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Case Report

Cantú Syndrome With Acromegaloid Features, Multiple Endocrinopathies, and Infection Susceptibility

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Abstract

Cantú syndrome involves fetal polyhydramniosis, congenital hypertrichosis, and macrosomia. Distinctive features include acromegaloid features with broad nasal bridge and macroglossia as well as cardiac abnormalities, including patent ductus arteriosus. We present a case in a male patient, who presented with cardiac abnormalities in childhood, but was diagnosed with the syndrome in adulthood after many years of atypical symptoms such as multiple endocrinopathies and infection susceptibility. He had surgery for a patent ductus arteriosus in early childhood. During adulthood, he developed idiopathic pericarditis. Extensive rheumatological investigations were made, and in parallel, several endocrinopathies were found. These included thyroiditis with subsequent hypothyroidism, idiopathic partial hypocortisolism, and GH insufficiency. In addition, he had mild neutropenia and required hospitalization twice because of *Streptococcus pyogenes* infections. Immunodeficiency screening has not revealed a specific primary immunodeficiency, yet transient neutropenia, low count of CD8+ effector memory T cells, as well as lymphocyte responses, was seen during bacteremia. The diagnose was made after a trio-whole genome sequencing identified a pathogenic missense variant of the gene *ABCC9* (c.3460C > T;p. (Arg1154Trp)) causing Cantú syndrome.

Key Words: Cantu syndrome, hormone insufficiency, acromegaloid facial appearance syndrome, *Streptococcus pyogenes*, immunodeficiency

Introduction

No formal diagnostic criteria of Cantú syndrome, which was first described in 1982 [1], exist [2]. It occurs due to a gain-of-function mutation, typically occurring in the *ABCC9* gene (OMIM no. 239850). Less common, and more uncertainly associated to Cantú syndrome, are mutations in the *KCNJ8* gene (OMIM no. 600935). They code for subunits of ATP-sensitive potassium channels [3-6]. Inheritance is autosomal and dominant. Approximately 100 cases have been reported from most areas of the world [2]. The noneponymous name for the condition is Hypertrichosis-Osteochondrodysplastic-Cardiomegaly syndrome. Similar mutations in the *ABCC9* gene, with phenotypes with descriptive names such as acromegalic facial appearance and hypertrichosis with acromegalic facial features have been described [7-9].

Common features include congenital hypertrichosis and macrosomia. Distinctive facial features as well as cardiac abnormalities, such as patent ductus arteriosus, enlarged heart with enhanced systolic function, or pericardial effusion [2, 10-12], have been described. GH deficiency and panhypopituitarism have rarely been reported [11]. Immunodeficiency is not typically reported. However, in 1 study, 7 cases were reported to be susceptible to respiratory tract infections [10]. Psychiatric diagnoses associated with the syndrome include autism spectrum disorder as well as anxiety and depression [2, 12]; however, intellect is typically normal.

Case Presentation

We describe a case of Cantú syndrome diagnosed in a 38-year-old Scandinavian male. He was diagnosed in 2022, following trio-whole genome sequencing where a heterozygous carriage of a pathogenic missense variant of the gene *ABCC9* (NM_005691.3(*ABCC9*)): c.3460C > T;p. (Arg1154Trp)) was identified, causing a gain-of function mutation. At the age of 9 months, the patient had surgery for a patent ductus arteriosus. In 2014, he was diagnosed with Bell palsy, which was treated with oral steroids; he subsequently developed pericarditis. He had pericardial effusion, and pericardiocentesis was performed. Bacterial cultures and viral PCR for viruses were negative. Serologies for Borrelia, *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, and parvovirus B19 did not indicate acute infection. He was treated with nonsteroidal anti-inflammatory drugs, followed by colchicine and prednisolone for idiopathic pericarditis. He developed pleural effusions without significant inflammatory response clinically or biochemically. Subsequently, in 2015, thoracoscopic fenestration of the pericardium was performed. Recurrent serositis prompted an extensive investigation for systemic inflammatory diseases,

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Table 1. Endocrinological laboratory investigations from 2016-2023

