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Acromegaly in Carney complex

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Abstract

Purpose Carney complex (CNC) is a rare autosomal dominant syndrome, characterized by mucocutaneous pigmentation, cardiac, cutaneous myxomas and endocrine overactivity. It is generally caused by inactivating mutations in the *PRKAR1A* (protein kinase cAMP-dependent type I regulatory subunit alpha) gene. Acromegaly is an infrequent manifestation of CNC, reportedly diagnosed in 10% of patients.

Methods We here report the case of a patient who was concomitantly diagnosed with Carney complex, due to a new mutation in *PRKAR1A* ((NM_002734.3:c.80_83del, p.(Ile27Lysfs*101 in exon 2), and acromegaly. In parallel, we conducted an extensive review of published case reports of acromegaly in the setting of CNC.

Results The 43-year-old patient was diagnosed with an acromegaly due to a GH-secreting pituitary microadenoma resistant to somatostatin analogs. He underwent transsphenoidal surgery in our tertiary referral center, which found a pure GH-secreting adenoma. In the literature, we identified 57 cases (24 men, 33 women) of acromegaly in CNC patients. The median age at diagnosis was 28.8 ± 12 year and there were 6 cases of gigantism. Acromegaly revealed CNC in only 4 patients. 24 patients had a microadenoma and two carried pituitary hyperplasia and/or multiple adenomas, suggesting that CNC may result in a higher proportion of microadenoma as compared to non-CNC acromegaly.

Conclusions Although it rarely reveals CNC, acromegaly is diagnosed at a younger age in this setting, with a higher proportion of microadenomas.

Keywords Acromegaly · Carney complex · PRKAR1A · Microadenoma · Myxoma

Introduction

First described in 1985, Carney complex (CNC) is a rare, autosomal dominant and familial neoplastic syndrome, characterized by the occurrence of abnormal cutaneous and mucosal pigmentation, myxomas, predominantly of the heart, and signs of endocrine overactivity [1]. Other lesions such as psammomatous melanotic schwannomas, breast ductal adenomas, osteochondromyxomas can also be observed in the spectrum of this syndrome [1]. Based on current guidelines [2], the diagnosis of CNC is established on the presence of ≥ 2 main clinical manifestations or one major plus one minor criteria (Table 1). CNC is caused by germline inactivating mutations of *PRKAR1A* (protein kinase A regulatory subunit 1 alpha) gene, located at 17q22-24, or large deletions involving this region [3]. A mutation of *PRKAR1A* is found in 37% of patients with sporadic CNC and more than 70% of patients with familial CNC, with a complete penetrance of the disease [4]. A previous study

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Table 1 Diagnostic criteria for Carney complex

Main criteria
Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
Myxoma (cutaneous and mucosal)**
Cardiac myxoma**
Breast myxomatosis** or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
PPNAD** or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during 6-day modified Liddle test
Acromegaly due to GH
LCCSCT** or characteristic calcification on testicular ultrasonography
Thyroid carcinoma** or multiple, hypoechoic nodules on thyroid ultrasonography
Psammomatous melanotic schwannoma**
Blue nevus, epithelioid blue nevus (multiple)**
Breast ductal adenoma (multiple)
Osteochondromyxoma of bone**
Supplemental criteria
Affected 1st-degree relative
Inactivating mutation of the *PRKAR1A* gene

According to Stratakis et al. [2] the diagnosis is made if the patient: exhibits ≥ 2 main criteria, or exhibits one main criterium and one supplemental criterium, **with histologic confirmation

suggested that, deletions of the *PRKAR1A* locus at 17q24.2-q24.3 could be associated with unusual and more severe phenotypes of CNC [5].

PRKAR1A codes for the regulatory subunits (called R1 alpha) of the protein kinase A (PKA). PKA is a heterotetramer composed of two regulatory and two catalytic subunits, and a downstream effector of the cAMP signaling pathway [6]. In normal conditions, cAMP triggers the separation of regulatory from catalytic subunits, which switches the PKA complex from an inactivated to an activated state, leading to transcription of targeted genes. Inactivating mutations of *PRKAR1A* in CNC lead to a loss-of-function of the regulatory subunits, therefore to a constitutive activation of the cAMP-PKA signaling pathway, which results in both proliferative and secretory overactivities in endocrine cells. The genetic causes of CNC remain unknown in a part of patients. While the 2p16 locus have been associated to CNC through linkage analysis, the gene in this region responsible for the CNC phenotype remains unknown [6]. In one study, an amplification of the *PRKACB* gene have been involved in CNC [7]. To date, there are more than 750 cases of CNC that have been reported worldwide [8]. Amongst endocrine lesions observed in CNC, an acromegaly due to a GH-secreting pituitary adenoma (PA) can be found in around 10% of patients.

