

CASE REPORT

Open Access



A case report and literature review of Carney complex with atrial adenomyxoma

Jing Xu¹, Meng Ye¹, Po Li², Shujing Xu¹, Miao Zhang¹, Lixin Shi³ and Juan He^{1*} 

Abstract

Background Carney complex (CNC) is a rare multiple endocrine neoplasia syndrome characterized by mucocutaneous lentiginos/blue nevi, cardiac myxoma and endocrine overactivity. Here, we report a CNC case with *PRKAR1A* gene mutation characterized by left atrial adenomyxoma to explore the diagnosis and treatment of CNC.

Case presentation A 42-year-old woman with a history of cardiac tumour surgery presented with typical features of Cushing syndrome, including central obesity, buffalo hump, mild facial plethora, purple striae on the lower abdomen, and spotty skin pigmentation. Left atrial adenomyxoma and thyroid papillary carcinoma were identified by postoperative histologic assays. Genetic screening revealed a pathogenic germline heterozygous mutation of c.682C > T (p.R228X) in exon 7 of the *PRKAR1A* gene. The clinical features and normal ACTH levels suggest this patient suffered the ACTH-independent primary pigmented nodular adrenocortical disease (PPNAD) with cyclic hypercortisolism or ACTH-dependent Cushing syndrome.

Conclusion CNC is uncommon, however, if a patient develops clinical features involving multiple endocrine and non-endocrine tumors, especially Cushing syndrome and cardiac myxoma, CNC should be considered. Genetic analysis is recommended in patients with suspected CNC.

Keywords Carney complex, Adenomyxoma, Cushing syndrome, *PRKAR1A* gene, Case report

Background

Carney complex (CNC) is a rare autosomal dominant multiple endocrine neoplasia syndrome characterized by mucocutaneous lentiginos/blue nevi, cardiac myxoma, and endocrine overactivity [1]. Patients may present with two or more endocrine tumors, including primary pigmented nodular adrenocortical disease (PPNAD), growth-hormone-secreting pituitary adenoma or prolactinoma, thyroid adenoma or carcinoma, and gonadal

tumors. Non-endocrine tumors associated with CNC include myxomas of the heart, skin or breast [2]. Mutations in the *PRKAR1A* gene encoding the cAMP-dependent protein kinase A (PKA) type 1 α subunit have been identified in more than 70% of CNC cases [3]. Here, we report a CNC case with mutated *PRKAR1A* which was characterized by left atrial adenomyxoma.

Case presentation

A 42-year-old woman was admitted to our department because of elevated blood glucose and blurred vision. This patient was diagnosed with diabetes in a local hospital during pregnancy 7 years ago, then developed blurred vision and extremity numbness. She was treated with metformin and underwent a cardiac mass surgery in our hospital 3 years ago. Postoperative histologic assays indicated this patient may have suffered a “left atrial mucinous adenocarcinoma”. In addition, the patient

*Correspondence:

Juan He

gracehj76@163.com

¹ Department of Endocrinology and Metabolism, the Affiliated Hospital of Guizhou Medical University, Guiyang 550004, China

² Department of Pathology, the Affiliated Hospital of Guizhou Medical University, Guiyang 550004, China

³ Department of Endocrinology and Metabolism, Guiqian International General Hospital, Guiyang 550004, China



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

had a history of hypertension for over 10 years and was treated with enalapril maleate. Her menarche was at the age of 15, having a menstrual period and cycle of 5–7 and 27–30 days, respectively. She had been experiencing menstrual disorders 1 year prior to this admission, manifested as a longer menstrual cycle (2–4 months) and decreased menstrual flow (2–3 days). The patient denied having relatives with a similar medical family history.

