ISSN 2472-1972

Unusual Combination of MEN-1 and the Contiguous Gene Deletion Syndrome of CAH and Ehlers-Danlos Syndrome (CAH-X)

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The contiguous gene deletion syndrome of congenital adrenal hyperplasia and Ehlers-Danlos syndrome, named CAH-X, is a rare entity that occurs because of a deletion of a chromosomal area containing 2 neighboring genes, *TNXB* and *CYP21A*. Here, we describe a patient from a consanguineous family in which coincidentally MEN-1 syndrome is associated with CAH-X, causing particular challenges explaining the phenotypic features of the patient. A 33-year-old man with salt-wasting congenital adrenal hyperplasia and classic-like Ehlers-Danlos syndrome presented with an adrenal crisis with a history of recurrent hypoglycemia, abdominal pain, and vomiting. He was found to have primary hyperparathyroidism, hyperprolactinemia, and pancreatic neuroendocrine tumors, as well as primary hypogonadism, large adrenal myelolipomas, and low bone mineral density. A bladder diverticulum was incidentally found. Genetic analysis revealed a heterozygous previously well-described *MEN1* mutation (c.784-9G > A), a homozygous complete deletion of *CYP21A2* (c.1-?_1488+? del), as well as a large deletion of the neighboring *TNXB* gene (c.11381-?_11524+?). The deletion includes the complete *CYP21A2* gene and exons 35 through 44 of the *TNXB* gene. CGH array found 12% homozygosity over the whole genome. This rare case illustrates a complex clinical scenario with some initial diagnostic challenges.

Freeform/Key Words: congenital adrenal hyperplasia, Ehlers-Danlos syndrome, contiguous gene deletion syndrome, multiple endocrine neoplasia type 1, adrenal myelolipoma, neuroendocrine tumor

Salt-wasting congenital adrenal hyperplasia (CAH) and classic-like Ehlers-Danlos syndrome (EDS) were initially linked more than 20 years ago [1]. The gene leading to this form of EDS is *TNXB* (OMIM 600985), coding for Tenascin-X (TN-X), a protein involved in the stabilization of collagen fibers. Classic-like EDS is phenotypically similar to classic EDS, except for the absence of the characteristic scarring. It is caused by a different gene, and usually the full syndrome occurs when both alleles are affected. Clinical symptoms, such as velvety skin, joint hypermobility, cardiac valve abnormalities, among others, can

Abbreviations: CAH, congenital adrenal hyperplasia; EDS, Ehlers-Danlos syndrome; MEN-1, multiple endocrine neoplasia type 1; TN-X, Tenascin-X.

Received 9 April 2020
First Published Online 27 June 2020
Corrected and Typeset 20 July 2020

be detected even when 1 allele is affected [2]. *CYP21A2* (OMIM 201910), the gene mutated in salt-wasting CAH resulting from 21-hydroxylase deficiency, and *TNXB*, are both located close to each other on the short arm of chromosome 6, within the HLA locus. This region is particularly susceptible to recombination abnormalities resulting from the highly homologous nearby *CYP21A1P* and *TNXA* pseudogenes. Abnormal recombination can lead to larger deletions, resulting in contiguous gene deletion syndrome involving *CYP21A2, TNXB*, and its corresponding pseudogenes *CYP21A1P* and *TNXA* [3], named CAH-X. Here, we report a case that had a complex clinical presentation of the contiguous gene deletion syndrome of CAH-X and the multiple endocrine neoplasia type 1 (MEN-1) syndrome, a combination that has not been previously reported in the literature. Interestingly, in trying to find an association between these 2 syndromes, we found that both CAH-X and MEN-1 can disrupt the TGF-β signaling pathway, however in different ways [4, 5].

Case Presentation

A 33-year-old man with a history of learning disability, salt-wasting CAH, and MEN-1 syndrome resulting from a heterozygous hotspot *MEN1* mutation c.784-9G > A (rs794728625) presented with recurrent hypoglycemia, abdominal pain, and vomiting for 6 weeks. His physical examination was significant for short stature 135 cm (4 ft, 5 in.), wrinkled forehead, teeth malocclusion, mild prognathism, short fingers and toes, hyperextensible and loose joints, and soft and velvety skin (Fig. 1A-D). His parents were first cousins. His father died at age 56 from liver cancer. Of his 10 full siblings, 2 had MEN-1, but none were known to have CAH. The proband had adrenal insufficiency since birth secondary to CAH, but was poorly compliant with glucocorticoid replacement. He had low cortisol and undetectable aldosterone levels at baseline and during the ACTH stimulation test, along with elevated 17-hydroxyprogesterone and ACTH levels (Table 1). He had primary hyperparathyroidism, hyperprolactinemia with no visible lesion on pituitary magnetic resonance imaging