The aim of this paper is:

1. To describe a new clinical case of a CNC-related acromegaly in a patient carrying a new mutation in the *PRKAR1A* gene.
2. To review all the well-characterized cases of acromegaly due to CNC, published in the literature so far.

Case presentation

In 2012, a 43-year-old male was transferred to the emergency department for an epileptic seizure. He was diagnosed in 2009 with a 71 × 27 mm cardiac myxoma in the left atrium for which a complete surgical resection was performed the same year. He suffered from several recurrent ischemic stroke after surgery. In his past medical history he had arterial hypertension, dyslipidemia, several cerebrovascular accidents and a mixed (i.e. central and obstructive) sleep apnea syndrome. There was no familial history of pituitary disease and/or cardiac failure in his kindred.

Physical exam revealed obvious acromegalic features, with prognathism, pronounced brow protrusion, and nasolabial fold thickening (Fig. 1). Skin inspection revealed the presence of pigmented and café-au-lait spots, blue nevi and cutaneous myxomas (Fig. 1). According to the guidelines, the patient was therefore diagnosed with CNC. A new cardiac ultrasonography did not identify any relapse of cardiac myxomas. An enhanced adrenal CT scan revealed adrenal glands of normal size and structure (especially without aspect of primary pigmented micronodular adrenal disease [PPNAD]). Eventually, thyroid ultrasound showed a multinodular goiter with the largest thyroid nodule that was proved to be benign after fine needle aspiration. The testicular ultrasound showed a macrocalcification