A physical examination revealed typical features of Cushing syndrome (centripetal obesity, buffalo hump, mild facial plethora and purple striae on the lower abdomen) and spotty pigmentation of facial skin and lips (Fig. 1 A-C). Laboratory findings are detailed in Table 1. Adrenal and brain computed tomography (CT) scans are shown in Fig. 1 D-F and Fig. 1 G-I, respectively. A cardiac ultrasound revealed tricuspid regurgitation. A thyroid ultrasound revealed a 6 × 6 mm slightly hypoechoic nodule in the right thyroid, classified as 4a by the thyroid imaging reporting and data system (TI-RADS),

whilst another 8 × 5 mm hypoechoic nodule in the right thyroid, as TI-RADS classification 4b (Fig. 2 A, B). Thyroid fine needle aspiration (FNA) biopsy was suspicious for right papillary thyroid carcinoma, Bethesda V (Figure S1). A breast ultrasound showed a hypoechoic nodule in the right breast suspicious for tumor-like hyperplasia with a breast imaging reporting and data system (BI-RADS) classification of 4a; double breasts with multiple hypoechoic nodules with a BI-RADS classification of 3 (Fig. 2 C, D). Furthermore, a vaginal ultrasound showed a cystic mass in the left ovarian attachments and cervical Nessler’s cyst. The bone mineral density of the lumbar vertebrae (L1, L2, L3, L4) of the patient was measured by dual-energy X-ray absorptiometry (DXA). The Z values (compared with a population of the same race, gender and age group) of the lumbar vertebrae were -3.2, -2.4, -3.1 and -2.4 for L1, L2, L3 and L4, respectively, and the total Z value of the lumbar vertebrae was -2.8, clearly indicating the presence of osteoporosis.

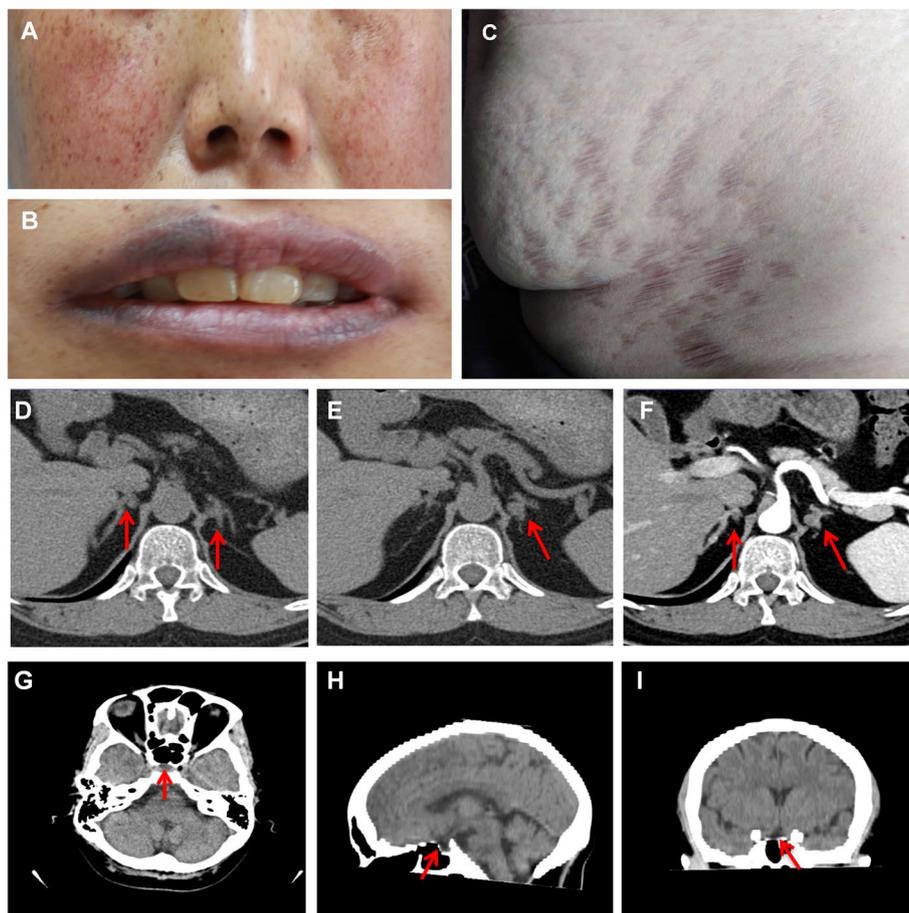


Fig. 1 Clinical characteristics and imaging of the patient. (A) Mild facial plethora, pigmented spots on the face; (B) Pigmented spots on lips; (C) Purple striae on the lower abdomen. (D-F) Adrenal computed tomography (CT) showed multiple small nodules on both sides of the adrenal glands (the larger diameter is 8 mm), considered adenomas; (G-I) Brain CT showed the ischaemic focus of the left half oval centre and the partial empty sella