Laboratory investigations with reference ranges	February 2016	March 2016	April 2016	August 2016	January 2017	September 2017	2018	2019	2023
TSH 0.4-3.7 mIU/L (0.4-3.7 µIU/mL)	**0.01** mIU/L (**0.01** µIU/mL)	**6.3** mIU/L (**6.3** µIU/mL)	**12** mlU (L (**12** IU/mL)	**4.6** mIU/L (**4.6** µIU/mL)	**3.9** mIU/L (**3.9** µIU/mL)	2.1 mIU/L (2.1 µIU/mL)	2.1 mIU/L (2.1 µIU/mL)	**0.39** mIU/L (**0.39** µIU/mL)	1.9 mIU/L (1.9 µIU/mL)
fT4 12-23 pmol/L (0.93-1.79 ng/dL)	**24** pmol/L (**1.86** ng/dL)	**5.8** pmol/L (**0.45** ng/dL)	**5.4** pmol/L (**0.42** ng/dL)	**11** pmol/L (**0.85** ng/dL)	13 pmol/L (1.0 ng/dL)	12 pmol/L (0.93 ng/dL)	15 pmol/L (1.17 ng/dL)	17 pmol/L (1.32 ng/dL)	12 pmol/ L (0.93 ng/dL)
Prolactin 2.82-12.2 µg/L (60-260 mL U/L)		**38.0** µg/L (**808** mIU/L)		**39.0** µg/L (**829** mIU/L)	**35.2** µg/L (**749** mIU/L)	**37.0** µg/L (**785** mIU/L)	**25.2** µg/L (**537** mIU/L)	**33.2** µg/L (**706** mIU/L)	**17.4** µg/L (**370** mIU/L)
IGF-1 71-239 µg/L (543-1828 ng/mL)		93 µg/L (711 ng/mL)			103 µg/L (788 ng/mL)	105 µg/L (803 ng/mL)	88 µg/L (673 ng/mL)	85 µg/L (650 ng/mL)	188 µg/L (1438 ng/mL)
Testosterone 5.7-24.3 nmol/L (164-701 ng/dL)		12.0 nmol/L (346 ng/dL)		14.3 nmol/L (412 ng/dL)	11.3 nmol/L (326 ng/dL)	14.5 nmol/L (418 ng/dL)	10.1 nmol/L (291 ng/dL)	13.9 nmol/L (401 ng/dL)	12.2 nmol/L (352 ng/dL)
FSH 1.4-18 IU/L (1.4-18 mIU/mL)				4.4 IU/L (4.4 mIU/mL)	5.4 IU/L (5.4 mIU/mL)	5.4 IU/L (5.4 mIU/mL)			4.8 IU/L (4.8 mIU/mL)
LH 1.5-9.3 IU/L (1.5-9.3 mIU/mL)				5.0 IU/L (5.0 mIU/mL)	5.4 IU/L (5.4 mIU/mL)	5.9 IU/L (5.9 mIU/mL)			3.4 IU/L (3.4 mIU/L)
ACTH 07.00-10.00: 1.5-14 pmol/L (6.8-63.6 pg/mL)		9.9 pmol/L (45 pg/mL)		**19** pmol/L (**86.3** pg/mL)	**15** pmol/L (**68.1** pg/mL)		5.4 pmol/L (24.5 pg/mL)	5.7 pmol/L (25.9 pg/mL)	12 pmol/L (54.5 pg/mL)
Cortisol 06.00-10.00: 133-537 nmol/L (4.8-19.5 µg/dL)		135 nmol/L (4.9 µg/dL)		—	186 nmol/L (6.7 µg/dL)		**63** nmol/L (**2.3** µg/dL)	**626** nmol/L (**22.7** µg/dL)	**13** nmol/L (**0.5** µg/dL)
TPO-Ab < 35 KIU/L (<35 IU/mL)	14 KIU/L (14 IU/mL)								
TR-Ab < 1.3 IU/L (ECLI-assay)	<1,0 IU/L								
Thyroglobulin-Ab < 116 KIU/L (<116 IU/mL)	408 KIU/L (408 IU/mL)								

Values presented in International System of Units (SI). Values in parentheses are conventional units. Abnormal values are shown in bold font.
Abbreviations: ECLI, ElectroChemiLumiscence Immunoassay; fT4, thyroxine free; TPO-Ab, thyroid peroxidase antibodies; TR-Ab, anti-TSH receptor antibodies.

including systemic lupus erythematosus, without any positive findings. There were no signs of rheumatologic joint manifestations, and the last symptomatic episode of serositis occurred in 2018.