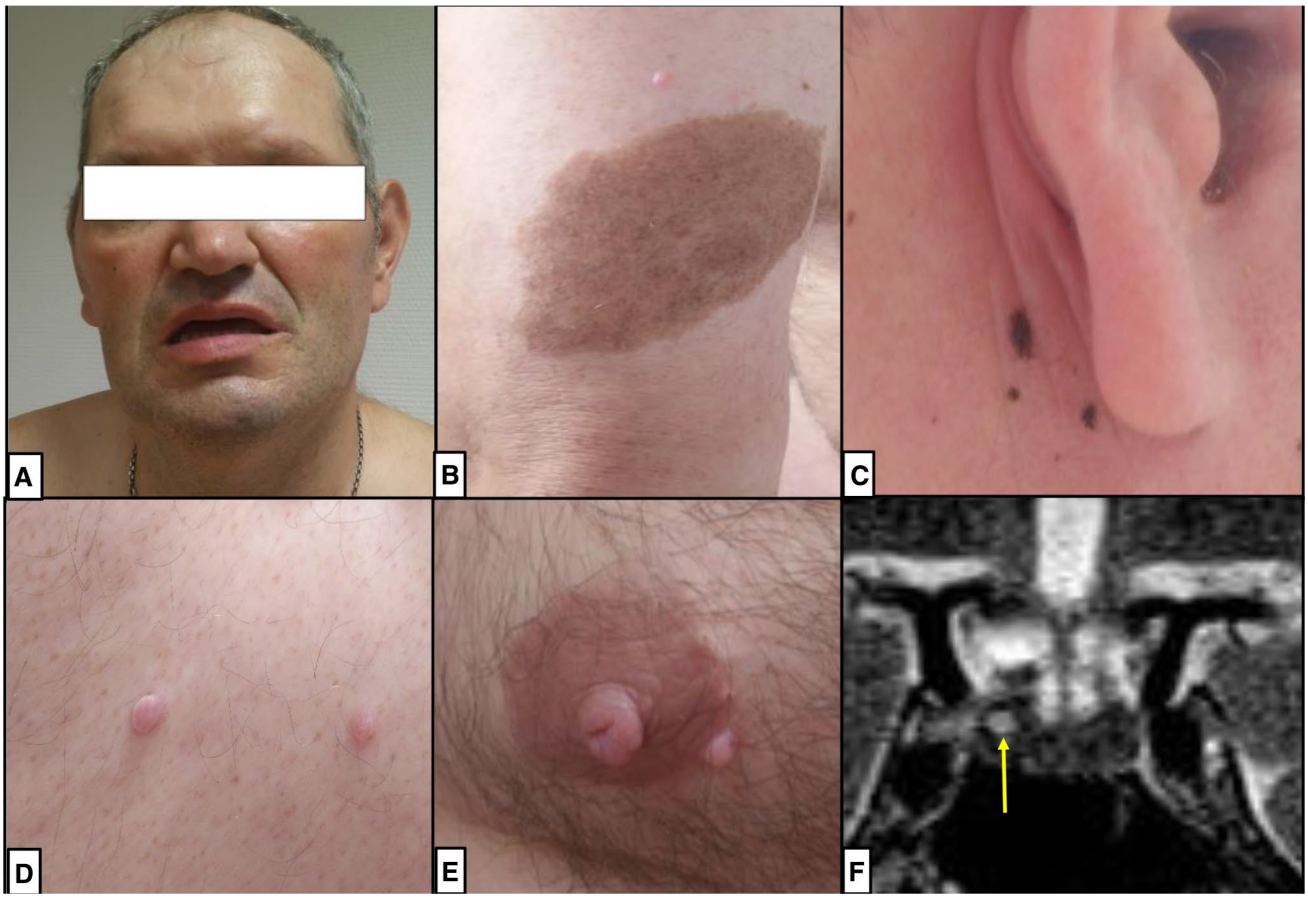

Fig. 1 Phenotypic and pituitary MRI aspect of the patient. Note the acromegalic features of the face with prognathism and naso-labial fold thickening (**a**) and typical dermatologic lesions observed in Carney complex such as "café-au-lait" spots (**b**), nevi (**c**) and cutaneous myxomas (**d**, **e**). Right-sided, hyperT2 pituitary microadenoma (**f**, yellow arrow). Note that the patient gave informed consent for publication

at the lower pole, however there was no other signs in favor of a large cell calcifying sertoli cell tumor (LCCSCT).

The pituitary MRI confirmed the presence microadenoma of 3 mm on the right side (Fig. 1). The pituitary hormones profile was normal, except for the somatotroph axis with a GH that was unsuppressed during a 75 g-oral glucose tolerance test (OGTT) with a nadir of 3 ng/mL (9 mUI/L), suggesting an active acromegaly [9]. The IGF-1 was increased, up to 640 ng/mL (normal range for gender/age: 88–246).

We performed a genetic analysis of the *PRKAR1A* gene which found a 4-nucleotide deletion in exon 2 () (NM_002735.3:c.80_83del, p.(Ile27Lysfs*101), never previously described (Fig. 2). This deletion resulted in frameshift changes generating a premature stop codon, which should lead to the subsequent degradation of the mRNA transcript by the non-sense mRNA decay (NMD), or less probably to a truncated protein. Screening of his mother was negative and no other family members were available for genetical analysis.

He was treated as a first-line therapy by long-acting somatostatin analogs (SSA, octreotide 30 mg/28 days), however after 9 months of medical treatment, a slight decrease of IGF-1–80 ng/mL (88–246 ng/mL) was observed with a persistent random GH of 5 ng/mL at the last follow-up. Tumor volume remained stable. A surgical procedure was eventually performed by an endoscopic transsphenoidal approach. Histopathology and immunohistochemistry of the tumor revealed a pure GH pituitary adenoma, with Ki67 < 1% (Clone: Mib-1) and absence of P53 expression (Clone: DO.7).

In the post-operative period, a biochemical remission of acromegaly was obtained with an IGF-1 concentration of 125 ng/mL, fasting basal GH levels of 0.6 ng/mL and 0.09 ng/mL during OGTT. Pituitary MRI revealed post-operative alterations, stroke sequelae and no evidence of residual pituitary adenoma tissue.

