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Discovery of a Novel PRKAR1A Gene Mutation in a Case of Carney Complex

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Abstract

The primary objective of this study is to explore the clinical manifestations, diagnostic procedures, and therapeutic approaches concerning novel pathogenic mutations in the PRKAR1A gene, which lead to Carney complex.

Methods: We present a retrospective analysis of clinical data pertaining to a single patient.

Results: In this study, we detail the case of a 13-year-old patient diagnosed with Carney complex. Through comprehensive testing, including genetic analysis, a new mutation locus (C.1-2942G>A) in the PRKAR1A gene was identified as the causative factor.

Conclusion: Diagnosing Carney complex can pose challenges in clinical settings, often leading to delayed recognition. Hence, it is imperative for healthcare professionals to enhance their understanding of this condition for early detection and timely intervention.

Keywords: Carney complex; Cushing's syndrome; PPNAD; PRKAR1A.

Introduction

Carney complex (CNC) is a rare syndrome characterized by irregular skin and mucous membrane pigmentation alongside various non-endocrine and endocrine tumors, including Primary Pigmented Nodular Adrenocortical Disease (PPNAD). It typically follows an autosomal dominant inheritance pattern. Studies have shown that most cases of PPNAD or Carney syndrome are linked to mutations in the PRKAR1A gene, with additional mutations found in the PDE11A and PDE8B genes. Here, we present a case of Cushing's syndrome associated with PPNAD, diagnosed as CNC, attributed to a new genetic variant in PRKAR1A. This novel mutation, previously unreported, is specifically linked to PPNAD [1-7].

Two years ago, a 13-year-old boy presented with facial rounding and hyperpigmentation on his face, eyelids, and lips. His growth rate was notably slow, approximately 3 cm over the past two years. Six months ago, he developed facial acne, followed by lower back pain and activity limitations half a month ago. His medical history included postural lithotripsy in August 2017 and April 2018. Family history revealed similar facial and lip hyperpigmentation in his father, aunt, and grandmother, who did not share his obese body type but led normal lives.

During physical examination, he measured 148 cm in height and weighed 70 kg (BMI 31.95 kg/m2) with a blood pressure of 120/80 mmHg. He exhibited a full moon face, obese body type, upper body circumference of 66 cm, lower body circumference of 82 cm, and finger spacing of 142 cm (Figures 1 and 2). Patchy pigmentation was visible on his mouth, lips, and eyelids, along with facial acne and acanthosis nigricans on his neck and axillae. He was at Tanner stage 3 for breast development and pubic hair growth, with a short penis but normal testicular development, also at Tanner stage 3. Additionally, he had a red rash in the groin area and rough, grayish-white toes. No abnormalities were noted in his heart, lungs, or abdomen [8,9].