Table 1 Laboratory parameters of the patient

Laboratory parameters	First visit	1 year	Reference ranges	Unit
Fasting Glucose	5.64	6.49	3.90–6.10	mmol/L
HbA1c	6.9	7.1	4.3–5.7	%
LH	7.32	33.22	1.90–12.50	IU/L
FSH	44.01	51.31	2.50–10.20	IU/L
Estradiol	114.87	293.80	71.60–529.20	pmol/l
Progesterone	0.58	0.94	0.48–4.45	ng/ml
PRL	450.51	443.00	59.00–619.00	mIU/L
Testosterone	0.63	0.09	0.29–1.67	nmol/L
ACTH 8:00 am	24.40	45.40	5.00–46.00	pg/ml
Cortisol 8:00 am (baseline)	11.21	11.40	4.30–22.40	µg/dl
Cortisol 8:00 am (1 mg dexamethasone suppression)	10.06	-	<1.8	µg/dl
Cortisol 8:00 am (low-dose dexamethasone suppression)	10.02	12.40	<1.8	µg/dl
Cortisol 8:00 am (high-dose dexamethasone suppression)	11.19	13.70	Suppression>50% of baseline	µg/dl
TSH	0.566	2.070	0.270–4.200	mIU/L
FT3	4.10	4.50	3.10–6.80	pmol/L
FT4	16.50	17.93	12.00–22.00	pmol/L
CA125	44.47	44.37	0.00–35.00	U/ml
CA199	29.82	45.30	0.00–27.00	U/ml
CEA	5.07	6.96	0.00–6.50	ng/ml
Thyroglobulin	11.50	9.20	0.73–55.00	ng/ml

Consented by the patient, her peripheral blood was collected and sent to the Maikino Medical Laboratory (Beijing, China). Mutation in *PRKARIA* was detected by the whole exome sequencing and verified by the Sanger sequencing using the forward (5'-TCGTCAGAAATC ACCTATTCTTCTC-3') and reverse (5'-GCTAAGCTG GGCTTAATGCAA-3') primers. A known pathogenic germline mutation of the *PRKARIA* gene (c. 682C>T) in exon 7 was found. This point mutation introduced a premature stop codon that substitutes the arginine (Arg) codon (p. R228X) in *PRKARIA*. Consequently, the mutated *PRKARIA* can only translate a C-terminus truncated loss-of-function *PRKARIA* polypeptide in CNC. However, children (son and daughter) of this patient did not carry this mutation (Fig. 3). The cardiac tumor that occurred 3 years ago was rechecked and finally confirmed as "left atrial adenomyxoma" via Hematoxylin and eosin (HE) staining (Fig. 4 A) and immunohistochemistry (Fig. 4 C, D, E). All the pathology images were taken using Leica DM6B upright microscopes and the Leica Application Suite as the acquisition software. The resolution of each original image is 300dpi and there is no downstream processing or averaging that enhances the resolution of the image.

The patient was then transferred to the surgery department of our hospital for radical thyroid surgery undergoing right thyroid gland lobe removal, isthmus and central lymph node dissection plus right recurrent laryngeal

nerve exploration under general anesthesia. The postoperative histopathology indicated papillary carcinoma of the right thyroid (Fig. 4 B). Based on the clinical symptoms, physical examination and relevant laboratory results, the patient's adrenal lesions were considered to be PPAD-associated Cushing syndrome and bilateral adrenalectomy was recommended. However, due to personal reasons, she refused any further surgery. Adrenal steroidogenesis inhibitors, including ketoconazole, metyrapone, and osilodrostat, are recommended for medical therapy when surgery is not feasible [4]. However, these drugs are not available in China. Additionally, the glucocorticoid receptor blocker mifepristone can also improve key clinical features associated with hypercortisolism, specifically hyperglycemia and weight gain [4]. However, it is only used as an abortifacient in the first months of pregnancy in China. Therefore, the appropriate treatments were given to protect against Cushing syndrome-related complications, including glycemic control (Metformin 2.0 g/d and Acarbose 150 mg/d), blood pressure control (Enalapril Maleate 10 mg/d, Metoprolol Succinate Sustained-release Tablet 23.75 mg/d), and osteoporosis management (Calcium Acetate 0.6 g/d and Alendronate Sodium/Vitamin D3 combination Tablet, 1 tablet/week). The patient was followed up 1 year later, and some relevant results are shown in Table 1 and Figure S2. She was perimenopausal at that time. Despite a previously suspected malignant nodule in the right