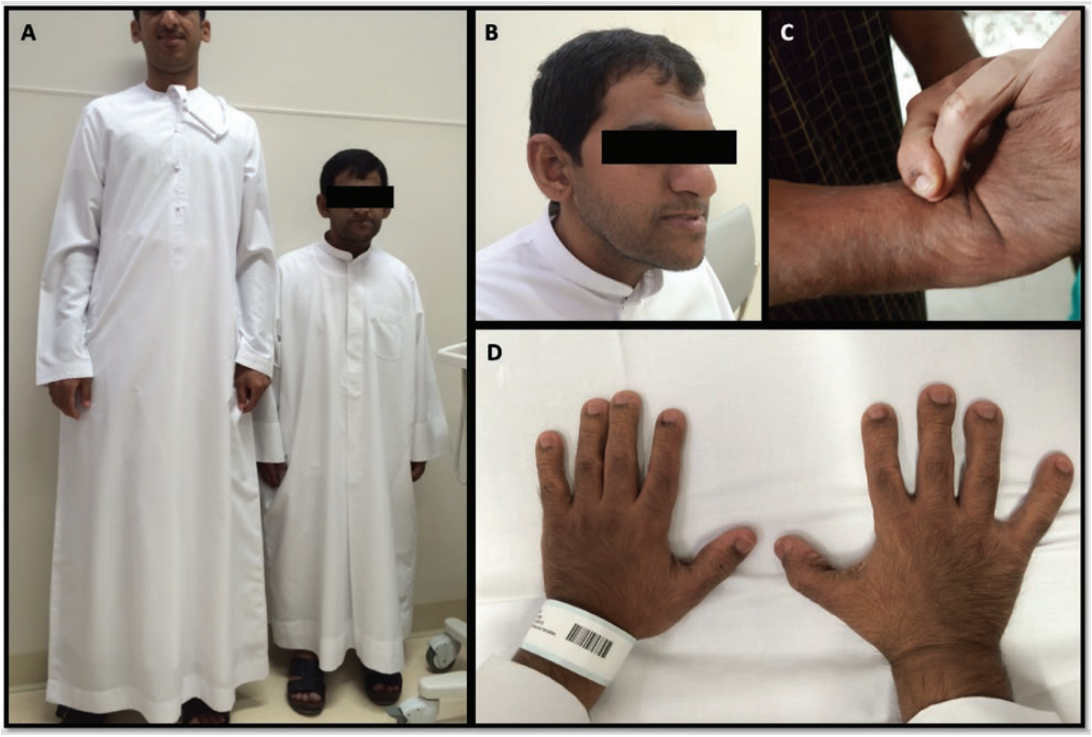

Figure 1. Clinical features, (A) short stature 135 cm (4 ft, 5 in.) compared with his brother; (B) wrinkled forehead, prognathism, jaw malocclusion; (C) short fingers, and (D) hyperextensible and loose joints.

Table 1. Cortisol, 17 OH Progesterone, and Aldosterone Levels During Synacthen Stimulation Test

Hormone	Reference Range	Baseline	60 Min
Cortisol*a*	64-536 nmol/L	22	23
17-Hydroxyprogesterone*a*	0.8-6.0 nmol/L	10.2	20.5
Aldosterone*a*	0-832 pmol/L	<28	<28

aHydrocortisone was held for 24 hours before the test.

(Fig. 2A-B), and a normal IGF-1 (Table 2). Additionally, he had primary hypogonadism with small, soft testicles of 8 to 10 mL bilaterally, a 1.6-cm enhancing pancreatic mass, and replacement of the normal adrenal tissue with large bilateral (left 5.7 × 10.6 cm and right 8.5 × 3.7 cm) lipomatous lesions resembling myelolipomas (Fig. 2C-D). A dual-energy X-ray absorptiometry scan reported Z-scores consistent with low bone mineral density for his age (lumbar spine, –2.9, femoral neck, –1.8,and distal on-third forearm, –1.7). A bladder diverticulum, typical of EDS, was incidentally found (Fig. 2E). An echocardiogram revealed mild left atrial dilation and mild mitral valve regurgitation. He had an elevated proinsulin level with inappropriately normal insulin and C peptide in the setting of hypoglycemia of 47 mg/dL, consistent with endogenous hyperinsulinemia (Table 2). Chromogranin A and gastrin were elevated (while using pantoprazole 40 mg daily), whereas glucagon level was normal. Endoscopy revealed extensive duodenal and lower esophageal ulceration suggestive of Zollinger-Ellison syndrome.