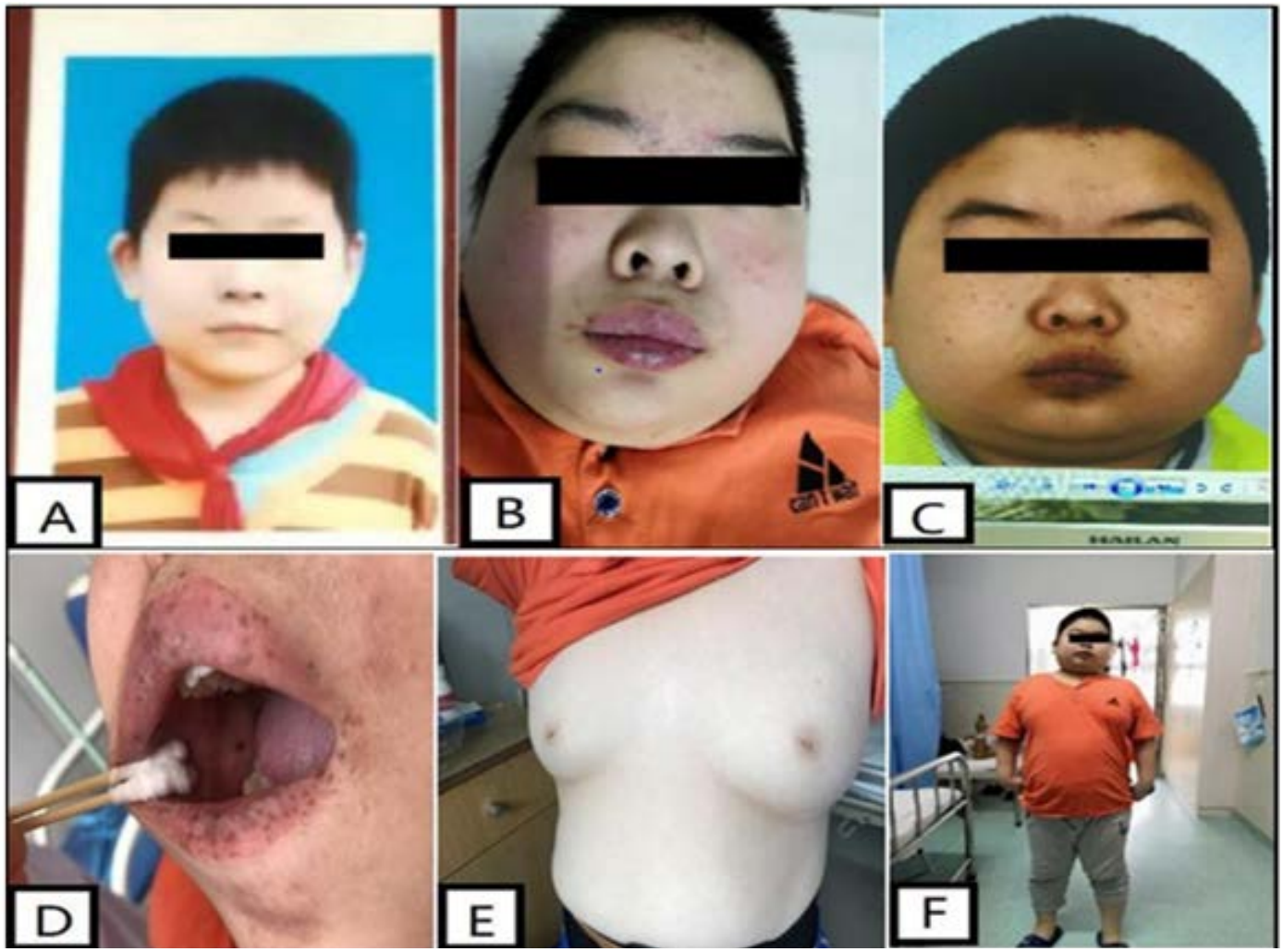

Figure 1: (ABCDEF) Physical signs of the patient before adrenalectomy. Cushing-like features include moon face before surgery (BC), central obesity (F), breast development (E), spots on the face, lips, oral mucosa and skin pigmentation (CD).

Laboratory findings indicated hypercortisolism, with cortisol levels remaining elevated after a 1 mg dexamethasone suppression test, suggesting that his Cushing's syndrome was not ACTH-related.

Adrenal computed tomography (CT) revealed multiple small nodules in the left adrenal inner branch and body, suggestive of adenomas or adrenal tuberculosis. Enhanced CT of the pituitary gland showed no abnormalities. Magnetic resonance imaging of the thoracic spine identified a compression fracture at T11, confirmed by whole-body bone single-photon emission computed tomography (SPECT). Echocardiography did not reveal any cardiac mucosal tumors. Based on the patient's history, physical examination, and imaging results, non-ACTH-dependent adrenal nodular hyperplasia was suspected [10].