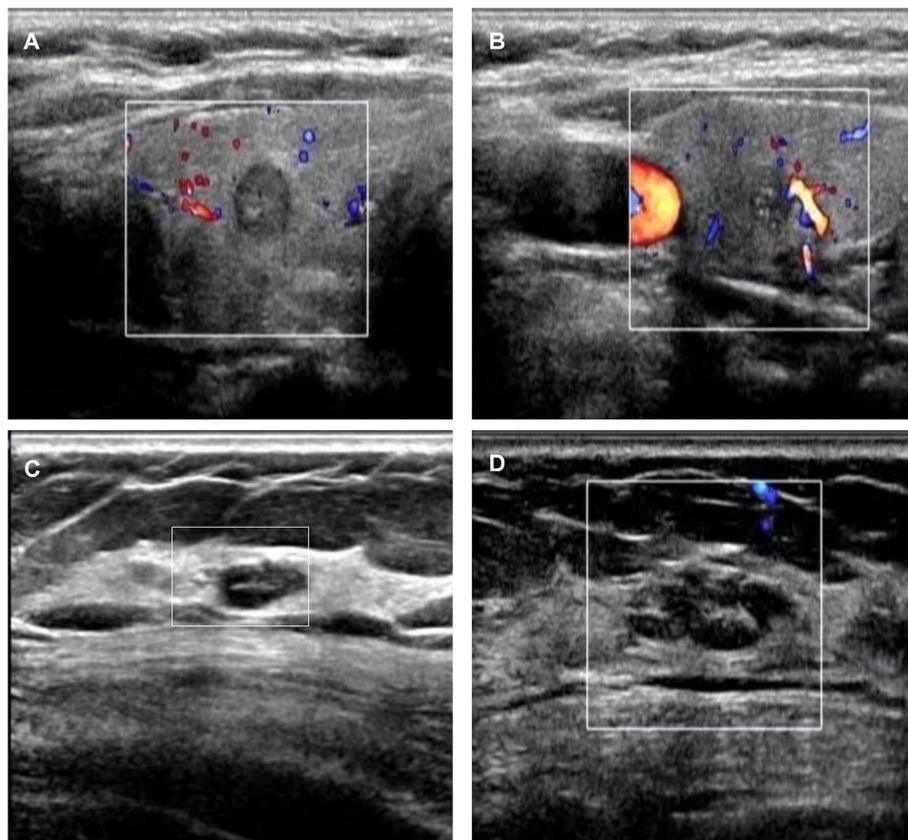


Fig. 2 Thyroid ultrasound and breast ultrasound. **(A)** Preoperative thyroid ultrasound revealed a slightly hypoechoic nodule in the right thyroid, 6 × 6 mm in size, regular in shape, clear in boundary, punctate blood flow signals, and microcalcifications, with a thyroid imaging reporting and data system (TI-RADS) classification of 4a. **(B)** Preoperative thyroid ultrasound revealed a hypoechoic nodule in the right thyroid, 8 × 5 mm in size, irregular in shape, less clear in boundary, rich in blood flow signals, and microcalcifications, with a TI-RADS classification of 4b. **(C)** Breast ultrasound at the first visit showed the left breast with multiple hypoechoic nodules, maximum size of 9 × 5 mm, regular in shape, clear in boundary, no blood flow signal, with a breast imaging reporting and data system (BI-RADS) classification of 3. **(D)** Breast ultrasound at the first visit showed multiple hypoechoic nodules in the right breast, one of which was tumor-like hyperplasia, 18 × 7 mm in size, less regular in shape, less clear in boundary, no blood flow signal, with a BI-RADS classification of 4a

mammary gland, a re-examination via ultrasound considered the nodule to be benign (Figure S2 C).

Discussion and conclusions

In 1985, Carney first described a syndrome characterized by myxoma, skin pigmentation and endocrine overactivity [1]. The incidence of CNC is unclear. A previous study reported more than 750 cases of CNC, including whites, African Americans and Asians from the Americas, Europe and Asia [5]. Another study enrolled 353 patients showed that 63% of cases were women [6]. The progression of CNC takes many years. Patient age at diagnosis ranges from newborn to adults in their 50 s (the median age is 20 years) [5].

