Scholl et al.(2022). This gene has not yet been reported to be associated with multiple endocrine neoplasia. However, this gene has been confirmed to be pathogenic for primary aldosteronism, epileptic seizures, and neurological abnormalities (OMIM: 615474). Another heterozygous variant of MYH8, NM_ 002472.2: c.5351G>A (p.Arg1784Gln), was detected, but there are no relevant reports about multiple endocrine neoplasia harboring this variant.

Figure 5: Clinical whole-exome detection

Sequence number	Gene	Chromosomal location	Transcript number; nucleotide change	Gene subregion	Genotype	Pathogenic classification	Associated disease/inheritance patterns
1	CACNA 1D	chr3:53814173	NM_000720.2: c.4750+18G>A	IVS39/IC39	heterozygosis	undetermined significance	primary aldosteronism, seizures and Neurological abnormalities (OMIM: 615474)/AD sinus node dysfunction with deafness (OMIM: 614896)/AR
2	MYH8	chr17:10296260	NM_002472.2: c.5351G>A (p.Arg1784Gln)	EX37/CDS35	heterozygosis	undetermined significance	type 7 Distal joint contracture (OMIM: 158300)/AD variant Carney syndrome (OMIM: 608837)

Note: The variations related to clinical phenotype. The MYH8;NM_ 002472.2:c.5351G>A (p.Arg1784Gln) mutation was detected. There were no reports of this mutation. According to the ACMG guidelines (appendix), this variant was identified as a variant of unknown significance, PM2+PP3, with the following evidence items: PM2: Mutations (or extremely low frequency loci in recessive genetic diseases) not found in the normal control population in the ESP databases, thousand person databases, and EXAC databases. PP3: Multiple statistical methods predict that this mutation will have harmful effects on genes or gene products, including conservative prediction, evolutionary prediction, and splicing site influence. For example, in the case of CACNA1D, the mutation NM_ 000720.2:c.4750+18G>A was detected, but there are no reports of this mutation. According to the ACMG guidelines (appendix), this variant has been identified as a significant unknown variant, PM2, with the following evidence items: PM2: Variations (or extremely low frequency loci in recessive genetic diseases) not found in the normal control population in the ESP databases, thousand person databases, and EXAC databases.

Based on the improved inspection results, the doctors in the Endocrinology Department diagnosed the patient as follows:

1. Primary aldosteronism-induced hypertension; 2. multiple endocrine neoplasia; 3. rhabdomyolysis; 4. hyperlipidemia; 5. fatty liver disease; 6. lumbar disc herniation; 7. fascia inflammation of the lower back.

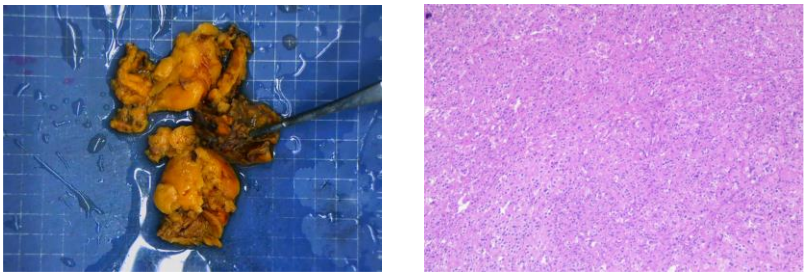
Further treatment Based on the above diagnostic and treatment steps, the patient was subjected to adrenal vein sampling (AVS) and localization examination. The AVS results indicated dominant secretion from the left adrenal gland, which was consistent with the morphological manifestations of adrenal CT (Table 5). The main treatment method for functional MEN is surgery. The adrenal tumors of this MEN1 patient were unilateral lesions, so unilateral resection was feasible. Therefore, the patient had indications for surgical intervention. The next step was to perform left adrenal resection surgery in the Urology Department. Postoperative pathological specimen examination suggested a (left adrenal tumor) cortical adenoma (Figure 6).

Follow-up The patient underwent a follow-up examination of serum potassium (3.91 mmol/L) on the second day after surgery. Additionally, spironolactone and potassium chloride supplementation therapy were discontinued. Regular postoperative follow-up was performed. At 1 month after surgery, his blood pressure was 130/80 mmHg, his serum potassium concentration was 4.88 mmol/L,

Table 5: Localization examination of adrenal vein samples.

	ALD (ng/dL)	**DRC (mU/L)**	**Cor (nmol/L)**	**Standardization ALD %**
Periphery	106	<0.5	314.91	33.66
Left 1	366	<0.5	10703.6	3.42
Left 2	498	<0.5	11015.69	4.52
Right	127	<0.5	11641.85	1.09
	SI	CI		L1
Right/inferior vena cava	36.97	0.03	Right/left 1	0.32
Left 1/inferior vena cava	33.99	0.1	Left 1/Right	3.13
LI>2	Left dominant secretion			

Figure 6: Gross and pathological specimen.