The CAH genetic test revealed a homozygous complete deletion of *CYP21A2* (c.1-?_1488+? del) as well as a large deletion of the neighboring *TNXB* gene (c.11381-?_11524+?). The deletion included the complete *CYP21A2* gene and exons 35 through 44 of the *TNXB* gene. Because of the consanguinity and learning disability, a chromosomal microarray analysis was performed using the Cytoscan HD platform (Affymetrix) containing 2 699 550 markers

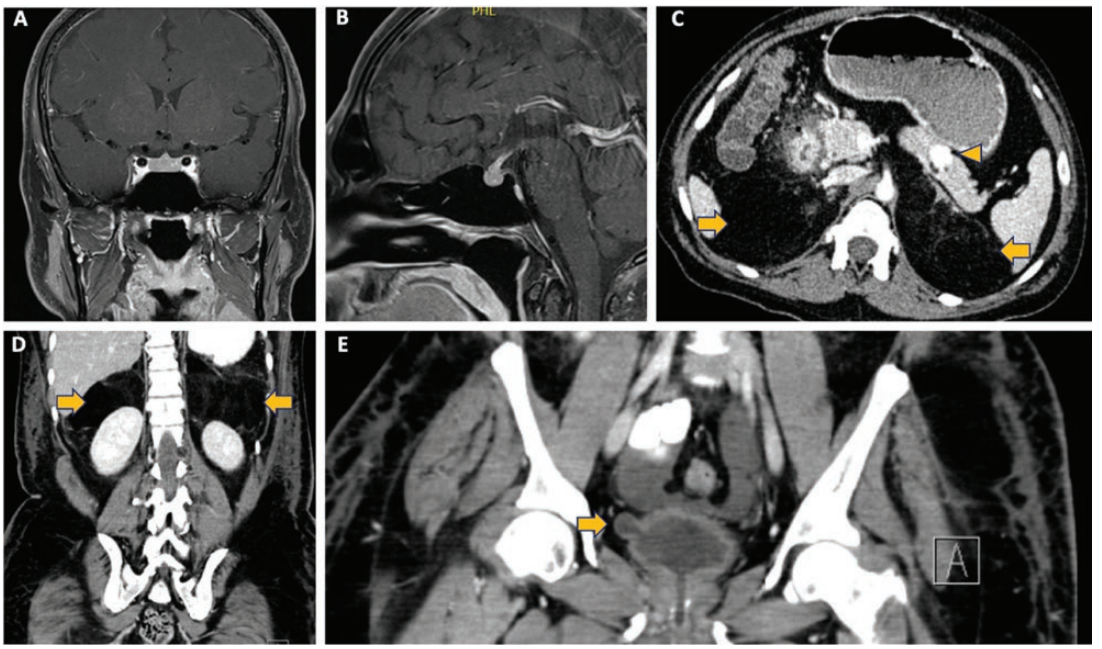

Figure 2. T1 post-contrast pituitary magnetic resonance imaging scan. (A) Coronal view and (B) sagittal view showing a normal-appearing pituitary gland with a prominent infundibulum, but no mass. Computed tomography of the abdomen with (C) transverse and (D, E) coronal view showing bilateral enlargement of the adrenal glands because of adrenal myelolipomas (C-D, arrows, 5.7 × 10.6 cm on the left and an 8.5 × 3.7 cm on the right). (C, arrowhead) A 1.6-cm enhancing pancreatic mass and (E, arrow) bladder diverticulum.