The criteria for the diagnosis include major and supplementary criteria, which are listed in Table 2. Patients who meet any two of the major criteria (confirmed by histological evaluation, biochemical testing or imaging) or one

major and one supplementary criterion can be diagnosed [2, 5, 7]. Genetic analysis is helpful for the diagnosis of CNC. More than 70% of CNC patients have *PRKARIA* gene mutations. To date, at least 130 mutations involving 10 exons and adjacent intron sequences have been reported. These mutations (nonsense or missense mutations, short frameshift insertions or deletions and rare large fragment deletions) lead to the loss of functions of the PKA regulatory subunits and the unrestricted activity of the catalytic subunits, resulting in cell proliferation and tumor formation. In addition to the *PRKARIA* gene, mutations in the *PRKACB* and *PRKACA* genes encoding PKA β and α catalytic subunits, respectively, are also related to the pathogenesis of CNC [5, 7]. Our patient presented with typical features of CNC, including spotty skin pigmentation, thyroid carcinoma and a reported pathogenic mutation of the *PRKARIA* gene (c.682C > T) in exon 7 [8, 9], which met 2 major criteria

Table 2 Diagnostic criteria of CNC

Major criteria

- (1) Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa);
- (2) Myxoma (cutaneous and mucosal);
- (3) Cardiac myxoma;
- (4) Breast myxomatosis or fat-suppressed MRI findings suggestive of this diagnosis;
- (5) PPNAD or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test;
- (6) Acromegaly due to GH-producing adenoma;
- (7) Large cell-calcifying sertoli cell tumors (LCCSCT) or characteristic calcification on testicular ultrasonography, in a young patient;
- (8) Thyroid carcinoma or multiple hypoechoic nodules on thyroid ultrasonography;
- (9) Psammomatous melanotic schwannoma;
- (10) Blue nevus, epithelioid blue nevus (multiple);
- (11) Breast ductal adenoma (multiple);
- (12) Osteochondromyxoma of bone

Supplementary criteria

- (1) Affected first-degree relatives;
- (2) Inactivating mutation of the *PRKARIA* gene

Diagnosis of adenomas and tumors requires corresponding histological confirmation

and 1 supplemental criterion. Taken together, the diagnosis was clear.

Approximately 20–40% of patients have cardiac myxoma, which is the leading cause of mortality in over 50% of CNC patients [2]. Therefore, clinicians should pay attention to the consultation and physical examination of CNC-related symptoms in patients with cardiac myxoma. Our patient was previously diagnosed with "atrial mucinous adenocarcinoma" due to the postoperative pathology. Given that primary atrial mucinous adenocarcinoma is extremely rare [10], and no cases with CNCs have been reported, we performed immunohistochemistry to confirm the diagnosis. The positive calretinin and vimentin and negative MOC-31 proved that the cardiac myxoma with glandular differentiation was mesenchymal-derived (Fig. 4 C, D, E), so the final revised diagnosis should be "atrial adenomyxoma". A cardiac adenomyxoma is rare, affecting females and the left atrium predominantly. It may be derived from the glandular differentiation of foregut embryonic remnants or myocardial precursor cells with multi-differentiation potential [11]. The clinical features are similar to classic cardiac myxoma but may have recurrence and metastasis [12, 13], emphasizing the necessity of a long-term follow-up observation of this patient.

PPNAD accounts for 45–70% of CNC-related endocrine tumors, leading to adrenocorticotrophic hormone (ACTH)-independent Cushing syndrome [7]. The characteristic imaging manifestations are bilateral adrenal pigmented nodules, and the final diagnosis depends on adrenal pathology [7]. This patient had typical features of Cushing syndrome, diabetes, hypertension, and