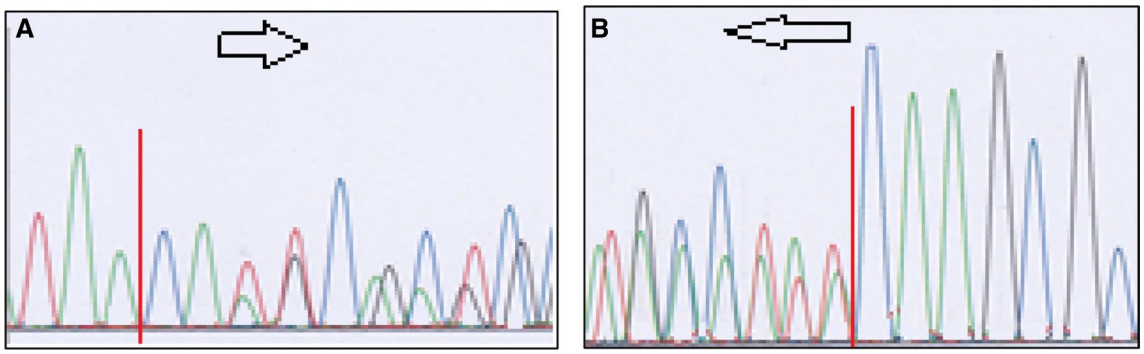

Fig. 2 Sequence analysis around the breakpoints PRKAR1A c.80_83del; p.Ile27Lysfs (NM_002734, HGVS recommendations March 22, 2016). **a** A. Black arrow, forward primers sequencing 5′3′. Red line, breakpoint. **b** Black arrow, reverse primers sequencing 3′5′. Red line, breakpoint

Acromegaly in Carney complex: a literature review

Acromegaly due to a GH-secreting PA is a relatively infrequent manifestation of CNC, encountered in up to 10% of patients affected by the syndrome [4, 10]. Familial acromegaly are rare and mainly found in familial isolated pituitary adenomas (FIPA) syndrome (in which *AIP* mutations can be identified) and multiple endocrine neoplasia type 1 (MEN1). Because of their rarity, Multiple endocrine neoplasia type 4 (MEN4) and CNC are two exceptional conditions that can predispose to acromegaly [11]. McCune Albright Syndrome (MAS) is another syndrome of genetic predisposition to acromegaly, however in this disease, the genetic defect is not at the germline level but occurs at the postzygotic step on the gene GNAS and is therefore found in mosaic state. In CNC, GH-secreting PA can cause either acromegaly or gigantism depending on the age of onset. In the children population, the prevalence of *PRKAR1A* mutation amongst patients with GH-secreting PA is close to 10% [12]. However, the work conducted by Beckers group over a specific population of giant patients showed us that, with less than 1% of cases identified, CNC remains, as compared to *AIP* mutations (29%), X-LAG syndrome (10%) or even MAS, an exceptional condition that leads to gigantism [13].

In up to 70% of patients with CNC, subtle abnormalities of the GH axis, including elevated (asymptomatic) baseline GH or IGF1 or non-suppressible GH to an oral glucose tolerance test (OGTT) can be observed [14]. This hormonal profile is attributed to the development of a certain degree of pituitary hyperplasia which may precede tumor development [14, 15]. This peculiar lesional aspect is similar to the one observed in patients with MAS, where somatotroph hyperplasia is, besides the potential occurrence of a PA, also frequently observed [16]. Interestingly, MAS also results from an overactivation of the cAMP signaling pathway due to mosaic mutation of the *GNAS* gene, which leads to overactivation of the Gsalpha subunit. In turn, the mutated Gsalpha protein causes the adenylate cyclase enzyme to be constantly turned on (constitutively activated) and therefore triggers a sustained activity of the cAMP signaling pathway. To date, there are very few well-characterized case reports of acromegaly in CNC, however it should be underlined that the first historical case of acromegaly described by Harvey Cushing in 1914 was presumably due to a CNC [17].

We performed an extensive analysis of the literature and identified 57 cases of CNC-related acromegaly (Table 2). We scrupulously paid attention not to include the same patient twice in the table, as many of them have been reported in different studies, especially when they were described by the same group of authors. There were 24 men and 33 women, with a median age at diagnosis of 28.8 ± 12 years, which is earlier as compared to sporadic acromegaly (median age at diagnosis of 40–48 years) [18]. There were six reported cases of gigantism; however in this specific population, CNC remains a rare condition as it is found in only 1% of this subgroup of patients [13].