Diagnostic Assessment

The patient presented in 2016 to the endocrinology department with typical thyrotoxic symptoms (fatigue, heart palpitations, weight loss, and depressive symptoms). Laboratory tests are presented in Table 1. The palpation of the thyroid was normal. Thyroiditis was considered the most likely diagnosis. After the development of hypothyroidism, levothyroxine-replacement therapy was initiated. However, an acromegaloid facial appearance, including prominent lips and a slightly bulbous nose was noted (Fig. 1) and an endocrine investigation was started. Morning cortisol levels were low and subsequent Synacthen test revealed an impaired cortisol response with plasma cortisol starting at 123 nmol/L (4.46 µg/dL) and increasing to 283 nmol/L (10.26 µg/dL) (normal reference range, 133-537 nmol/L; 4.8-19.5 µg/dL) after 60 minutes. ACTH levels were 11 pmol/L (50 pg/mL) and 14 pmol/L (63.6 pg/mL) (normal reference range, 1.5-14 pmol/L; 6.8-63.6 pg/mL), respectively. Antiadrenal gland antibodies and anti-21-hydroxylase were both negative. Computed tomography scan of the adrenal glands was normal. Replacement therapy with hydrocortisone was started and mineralocorticoid therapy was added because of fatigue and hypotension and a suspicion of partial adrenal insufficiency. In addition, a slightly elevated prolactin, low IGF-1 and testosterone levels in the lower part of reference range with normal gonadotropins was found (Table 1). He had no symptoms of hypogonadism. Magnetic resonance imaging of the sella region was performed twice at a 3-year interval, with normal findings. Because of the suspicion of idiopathic partial pituitary insufficiency and IGF-1 levels at 85 µg/L (650 ng/mL) (normal reference range, 71-239 µg/L; 543-1828 ng/mL) a GHRH-arginine test was performed with a poor response in GH elevation, to a maximum of GH 5.3 µg/L (5.3 ng/mL) (body mass index-specific diagnostic value for GH deficiency <8 µg/L). The patient complained about fatigue and low physical performance. GH replacement therapy was initiated in 2019, with increased IGF-1 values (Table 1) as a result and improved physical performance.

He also displayed persistent secondary anemia and neutropenia. Hemoglobin levels were decreased at 11 to 12 g/dL (normal reference range, 13.4-17.0 g/dL) with white blood cell counts in the range of 4.0 to 6.0×10^9/L (normal reference range, 3.5-8.8 $\times 10^9$/L) with neutrophils in the range of 0.6 to 1.0×10^9/L (normal reference range, 1.7-8.0 $\times 10^9$/L). After consultation with a hematologist, anemia was regarded as secondary to inflammation, despite no correlation of anemia or neutropenia with infectious episodes. In addition, he has had an increased susceptibility to *S. pyogenes* infections specifically. In 2018, he was hospitalized because of sepsis, secondary to a pharyngeal infection with *S. pyogenes* bacteremia. A few months prior, he was screened for immune deficiencies by investigation of immunoglobulin subclasses, lymphocyte populations, and PhagoBurst-testing as part of an investigation of his complex clinical picture, which was suspected at this point to be of autoimmune rather than genetic origin. No immunoglobulin deficiencies were seen, B cells were found to be normal, as were T-cell lymphocyte counts except for a low count of CD8 + effector memory T cells. PhagoBurst testing showed normal phagocytosis functions of monocytes and granulocytes. However, when lymphocyte functions were assessed, lower responses than expected were seen (33%-75% compared to controls from healthy blood donors). A reexamination during existence of *S. pyogenes* bacteremia showed low total counts of lymphocytes as well as low CD4 counts (Table 2).