osteoporosis that do not match her age. Cortisol (8:00 am) could not be suppressed by a 1 mg dexamethasone overnight test and a low-dose dexamethasone suppression test, therefore arriving at the diagnosis of Cushing syndrome. However, her ACTH (8:00 am) level was normal, the high-dose dexamethasone inhibition test failed to inhibit below 50% of the baseline level of cortisol (8:00 am), and adrenal CT showed bilateral lesions, which indicated that either Cushing disease or ectopic ACTH/corticotropin releasing hormone (CRH) syndrome could not be excluded. Bilateral inferior petrosal sinus sampling (BIPSS) should be the gold standard for a differential diagnosis. However, the patient refused this invasive test. At the same time, the patient also refused to undergo adrenal surgery, leaving us without pathological findings to confirm the diagnosis of PPNAD. Considering the clear diagnosis of CNC and the presence of PPNAD in almost all CNC patients who underwent autopsy [5], it is speculated that the adrenal glands lesions are PPNAD-related. Previous studies have reported that ACTH may be at a normal or high normal level (more than 20 pg/ml) in PPNAD patients with periodic or irregular hypercortisolism (known as the cyclic Cushing pattern) [14, 15], which also supports our hypothesis. There are very rare case reports indicating that CNC patients might have pituitary ACTH tumors without PPNAD [16], or two types of Cushing syndrome appeared one after another [17], therefore, a long-term follow-up observation is very necessary for our patient. There is currently no specific treatment for the genetic defects of CNC. Surgeries for removing tumors in different locations or drugs such as ketoconazole, mitotane, and osilodrostat are

recommended [7, 14]. In addition, the LH, FSH, and E2 levels of this patient were high. A previous study showed that only 20.4% of patients with empty sella syndrome will develop central hypogonadism [18]. Our patient was considered perimenopausal according to the gynecological consultation in her first visit and was postmenopausal 1 year later, which could explain why the changes in her LH, FSH, and E2 levels.

CNC is a rare multiple endocrine neoplasia syndrome. When patients present with clinical features involving multiple endocrine and non-endocrine tumors, especially Cushing syndrome and cardiac myxoma, CNC should be considered. The ability to recognize CNC is crucial for the early diagnosis and prevention of severe complications. Genetic analysis is also recommended in patients with suspected CNC. All patients must be followed up for life.

Abbreviations

CNC	Carney complex
PPNAD	Primary pigmented nodular adrenocortical disease
PKA	Protein kinase A
TI-RADS	Thyroid imaging reporting and data system
FNA	Fine needle aspiration
BI-RADS	Breast imaging reporting and data system
DXA	Dual-energy X-ray absorptiometry
ACTH	Adrenocorticotropic hormone
CRH	Corticotropin releasing hormone
HE	Haematoxylin and eosin
BIPSS	Bilateral inferior petrosal sinus sampling

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12902-023-01285-7>.

Additional file 1: Figure S1. Thyroid fine needle aspiration (FNA) showed a cell group with nuclear crowding, irregularities in the nuclear membrane, intranuclear inclusions and nuclear grooves, which indicated suspicious papillary thyroid carcinoma, Bethesda V.

Additional file 2: Figure S2. Postoperative thyroid ultrasound and breast ultrasound at follow-up. (A) Postoperative thyroid ultrasound showed a postoperative image of the right thyroid carcinoma. (B) Postoperative thyroid ultrasound showed the left thyroid lobe was negative. (C) Breast ultrasound at follow-up showed multiple hypoechoic nodules in the right breast, cord-like slightly hyperechoic band, maximum size of 19×6 mm, regular in shape, clear in boundary, no blood flow signal, with a BI-RADS classification of 3.

Acknowledgements

We are grateful to the patient and her children who kindly consented to join the study.

Authors' contributions

Material preparation, data collection, and literature search were performed by J.H. and M.Y. The first draft of the manuscript was written by J.X. and all authors commented on previous versions of the manuscript. S.X. and M.Z. provided diagnoses and treatments to the patient reported in this study. P.L. managed the pathological studies. J.H. and L.S. supervised and finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Availability of data and materials

The raw sequence data reported in this paper will be made available by the corresponding author without undue reservation and have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation/ Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA003792) that are publicly accessible at <https://ngdc.cncb.ac.cn/gsa-human>.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University and was performed in accordance with the Declaration of Helsinki. Informed consent to participate was obtained from the patient. As the two children were under the age of 18, their informed consents were obtained from their mother (the patient).

Consent for publication

Written informed consent was obtained from the patient for the publication of any related images or data included in this manuscript. Because the two children were under the age of 18, their consents for the publication of any related images and data were obtained from their parent (the patient).

Competing interests

The authors declare that they have no competing interests.