When reported, a majority of patients (45/56, 80%) have been diagnosed because of features suggestive of acromegaly, while other symptoms of CNC already coexisted. Information about the size of the causing lesion (microadenoma vs. macroadenoma or enlarged sella) was available in 49 patients. In the earlier reports, MRI had not been systematically performed because unavailable at that time, however we assumed that an enlarged sella as observed by conventional tomograms of the sella turcica meant that the patient had a macroadenoma. As such, there were a roughly equivalent ratio of macroadenomas (i.e. maximal diameter > 10 mm, $n = 27$) and microadenomas (maximal diameter ≤ 10 mm, $n = 24$) while in non-CNC acromegaly a higher prevalence of macroadenoma (ranging from 70 to 90% depending on the study) is generally observed [18]. This specificity is illustrated by our clinical case where the size of the adenoma did not exceed 5 mm. The mean value of GH was 35 ± 89 ng/mL ($n = 43$) at diagnosis and, according to the current guidelines [9], GH under oral glucose

Table 2 Summarizing table of acromegalic cases described in the context of Carney complex

n	Country (Center)	Year of publication	Sex	Age at diagnosis	Presentation	Adenoma size (mm)	Invasion	GH (ng/mL)		IGF-1 at diagnosis (for age and sex)	Treatment	Histopathological description	Other features of CNC	*Germinal PRKAR1A* mutation	Ref
								Baseline	After OGTT						
1	USA (BET)	1979	M	16	Gigantism	Enlarged sella	NR	17	9*	1.4 × ULN	Surgery	GH	PPNAD, LCCSCT, LEN	NP	[33]
1	USA (BOS)	1980	M	11	Gigantism	NR	NR	NR	NR	NR	Radiation	Acidophil cells (GH)	LCCSCT	NP	[19]
1	UK	1984	F	28	Incidentaloma	Enlarged sella	NR	NR	NR	NR	Surgery	Chromophobe	AM	NP	[26]
4**	USA (ROC)	1985	M	21	Acromegaly	Asymetric enlargment	NR	NR	NR	NR	Surgery	GH	SP, CM	NP	[1]
			F	27	Acromegaly	NR	NR	NR	NR	NR	Surgery	GH	MF, SP, AM	NP	
1	AUS (PER)	1986	M	40	Acromegaly	Enlarged sella	NO	15	12	NR	Bromocriptine	NR	CM, LCCSCT	NP	[20]
1	IRE	1992	F	15	Mass effect	Macro	YES	N (elevated PRL)	N	N	Surgery/ Bromocriptine	Cystic adenoma GH/ PRL	SP, CM	NP	[21]
1	USA (IRVINE)	1992	F	22	Acromegaly	Macro (26)	NO	126	NR	7 × ULN	NR	NR	AM, SP, BN	NP	[34]
5***	USA (BET, ROC)	2000	F	39	Acromegaly	Micro (6)	NO	5.6	3.3	1.9 × ULN	Surgery	GH/PRL	AM, SP, CM, PPNAD	NP	[10]
			F	44	Acromegaly	Macro	YES	4.8	NR	1.3 × ULN	Surgery	GH	NR	NP	
			F	37	Acromegaly	Micro	NO	NR	NR	NR	Surgery	GH/PRL	NR	NP	
			F	19	Acromegaly	Macro (18)	YES	8.8	416	NR	Surgery	GH/PRL	NR	NP	
			M	20	Acromegaly	Macro	YES	NR	NR	NR	Surgery	GH	NR	NP	

Table 2 (continued)

n	Country (Center)	Year of publication	Sex	Age at diagnosis	Presentation	Adenoma size (mm)	Invasion	GH (ng/mL)		IGF-1 at diagnosis (for age and sex)	Treatment	Histopathological description	Other features of CNC	*Germinal PRKAR1A* mutation	Ref
								Baseline	After OGTT						
8	USA (BET)	2000	M	19	Acromegaly	Macro	YES	27	NR	1.3 × ULN	Surgery	GH/PRL	LEN, PPNAD	NP	[15]
			F	38	Screening	Micro	NO	5.4	NR	2.5 × ULN	Surgery	GH/PRL	LEN, PPNAD, CM	NP	
			F	44	Screening	Micro	NO	14.2	NR	1.5 × ULN	Surgery	GH/PRL	LEN, PPNAD, CM	NP	
			M	42	Screening	Micro	NO	4.8	NR	1.2 × ULN	Surgery	GH/PRL	LEN, PPNAD, CM	NP	
			M	18	Acromegaly	Macro	NO	12.6	NR	2.5 × ULN	Surgery	GH/PRL	LEN	NP	
			F	21	Acromegaly	Macro	NO	41	NR	4.7 × ULN	Surgery	GH/PRL	LEN, PPNAD	NP	
			M	38	Acromegaly	Micro	NO	8.3	NR	1.2 × ULN	Surgery	GH/PRL	LEN, PPNAD	NP	
			F	19	Acromegaly	Micro	NO	4.7	NR	1.2 × ULN	Surgery	GH/PRL	LEN, PPNAD, CM	NP	
1	USA (HOU)	2001	F	27	Acromegaly	Micro	NR	41.3	NR	1.1 × ULN	Surgery	GH	SP, AM, BN	NP	[35]
1	GER (DRE)	2001	M	15	Acromegaly	Micro (10)	NO	18.9	Unsuppressed	1.7 × ULN	Surgery	GH/PRL	LCCSCT, SP	NP	[36]
1	ITA	2001	M	NR	NR	Macro	NR	NR	NR	NR	NR	NR	AM, TN	NP	[37]
2	USA (ROC)	2002	F	18	Amenorrhea	Micro (10)	YES	27	15	1.1 × ULN	Surgery	GH/PRL	PPNAD, LEN	NP	[38]
			M	20	Acromegaly	Macro	YES	338	87	NR	Surgery	GH	PPNAD, LCCSCT	NP	
1	JAP (KAN)	2004	M	16	Acromegaly	Micro (5)	NO	16	NR	4 × ULN	NR	NA	AM, SP	c.407_408del, p.(Val136Alafs*6) exon4	[39]
1*****	JAP (TYO)	2005	M	55	Acromegaly	Micro (3)	NO	NR	NR	NR	Surgery	GH	AM, SP	c.140_143delinsGGT, p.(Met47Argfs*82) exon 2	[40]
1	GER (MAG)	2007	M	41	Acromegaly	Micro	NO	8.5	Unsuppressed	2 × ULN	Surgery	GH	SP	c.220_221delCG (p.Arg74 fs*6) exon 3	[41]