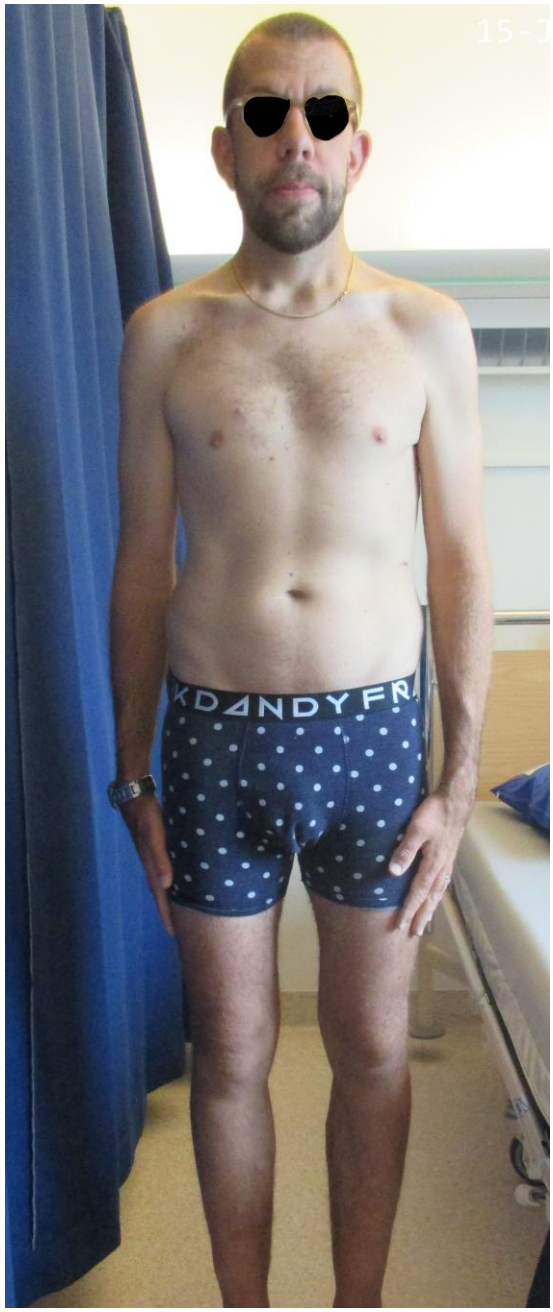

Figure 1. Photograph of the patient in the year 2019. © Region Skane, Lund University Hospital.

Following bacteremia in June 2018, he again was hospitalized with pharyngitis in October 2018. Blood cultures were negative, but *S. pyogenes* was isolated from the throat culture. After standard treatment with penicillin, oral amoxicillin prophylaxis was initiated.

Because of his scattered medical history, mixed symptoms and signs (Table 3), and relatives with the same distinct facial features, hypertrichosis, and a patent ductus arteriosus, the suspicion of a genetic condition was raised. A geneticist

Table 2. Analysis of the patient's number of lymphocytes without any ongoing infection and during bacteremia caused by *Streptococcus pyogenes*

Lymphocytes	Without infection	During bacteremia	Normal Range
No. of CD4+ T cells	0.87×10^9/L 870/μL	**0.28×10^9/L** **280/μL**	0.4-2.1 × 10^9/L 400-2100/μL
No. of CD8+ T cells	0.75×10^9/L 750/μL	**0.16×10^9/L** **160/μL**	0.18-0.9 × 10^9/L 180-900/μL
Subphenotypes of T cells	All subtypes were within normal range	The following cells were low (measured in percentage): **CD45RO 10%** (CD8), Ref. 13-64%, **Effector memory cells 1.4%**, Ref. 19-65% (CD8)	Analyzed cells: Naïve, Pre-Switched cells, classical Switched memory cells, marginal zone cells, transitional cells, plasma cells and memory cells.
No. of CD19 (B cells)	0.32×10^9/L 320/μL	0.14×10^9/L 140/μL	0.07-0.46 × 10^9/L 70-460/μL
No. of lymphocytes	2.46×10^9/L 2460/μL	**0.65×10^9/L** **650/μL**	0.82-2.6 × 10^9/L 820-2600/μL

Pathological results marked in bold.

Table 3. Summary of clinical features of our patient with Cantú syndrome

Clinical features in patient with Cantú syndrome
Acromegaloid facial features
Hypertrichosis (more prominent at young age)
Edema of lower extremities
Patent ductus arteriosus
Neutropenia
Hypothyroidism
Hypocortisolism
GH insufficiency
Mild hyperprolactinemia
Susceptibility to *Streptococcus pyogenes* infection

Table 4. The patient's current medications (August 2024)

Current medications	Doses
Levothyroxine	150 μg daily
Hydrocortisone	15 mg + 10 mg + 0 daily
Fludrocortisone	0.1 mg daily
Furosemide	20 mg 1-2 times daily
Vitamin B12	1 mg daily
Folic acid	1 mg daily
Somatropin	0.4 mg daily
Cholecalciferol	800 IE daily
Amoxicillin	500 mg daily
Acetylsalicylic acid	75-150 mg when needed
Ibuprofen	400 mg when needed

recommended a trio-wide whole genome sequencing and heterozygous carriage of a pathogenic missense variant of the gene *ABCC9* (c.3460C > T;p. (Arg1154Trp)) causing a gain-of-function mutation consistent with Cantú syndrome was found. The diagnosis was also confirmed in family members.

This mutation has been previously described and found to vary in its phenotypic presentation [6]. The patient's clinical features have been atypical, with the occurrence of immunodeficiency and multiple endocrinopathies, in addition to episodes of pericarditis and pedal edema more commonly seen as part of the syndrome.