Table 2. Hormonal Evaluation

Hormone	Patient Result	Reference Range
Plasma renin activity	14.1	0.167-5.380 ng/mL/hr
ACTH	27.8 (4:32 pm) 220.7 (11:07 am)	1.6-13.9 pmol/L
DHEA-S	0.1	3.7-12.8 µmol/L
Testosterone	155 (8:51 am)	348-1197 ng/dL
Free testosterone	4 (8:51 am)	90-87 pmol/L
LH	16.1	1.7-8.6 IU/L
FSH	20.5	1.5-12.4 mIU/mL
Normetanephrine	0.14	0-0.79 nmol/L
Metanephrine	0.09	0-0.31 nmol/L
Gastrin*a*	307	0-55 pmol/L
Glucagon*a*	127	50-150 ng/L
Pancreatic polypeptide	343	0-100 pmol/L
Somatostatin	39	<30 pg/mL
Vasointestinal peptide	16	0-17 pmol/L
Chromogranin A	33	0-5 nmol/L
Glucose*a*	47	70-100 mg/dL
C-peptide*a*	0.68	0.37-1.47 nmol/L
Insulin*a*	7.76	2.6-24.9 U/mL
Proinsulin*a*	46.1	0-10.0 pmol/L
Calcium	2.75	2.15-2.55 nmol/L
PTH	11.4	1.6-6.9 pmol/L
IGF -1	115	82-242 ng/mL
GH	2.8	0-10 µg/L
Prolactin	88.4	4-15.2 ng/mL

aPrepancreatic surgery.

distributed along the whole genome. This found 12% of the genome being homozygous but no obvious regions explaining the learning disability.

He underwent distal pancreatectomy and endoscopic duodenal tumor resection. Histopathological examination of the pancreatic specimen revealed 6 neuroendocrine tumors, from 0.5 to 1.8 cm in size. The neoplasms formed small nests, trabeculae, and glands composed of monomorphic cells with finely granular eosinophilic cytoplasm, round nuclei and coarsely clumped "salt and pepper" chromatin (Fig. 3A and C). The mitotic activity ranged from 0 to 1/10 high power field. Lymphovascular invasion was present. All the tumors were positive for chromogranin A. Three tumors showed cytoplasmic insulin positivity in the majority of cells, associated with very few cells staining for somatostatin and glucagon, most likely representing residual normal islet cells rather than secretion of multiple hormones by the tumor. One of the tumors stained only for glucagon (Fig. 3D), and 2 tumors did not stain with any of the 4 hormones insulin, glucagon, somatostatin, or gastrin. The distal pancreatectomy tumor was staged as pT1[m6]NX. The nonneoplastic pancreas showed a range of abnormalities, including islet cell hyperplasia, dysplastic islets, microadenomatosis, rare ductulo-insular complexes, and peliosis in islets (Fig. 3E and F). The duodenal biopsies and endoscopic resection showed multiple tumor nodules, the largest, 0.7 cm in size.

After distal pancreatectomy, hypoglycemic episodes ceased and his gastrin and chromogranin A levels normalized. He is on cabergoline 0.25 mg biweekly for prolactinoma; hydrocortisone 20 mg in the morning and 10 mg in the evening, and fludrocortisone 0.05 mg daily for CAH; alendronate 70 mg weekly for osteoporosis; and cinacalcet 30 mg for primary hyperparathyroidism. He was prescribed testosterone gel 1.62%; however, the family decided not to start testosterone replacement. On follow-up, a 1.2-cm liver lesion was detected, for which he underwent partial hepatectomy. The tumor cells were positive for chromogranin, synaptophysin, and gastrin, with no reactivity for insulin, glucagon, and