Table 2 (continued)

n	Country (Center)	Year of publication	Sex	Age at diagnosis	Presentation	Adenoma size (mm)	Invasion	GH (ng/mL)		IGF-1 at diagnosis (for age and sex)	Treatment	Histopathological description	Other features of CNC	*Germinal PRKAR1A* mutation	Ref
								Baseline	After OGTT						
4****	ITA (MIL)	2007	F	44	Acromegaly	Macro	NR	21	15	3.1 × ULN	Surgery/SMS	GH	LEN, MS	c.440 + 1G > A, p.(?) intron 4	[42]
			M	43	Acromegaly	Micro	NR	6.1	3.7	1.6 × ULN	NR	GH	LEN, CM		
			F	28	Screening	Micro	NR	6.2	9.7	1.2 × ULN	SMS	NA	LEN		
			F	21	Screening	Micro	NR	5.9	2.4	N	NR	NA	LEN		
2	ITA (BOL)	2008	F	18	Acromegaly	Micro	NR	NR	Unsuppressed	NR	Low dose OCT	NA	PPNAD, LEN	c.502 + 1G > A, p.(?) intron 5	[24]
			M	16	Gigantism	NR	NR	NR	NR	NR	SMS Resistant	NA	LEN		
3	JAP (GIFU)	2008	F	23	Acromegaly	Micro (9)	NO	5.9	1.12	N	Considering SMS	NR	PPNAD, SP	c.537del, p.(Gly180Glufs*26) exon 6	[23]
			F	40	Acromegaly	NR	NR	8.9	NR	1.8 × ULN	Surgery	NR	NONE		
			F	21	Galactorrhea	NR	NR	17.3	NR	1.8 × ULN	SMS resistant	NR	NONE		
1*****	JAP (TYO)	2009	F	40	Acromegaly	Micro (3)	NO	6.4	5.5	1.4 × ULN	Surgery	GH	AM, SP	c.140_143delinsGGT, p.(Met47Argfs*82) exon 2	[43]
1	KOR (SEL)	2009	F	25	Acromegaly	Macro (16)	NO	NR	19	2.1 × ULN	Surgery	GH	SP	c.537delA, p.5 exon 6	[44]
1	SPA (PNA)	2011	F	55	Incidentaloma	Macro (12)	NO	6.4	3.78	1.1 × ULN	Surgery/SMS	GH	AM, LEN, SP	NP	[45]
1	USA (NY)	2012	M	44	Acromegaly	Micro (4)	NO	NR	NR	2 × ULN	Surgery/CAB	GH/PRL	CM, BN, SP, LCCSCT	NP	[22]
1	IND (ND)	2014	M	30	Acromegaly	Micro (9)	NO	16	12.6	2.2 × ULN	Surgery	GH	AM	c.682_683ins22, p.(Arg228Profs*12) exon 7	[46]
1	JAP (OSA)	2015	F	NR	Gigantism	Macro (15)	NO	11	Unsuppressed	1.7 × ULN	Surgery	GH	SP	LGD	[47]