Treatment

There is no specific treatment for Cantú syndrome, but ATP-sensitive potassium channel inhibitors like glibenclamide, as well as genetic manipulation, have been tested in mice models [13]. At present, the patient is on the medications described in Table 4.

A timeline of the symptoms and the initiation of different treatments are presented in Fig. 2.

Outcome and Follow-up

Medical evaluation has been made every 3 to 6 months and medications have been titrated accordingly. He is of normal constitution 182 cm (6 ft) tall and weighs 84 kg (185 lb.) with a body mass index of 24 kg/m^2. He is employed full-time and exercises regularly. He has not had any severe infections during his prophylactic treatment with amoxicillin.

His main medical complaint is persistent edema of the lower extremities. He uses furosemide and compression socks with limited effect. Lymphoscintigraphy showed slow lymph transport from the lower extremities. A recent (2023) transthoracic echocardiography highlighted a dilated left ventricle, left ventricular internal dimension in end-diastole of 65 mm, with normal systolic and diastolic function, dilated atria bilaterally, a slightly dilated ascending aorta, and no pericardial effusion. Magnetic resonance imaging of the brain, thorax, and abdomen showed a slight dilation of the ascending aorta and the pulmonary trunk, but no other vessel malformations. He had no neurological symptoms. Bone density scan was normal. There were no symptoms or signs of osteochondrodysplasia or other skeletal abnormalities. In 2023, he was diagnosed with venous thrombophlebitis and lately had a second episode of Bell palsy.

Discussion

This report highlights the heterogenicity of the rare Cantú syndrome. The delay in identifying the diagnosis was due