The patient underwent laparoscopic resection of the left adrenal gland, yielding a grayish-yellow tissue measuring 863.5 cm. Pathological examination confirmed the diagnosis of Carney syndrome. Genetic analysis identified a novel mutation in the PPKAR1A gene (variant locus C.1-2942 G>A).

Postoperatively, the patient's ACTH level decreased to 0.488 pg/ml (normal range: 7-64 pg/ml), and plasma cortisol measured 14.38 ug/dl (normal range: 4.26-24.85 ug/dl) on the fourth day. Following discharge, the patient received prednisone 20 mg Qd. At 10 months postoperatively, he had grown 5 cm taller and lost 5 kg in weight compared to admission. Eighteen months postoperatively, ACTH and plasma cortisol levels normalized, with the patient reaching a height of 158 cm and a weight of 68 kg [11-14].

Discussion

We present a case of a patient exhibiting hallmark features indicative of Carney complex (CNC), including patchy pigmentation of the face, lips, and oral mucosa, as well as compression fractures of the thoracic spine leading to osteoporosis and Primary Pigmented Nodular Adrenocortical Disease (PPNAD). Genetic testing identified a variant in the PPKAR1A gene, meeting diagnostic criteria for CNC.

PPNAD represents a rare form of non-adrenocorticotropin-dependent Cushing's syndrome, characterized histologically by multiple small (<1 cm) dark brown nodules scattered throughout the adrenal cortex. Diagnosis typically requires histological examination due to normal or small adrenal gland size on imaging. In our case, multiple small nodules were observed in the left adrenal gland on CT imaging. Treatment options for PPNAD vary, with bilateral adrenalectomy often recommended, though unilateral adrenalectomy may suffice in certain cases [15].

CNC, first reported by JA Carney in 1985, is associated with inactivating germline mutations in the PRKAR1A gene, resulting in increased protein kinase A (PKA) activity. Clinical manifestations include skin pigmentation, cardiac myxomas, and various tumors of the nervous and endocrine systems. Genetic sequencing confirmed a variant in the PRKAR1A gene in our patient, specifically at locus c.1-2924G > A, associated with PPNAD.

While this variant's pathogenicity remains unclear, its detection in our patient, along with symptoms consistent with PPNAD, underscores the importance of considering CNC in such cases. Regular monitoring and timely diagnosis of CNC manifestations are crucial to prevent complications, particularly those related to cardiac myxomas. Screening recommendations include echocardiography, skin assessment, thyroid and pituitary imaging, and hormonal serum measurements [16].

Conclusion

Our cases contribute to the growing body of reported cases of Carney complex (CNC), a condition associated with the potential