Received: 12 September 2022 Accepted: 26 January 2023

Published online: 06 February 2023

References

- Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VL. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine*. 1985;64(4):270–83.
- Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J Clin Endocrinol Metab*. 2001;86(9):4041–6.
- Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA. Mutations of the gene encoding the protein kinase A type I- α regulatory subunit in patients with the Carney complex. *Nat Genet*. 2000;26(1):89–92.
- Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847–75.
- Kamilaris CDC, Faucz FR, Voutetakis A, Stratakis CA. Carney Complex. *Exp Clin Endocrinol Diabetes*. 2019;127(2–03):156–64.
- Bertherat J, Horvath A, Groussin L, Grabar S, Boikos S, Cazabat L, Libe R, René-Corail F, Stergiopoulos S, Bourdeau I, et al. Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. *J Clin Endocrinol Metab*. 2009;94(6):2085–91.
- Bouys L, Bertherat J. MANAGEMENT OF ENDOCRINE DISEASE: Carney complex: clinical and genetic update 20 years after the identification of the CNC1 (PRKAR1A) gene. *Eur J Endocrinol*. 2021;184(3):R99–r109.
- Courcoutsakis N, Patronas N, Filie AC, Carney JA, Moraitis A, Stratakis CA. Ectopic thymus presenting as a thyroid nodule in a patient with the Carney complex. *Thyroid*. 2009;19(3):293–6.
- Lowe KM, Young WF Jr, Lyssikatos C, Stratakis CA, Carney JA. Cushing Syndrome in Carney Complex: Clinical, Pathologic, and Molecular Genetic Findings in the 17 Affected Mayo Clinic Patients. *Am J Surg Pathol*. 2017;41(2):171–81.

10. Berger MD, Schneider J, Ballmer PE, Eckhardt BP, Dommann-Scherrer C. Mucin-producing adenocarcinoma arising in an atrial myxoma. *Ann Diagn Pathol*. 2013;17(1):104–7.
11. AlAhmadi HH, Alsafwani NS, Shawarby MA, Ahmed F. Cardiac Myxoma: Typical Presentation but Unusual Histology. *Case Rep Med*. 2021;2021:6611579.
12. Zhang M, Ding L, Liu Y, Xue L. Cardiac myxoma with glandular elements: a clinicopathological and immunohistochemical study of five new cases with an emphasis on differential diagnosis. *Pathol Res Pract*. 2014;210(1):55–8.
13. Uppin SG, Jambhekar N, Puri A, Kumar R, Agarwal M, Sanghvi D. Bone metastasis of glandular cardiac myxoma mimicking a metastatic carcinoma. *Skeletal Radiol*. 2011;40(1):107–11.
14. Memon SS, Thakkar K, Patil V, Jadhav S, Lila AR, Fernandes G, Bandgar TR, Shah NS. Primary pigmented nodular adrenocortical disease (PPNAD): single centre experience. *J Pediatr Endocrinol Metab*. 2019;32(4):391–7.
15. Navarro Moreno C, Delestienne A, Marbaix E, Aydin S, Hörtnagel K, Lechner S, Sznajder Y, Beauloye V, Maiter D, Lysy PA. Familial Forms of Cushing Syndrome in Primary Pigmented Nodular Adrenocortical Disease Presenting with Short Stature and Insidious Symptoms: A Clinical Series. *Hormone research in paediatrics*. 2018;89(6):423–33.
16. Kiefer FW, Winhofer Y, Iacovazzo D, Korbonits M, Wolfsberger S, Knosp E, Trautinger F, Höftberger R, Krebs M, Luger A, et al. PRKAR1A mutation causing pituitary-dependent Cushing disease in a patient with Carney complex. *Eur J Endocrinol*. 2017;177(2):K7–k12.
17. Hernández-Ramírez LC, Tatsi C, Lodish MB, Faucz FR, Pankratz N, Chittiboina P, Lane J, Kay DM, Valdés N, Dimopoulos A, et al. Corticotropinoma as a Component of Carney Complex. *J Endocr Soc*. 2017;1(7):918–25.
18. Carosi G, Brunetti A, Mangone A, Baldelli R, Tresoldi A, Del Sindaco G, Lavezzi E, Sala E, Mungari R, Fatti LM, et al. A Multicenter Cohort Study in Patients With Primary Empty Sella: Hormonal and Neuroradiological Features Over a Long Follow-Up. *Front Endocrinol (Lausanne)*. 2022;13:925378.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