Table 2 (continued)

n	Country (Center)	Year of publication	Sex	Age at diagnosis	Presentation	Adenoma size (mm)	Invasion	GH (ng/mL)		IGF-1 at diagnosis (for age and sex)	Treatment	Histopathological description	Other features of CNC	*Germinal PRKAR1A* mutation	Ref
								Baseline	After OGTT						
7	USA (BET)	2017	F	44	Acromegaly	MA	NR	4.8	Unsuppressed	N	Surgery	MA GH/PRL	PPNAD	NR	[48]
			F	19	Acromegaly	Macro (19)	NR	8.8	Unsuppressed	N	Surgery	GH/PRL	NONE	NR	
			F	38	Acromegaly	Micro (6)	NR	31	Unsuppressed	N	Surgery	GH/PRL	NONE	NR	
			M	34	Acromegaly	Macro	NR	4.5	Unsuppressed	N	Surgery	PRL + GH hyperplasia	NR	NR	
			F	27	Acromegaly	Macro (12)	NR	8.6	Unsuppressed	2.1 × ULN	Surgery	GH/PRL	NR	NR	
			M	18	Acromegaly	Macro (12)	NR	26.5	Unsuppressed	1.8 × ULN	Surgery	GH/PRL	NR	NR	
			F	28	Acromegaly	Macro (15)	NR	63.8	Unsuppressed	2.4 × ULN	Surgery	GH/PRL	NR	NR	
1	TUR (ANK)	2017	M	46	Acromegaly	Macro (12)	NR	5.3	Unsuppressed	1.5 × ULN	Surgery	GH/PRL	AM, myxoma, LCCSCT, PPNAD	c.170dup, p.(Leu57Phefs*25) exon 2	[49]
2	POL (WS)	2017	M	26	Acromegaly	Macro (12)	NO	35	29.2	4.3 × ULN	Not treated	NA	CM, AM, SP, myxomas	LGD	[50]
			F	25	Acromegaly	Micro (5.3)	NO	26.9	25	4.2 × ULN	Surgery	NR	SP, myxomas,	LGD	
2	JAP (TYO)	2018	F	17	Gigantism	Macro (19.5)	NR	8.9	NR	1.8 × ULN	SMS/surgery	GH	NR	NR	[12]
			M	18	Gigantism	Micro (9.9)	NR	8.3	NR	1.5 × ULN	Surgery	GH	NR	NR	

n number of patients, *NA* not applicable, *NP* not performed, *NR* not reported, *LGD* large gene deletion, *AM* atrial myxoma, *BN* blue naevi, *CM* cutaneous myxomas, *CNC* Carney complex, *LCCSCT* large cell calcifying sertoli cell tumor, *LEN* lentigines, *PPNAD* primary pigmented nodular adrenal disease, *SP* spotty pigmentation, *LEN* lentiginosis, *MF* myxoid fibroadenoma, *PMS* psammomatous melanotic schwannoma, *MS* melanotic schwannoma

*120 min after the ingestion of 100 g glucose

**Two cases already described in previous report ([18] and [28])

***Only new cases from this publication are reported here

****Acromegaly was the first clinical manifestation in those four case reports

*****Those two patients originating from the same region harbor the same *PRKAR1A* mutation

tolerance test (OGTT) was unsuppressed (i.e., GH > 1 ng/mL) in 29/30 cases. IGF-1 levels were not reported in 13 cases and were found normal in 7 cases. In patients with elevated IGF-1 (n = 36), the mean value was 2.1 ± 1.2 ULN.

A majority of patients (43/50, 86%) were surgically treated. One patient was treated by radiation therapy [19], others with bromocriptine alone [20] or in combination with surgery [21, 22]. Likewise, some patients have been treated with somatostatin analogs alone or combined with surgery (n = 7) and among them, two were considered as being resistant [23, 24], like in our case.

A majority of patients diagnosed with acromegaly had at the same time several other lesions of the CNC spectrum (Table 2); however acromegaly was the first manifestation of CNC in 4 patients reported in the literature [23, 25].

The histopathological reports were available in 43 patients, with two main types of lesion observed: either pure GH-secreting adenoma (n = 19) or mixed GH/PRL-secreting adenoma (n = 22). One patient had a chromophobe pituitary adenoma with an acromegaly [26]. When available, the genetic analysis did not show any obvious genotype–phenotype correlation (Table 2).