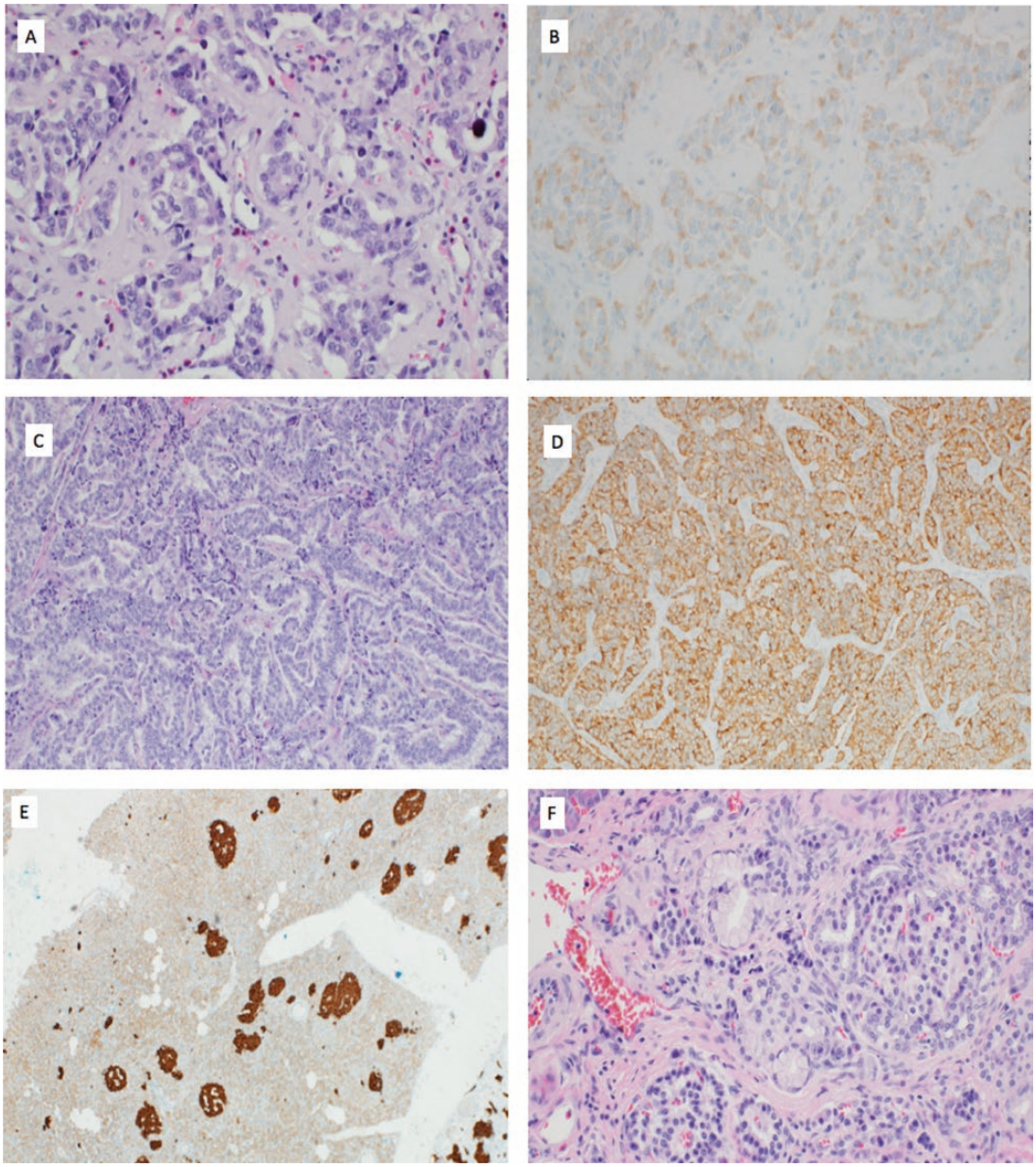

Figure 3. (A) NET forming small nests and follicles (H&E stain); tumor with faint insulin positivity in the (B) cytoplasm of tumor cells. (C) NET with trabecular architecture (H&E stain); tumor with (D) strong glucagon positivity in tumor cells. (E) Islet cell hyperplasia with islets of varying size highlighted by chromogranin stain. (F) Ductal insular complexes (H&E stain). H&E, hematoxylin and eosin; NET, neuroendocrine tumor.

somatostatin. The patient will be monitored by repeat abdominal and pituitary imaging, tumor markers, and pituitary hormones for any evidence of recurrent or new neuroendocrine and pituitary tumors. There are no specific clinical guidelines for monitoring patients with classic-like EDS; therefore, we follow recommendations for classic EDS, which include annual echocardiogram in patients with abnormal findings on initial evaluation.

Discussion

The combination of the contiguous gene deletion syndrome CAH-X and MEN-1 has not been previously described in the literature. It illustrates the complex clinical scenario resulting from the coexistence of three multiorgan diseases as well as learning disability most likely resulting from consanguinity.

His MEN-1 manifestations include primary hyperparathyroidism, hyperprolactinemia, and multifocal neuroendocrine tumors. The hypoglycemia workup performed in the setting of MEN-1 and multiple pancreatic lesions made us suspicious for insulinoma, which was confirmed on pathology. Insulinomas are the second most common functioning pancreatic neuroendocrine tumor in the setting of MEN-1 after gastrinomas, occurring in about 18% of patients [6]. Diffuse endocrine hyperplasia, dysplasia, and microadenomas are also features of MEN-1 [7]. In addition, ductal/insular complexes with neuroendocrine cells arising from ducts and peliosis (i.e., cyst-like blood-filled cavities in islets) may rarely be encountered in patients with MEN-1 syndrome [7, 8], as seen in this case. This patient's hypoglycemia was likely from insulinomas and islet cell abnormalities (hyperplasia, dysplasia, ductular-insular complexes), given the persistence of hypoglycemic episodes after resuming glucocorticoids while waiting for abdominal surgery.