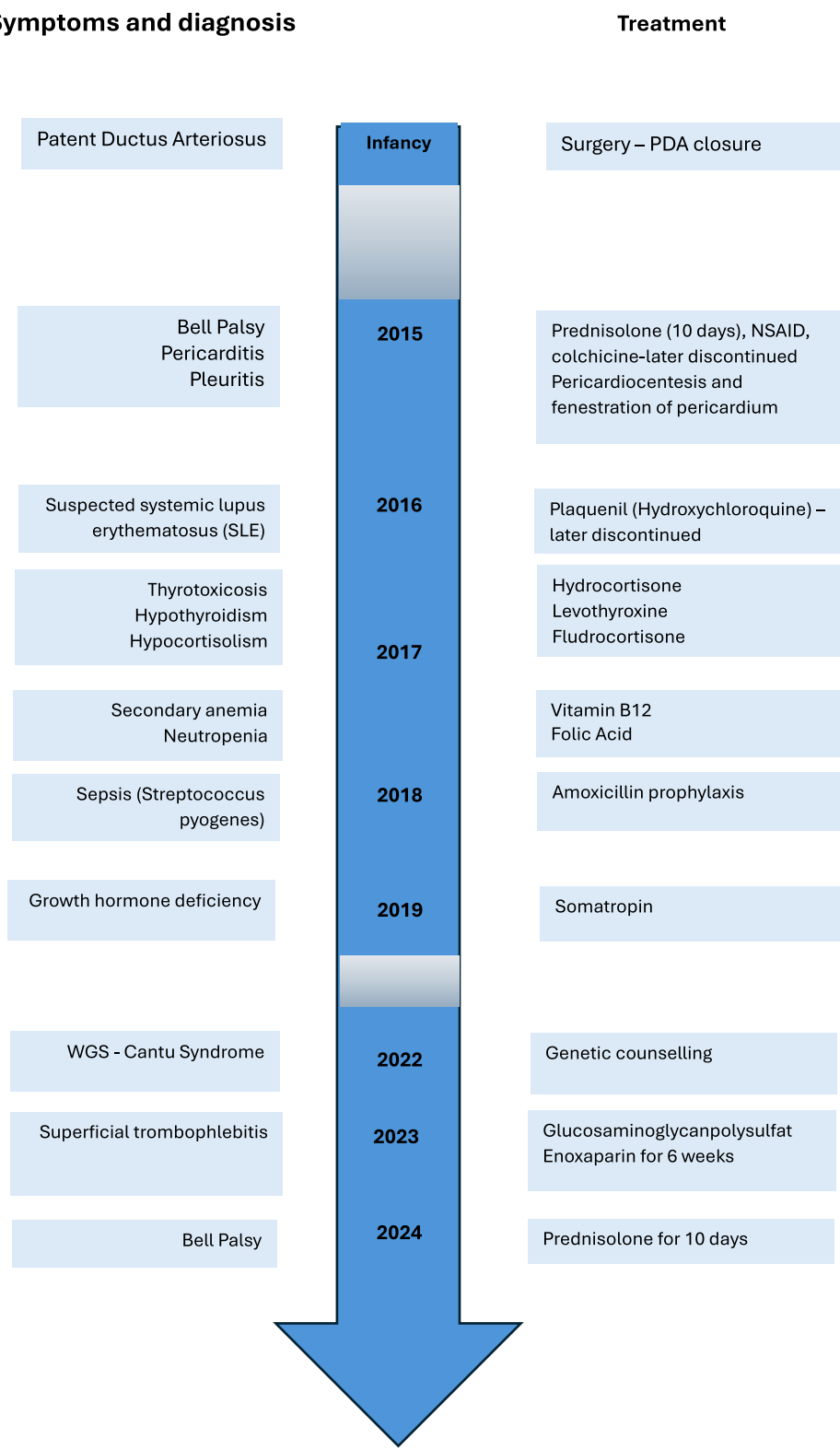

Figure 2. Timeline of the chronological appearance of the symptoms and treatments initiated.

to its rarity, yet also because of a phenotypic spectrum of symptoms. Common features of the syndrome have been summarized by Grange et al [2]. The combination of patent ductus arteriosus, acromegaloid features, pericarditis, and pedal edema are common [2]. Yet, the features of infection susceptibility and multiple endocrinopathies have not been previously described and are here highlighted.

While loss-of-function, homozygous, and recessive mutations of *ABCC9* have been described in Norway, with an opposing phenotype to Cantú syndrome including muscle weakness,

delayed psychomotor development, intellectual disability, and some shared dysmorphic features [14], we are unaware of any previous reported cases of Cantú syndrome from the Nordic countries.

Previously, a small case series summarized patients with suggested immunodeficiency secondary to the syndrome [10]. Our patient had no immunoglobulin deficiencies but displayed neutropenia and transiently decreased lymphocyte counts (both T and B cells). The cause of neutropenia is currently unknown. The lymphopenia that was noted when the patient was admitted due to *S. pyogenes* infection was probably related to his septicemia.

There are rare reports of panhypopituitarism, pituitary adenoma, and GH deficiency [2, 11, 15]. The cause of hypothyroidism in our patient was considered a primary autoimmune or an idiopathic thyroiditis. Levothyroxine was added in September 2016. However, the relatively modest elevation of TSH levels that persisted despite pronounced hypothyroid state lasting 6 months before initiation of levothyroxine treatment, suggests a subnormal pituitary secretion of TSH. In addition, his ACTH levels were never elevated despite low cortisol levels, making the diagnosis of primary adrenal insufficiency unlikely. 21-OH and 17-hydroxyprogesterone were normal. Hence, the cortisol deficiency is attributed to both relatively low ACTH levels and insufficient cortisol secretion. The IGF-1 levels were low and not consistent with the initial suspicion of acromegaly. The patient had normal puberty and pubertal growth and normal fertility, which suggests that the hormone deficiency commenced during adulthood. The patient confirmed that he had hypertrichosis as an infant but currently had a normal amount of facial and body hair.

The possible causative effect of the mutation on the patient's clinical presentation is not known. Speculatively endocrinopathies in Cantú syndrome are primarily due to mutation in the *ABCC9* gene, which has an unknown effect on the potassium channel in both hormone receptors and in hormone secretion mechanisms. Further research is needed to investigate the causative effects on hormone regulation and secretion by the mutation as well as its effect on the immune system.

Learning Points

- We highlight the multifaceted presentation of the rare Cantú syndrome, which adds to the knowledge on different phenotypes and clinical features of this disease.
- The benefit of whole genome sequencing in diagnosing patients with diffuse and elusive symptoms is worth mentioning.
- Additionally, we recommend physicians who are treating patients with Cantú syndrome to be attentive to signs of immune deficiency and to consider screening for endocrinopathies.

Contributors

All authors made individual contributions to authorship. D.N. wrote the main manuscript. U.M. was involved in the diagnosis and management of the patient and wrote and submitted the main manuscript. O.B. was involved in the management of the patient and wrote and edited the manuscript. G.J. was involved in the management of the patient and edited the manuscript. U.K. edited the manuscript. D.N., U.M., and G.J. prepared tables. U.M. prepared the figures. All authors reviewed, edited, and approved the final manuscript.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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