Note: The gross specimen was removed during surgery (left); the tumor was stained with HE.

his aldosterone concentration was 5.6 ng/dl, and his renin concentration was 15.9 mU/L (Table 6). This patient achieved complete biochemical success and partial clinical success.

Final Diagnosis 1. Primary aldosteronism-induced hypertension; 2. multiple endocrine neoplasia; 3. rhabdomyolysis; 4. hyperlipidemia; 5. fatty liver disease; 6. lumbar disc herniation; 7. fascia inflammation of the lower back.

Table 6: Postoperative follow-up examination results

	Before surgery	**2 days after surgery**	**1 month after surgery**
Serum potassium (mmol/L)	1.84	3.91	4.88
SBP/DBP (mmHg)	153/83	140/90	130/80
Aldosterone (ng/dl)	33	—	5.6
DRC (mU/L)	<0.5	—	15.9
ARR	—	—	0.35
medical treatment	nifedipine GITs 30 mg, Irbesartan 300 mg, Spironolactone 100 mg	Irbesartan 150 mg	Irbesartan 150 mg

Notes: ARR: plasma aldosterone/direct renin; SBP, systolic blood pressure; DBP, diastolic blood pressure.

DISCUSSION

This study reported a 52-year-old male sought medical because of neck and muscle pain. The main manifestations of this patient were hypokalemia and hypertension with elevated plasma aldosterone and decreased renin. Main diagnosises were primary aldosteronism-induced hypertension and multiple endocrine neoplasia. Whole-exome sequencing indicated the heterozygous variant of CACNA1D; NM_000720.2: c.4750+18G>A and heterozygous variant of MYH8, NM_ 002472.2: c.5351G>A (p. Arg1784Gln). The patient underwent left adrenal resection surgery. Postoperative pathological specimen examination suggested a (left adrenal tumor) cortical adenoma. Postoperative follow-up suggested the patient achieved complete biochemical success and partial clinical success.

MEN1 is an autosomal dominant disorder characterized by the presence of endocrine tumors in several organs. Although previous studies report that 20 to 73% of the MEN1 patients could develop adrenocortical tumors depending on laboratory and imaging examination methods, only few of them are functional or become functional during followup Zhao et al. (2024). Our case is an extremely unusual presentation because the patient developed these two infrequent features: multiple endocrine neoplasia and functional adrenal adnoma, and they presented synchronously in a middle-aged patient. When MEN diagnosis is a possibility, clinical suspicion allows for other tumors to be detected early, in mild or subclinical stages, and they usually turn out to be treatable. However, the more the comorbidities are found, the more difficult the treatment is and the worse the prognosis is.

Diagnostic criteria for MEN1 were proposed in the recommendations for clinical practice published in 2012. Thus, a diagnosis of MEN1 can be made based on Sahakian et al. (2024). The pathological/clinical significance of mild adrenal enlargement, sporadic and asymptomatic incidentalomas in MEN1 patients is unknown Gatta-Cherifi et al. (2012). Besides adrenal tumors are mostly benign in MEN1 patients, consensus about the management of adrenal lesions as not yet been reached Ventura et al. (2019). Surgery is still the first-line treatment whenever it is possible.

CONCLUSION

This study, performed on patients with genetically confirmed MEN1, demonstrates that adrenal lesions are a common feature of this syndrome regardless of their genotype. Although a predominance of stable adrenal disease was observed in terms of size and hormonal secretion, some of them may cause hormonal hypersecretion and, as such, may be associated with higher morbidity and mortality and may contribute to patients' impaired quality of life. Considering the variable prevalence of adrenal lesions reported by different authors and their potential to be hormonally active, adrenal evaluation should be considered in MEN1 patients; their prompt diagnosis would avoid delays and will enable an adequate treatment and follow-up of the affected patients.

ABBREVIATIONS

MEN multiple endocrine neoplasia; MRI magnetic resonance imaging; AVS adrenal vein sampling; MEN1 multiple endocrine neoplasia type 1

DECLARATIONS

Author contributions

Conception and design:X.L.L., L.L.. Analysis and interpretation of the data: K.H.Z.,L.J.W., and T.B.C., H.X.Z.. Drafting of the article: X.L.L., L.L. and Z.C.Y.. Critical revision of the article for important intellectual content: Z.G.Z. and H.B.H. Obtaining of funding: L.L.. Administrative, technical, or logistic support: H.B.H. and Y.L.X.

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Declarations of competing interests

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

None.

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Not Applicable.

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