Discussion

To date, more than 200 different *PRKAR1A* mutations have been identified in literature and online databases (PRKAR1A database https://prkar1a.nichd.nih.gov/hmdb/prkar1a.html, LOVD https://databases.lovd.nl, HGMD http://www.hgmd.cf.ac.uk/ac/all.php) in CNC-families of various ethnic origins. It should be noted that identifying a mutation in the *PRKAR1A* gene is highly relevant for genetic counseling, because the overall penetrance of CNC in patients with a *PRKAR1A* pathogenic variant is greater than 95% by age 50 years. To date, only two *PRKAR1A* pathogenic variants have led to an incomplete penetrance of the syndrome: the splice variant c.709-7_709-2del, and the initiation codon loss c.1A > G, p.(?), which are responsible of mild forms of CNC with PPNAD and lentigines [27].

In this paper, we report, to the best of our knowledge, a new *PRKAR1A* mutation, responsible for a 4-nucleotide deletion in exon 2 (c.80_83del, p.(Ile27Lysfs*101) in a patient with CNC revealed by atrial myxoma, spotty skin pigmentation, cutaneous myxomas and acromegaly due to a GH-secreting microadenoma. In CNC, it seems that acromegaly is more frequently due to a microadenoma as compared to sporadic acromegaly. This observation could be however the consequence of a systematic hormonal and/or imaging assessment as soon as the diagnosis of CNC is done or suspected. Another hypothesis could be that only a subset of somatotroph cells will exhibit loss of heterozygosity (LOH) at 17q22-24, consistent with the Knudson two-hit model of hereditary tumorigenesis of this syndrome [8], and therefore will result in an adenoma of small size. Another matter of the discussion is related to the rarity of "true" acromegaly in CNC (10%) contrasting with up to 70% of patients who will have subtle abnormalities of the GH axis. This is likely due to a certain degree of somatotroph hyperplasia which suggests, from a pathophysiological point of view, that *PRKAR1A* mutations may lead to GH hyperplasia, which in turn may sometimes result, albeit not systematically, to the development of a GH-secreting microadenoma or macroadenoma. This observation is further supported by the development of GH hyperplasia in patients with MAS, a pathology in which a sustained activation of the cAMP signaling pathway occurs as well [28]. Unlike FIPA [11] or the so-called X-linked acrogigantism (X-LAG) syndrome [13], CNC-related acromegaly does not seem to be correlated with higher concentrations of GH and/or IGF-1 as compared with non-syndromic acromegaly. On the contrary, it even appears that a higher proportion of microadenomas are likely to be found presumably due to an active screening in the population of patients with clinical patterns of CNC. However, it could not be entirely ruled out that CNC may predispose to mild forms of acromegaly, which will be diagnosed at a later stage of the disease as compared to other CNC symptoms. This is particularly highlighted in the cases from the literature by a very low proportion of patients for who acromegaly was the inaugural lesion of the syndrome.

Less is known about the efficacy of medical treatment of acromegaly in the setting of CNC. Previous work from our group and others suggested that when the cAMP signaling pathway was overactivated in somatotroph tumors, through mutation of the *gsp* oncogene, a greater inhibition of the GH secretion was observed under octreotide, as compared to non-mutated tumors [29, 30]. In CNC, a roughly similar molecular mechanism is likely to occur as the *PRKAR1A* mutation ultimately leads to a sustained activation of both c-AMP response element-binding protein (CREB) and gene transcription. However, in our patient as in other observations [23, 24], resistance to SMS occurred suggesting that other mechanisms could influence this therapeutic effect, paving the way for further investigations in this direction. Of note, the microadenoma presented by our patient appeared in hypersignal in T2-weighed sequences, which is consistent with the observation by several groups an association between T2 hypersignal and poor response to somatostatin analogues in acromegaly [31, 32]. There are currently no data existing about the T2-weighted signal of GH-secreting PA in the specific setting of CNC.

In conclusion, we report a novel deleterious *PRKAR1A* mutation in a case of CNC with a somatotroph microadenoma resistant to somatostatin analogs. Knowledge of the characteristic presentation of acromegaly in the context of CNC and its associated features such as cardiac myxoma or

typical skin lesions will aid the clinicians in timely diagnosis and appropriate management of this rare disease.

Compliance with ethical standards

Conflict of interest All the author declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals and human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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