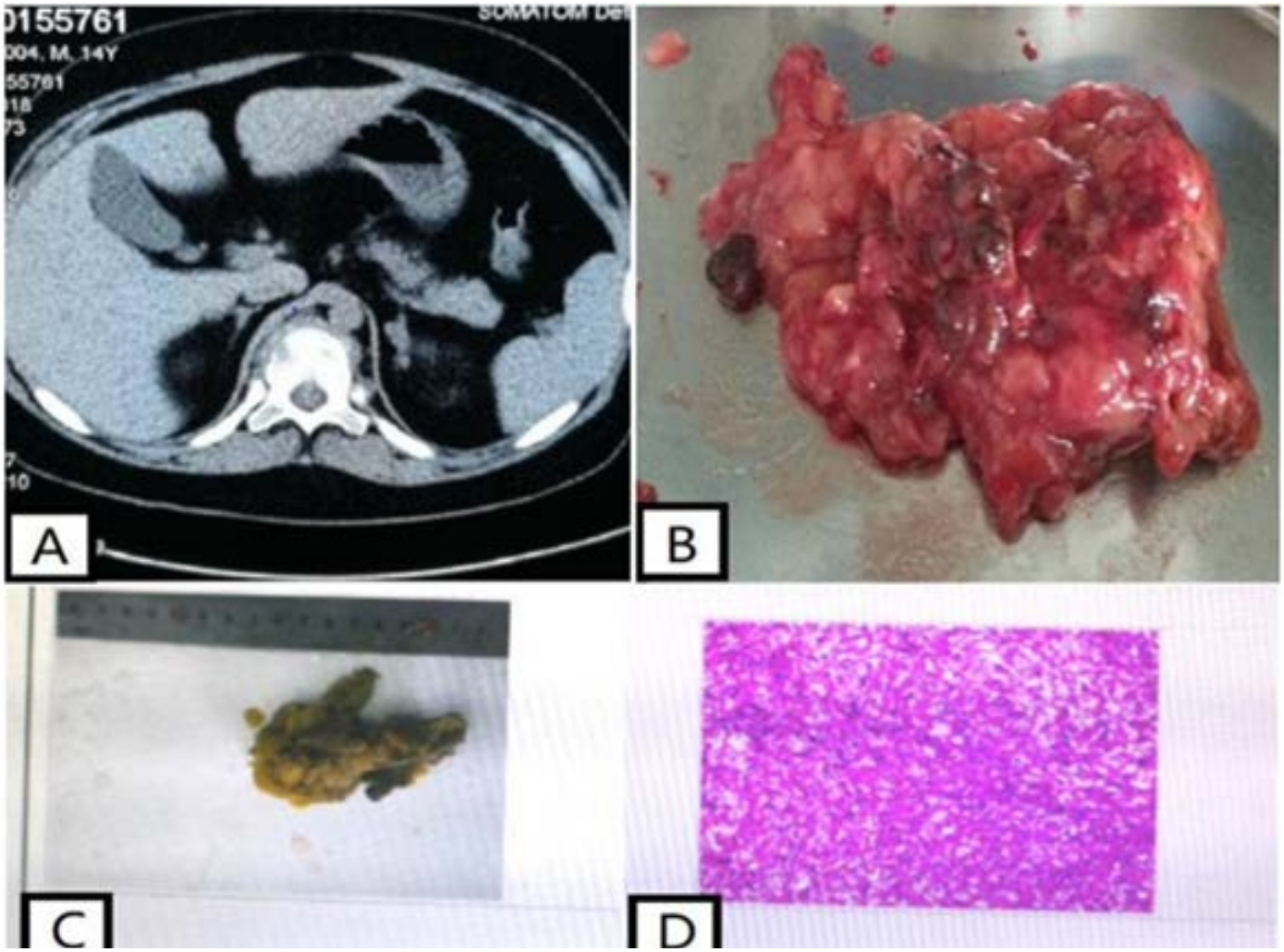

Figure 2: Computed tomography of the patient's adrenal gland showed multiple small nodules in the left adrenal inner branch and body (Figure A), considering adenoma or adrenal tuberculosis. The patient's left adrenal gland macroscopically showed a piece of grayish-yellow tissue measuring 8*6*3.5 cm, including an adrenal gland measuring 6.5*2.5*0.3 cm, with multiple small nodules of 0.2-0.7 cm in diameter attached to the surface (C). Microscopic examination of the patient's left adrenal gland showed multiple nodules in the adrenal cortex, without envelope, partially protruding from the adrenal gland, with clear cytoplasm and eosinophilic cells (D).

development of cardiac myxomas later in life. These patients require ongoing clinical evaluation and long-term follow-up to monitor for any emerging complications. Furthermore, our current cases of Cushing's syndrome, where CNC diagnosis was established through the identification of a novel predicted inactivating pathogenic variant in the PRKAR1A gene, underscore the significance of this gene mutation and its implications for genetic counseling.

Early diagnosis of endogenous cortisol excess remains a diagnostic challenge. Increasing awareness and enhancing clinicians' understanding of the disease are vital in facilitating early detection and timely intervention. The novel mutations identified in our study are considered causative factors of PPNAD. Timely diagnosis of CNC and vigilant surveillance are crucial in preventing potentially life-threatening complications associated with the disease.

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