Gastrinomas are seen in 20% to 70% of MEN-1 patients [6, 9]. Although gastrin stain was negative in the pancreatic and duodenal tumors, his liver metastases stained for gastrin. This may explain gastrointestinal lesions suggestive of Zollinger-Ellison syndrome, although his gastrin level was only moderately elevated while being on proton pump inhibitors. Similar to this case, neuroendocrine tumors metastases may produce hormones other than those found in the primary site [10].

Glucagonomas are seen in 1% to 6% of patients with MEN-1 [6, 11]. Despite positive glucagon immunostaining in 1 of the tumors, this patient did not present any of the clinical findings associated with glucagonomas such as necrolytic migratory erythema or diabetes. In addition, his glucagon level was within the reference range, suggesting a nonfunctioning pancreatic neuroendocrine tumor that stained positive for glucagon, which can occur in about 24% to 52% of the surgical specimens of MEN-1 patients [11-13].

MEN-1 syndrome most often is due to heterozygous loss-of-function mutations in the *MEN1* tumor suppressor gene (OMIM 613733), located in chromosome 11q13, and encoding a protein called Menin [14, 15]. His *MEN1* mutation, c.784-9G > A, affects intron 4 and has been described in 1.9% of 1133 reported *MEN1*-independent kindreds [16]. Pardi et al found 12 of 54 probands (22%) with this specific mutation [15]. Phenotypically, all of them developed primary hyperparathyroidism, 3 had pituitary tumors, and 10 had gastro-enteropancreatic tumors, consistent with this patient presentation.

Salt-wasting CAH is an autosomal recessive disease caused by mutations in *CYP21A2* in about 95% of the cases [17]. This patient's short stature seems secondary to excessive androgen exposure early in life because of noncompliance with glucocorticoids resulting in early epiphyseal fusion. His hormonal workup is consistent with hypergonadotropic hypogonadism. His gonadotropins were elevated despite hyperprolactinemia and persisted after prolactin was normalized, being consistent with a primary testicular dysfunction. Testicular ultrasound data are not available, but adrenal rest tumors can be present even in small testicles [18]. Therefore, the patient developed hypogonadism for 2 reasons: (1) hyperprolactinemia and (2) damaged testis from adrenal rest tumors. The past hyperandrogenism resulted in short stature, although other causes related to high level of homozygosity cannot be excluded.

In the abdominal computed tomography scan, we found bilateral adrenal lipomatous changes suggestive of large myelolipomas. Adults with CAH not adequately managed may present with a spectrum of imaging findings that includes large myelolipomatous changes of their adrenal glands, similar to our patient. It has been suggested that chronic elevations in ACTH and excessive androgen may act as the stimulatory factor to trigger polyclonal

hyperplasia and differentiation of adrenal tissue into adipose and hematopoietic tissue with similar characteristics of bone marrow [19-21].

Classic EDS is an autosomal dominant disease caused by mutations in the *COLA5A1* (OMIM 130000) or *COL5A2* (OMIM 130010) genes, coding for type V collagen subunits, in about 90% of the patients. In classic-like EDS, the mutations, either heterozygous or homozygous, are in the *TNXB* gene, which encodes for TN-X. TN-X is an extracellular matrix protein highly expressed in connective tissues [3]. It is involved processes related to cell adhesion, migration, and stabilization of collagen fibers, including types I, III, V, VII, and IX [22]. Therefore, when this protein is deficient, it is not surprising the resemblance with classic EDS. Classic-like EDS was first reported in 1997 in a patient with CAH and heterozygous large deletion of *CYP21A2* and part of *TNXB* [1]. In 2001, 5 additional cases were described, demonstrating a form of EDS with an autosomal recessive pattern of inheritance [23]. Our patient presented joint hypermobility, hyperextensible, and soft and velvety skin, all known features of classic-like EDS [2]. Interestingly, a bladder diverticulum was incidentally found; this has been observed in classic ED, but to our knowledge not previously reported in the classic-like form [24].

Classic-like EDS can occur without the presence of CAH when the defect is restricted to the *TNXB* gene, although in the original description of this form of EDS, the relationship with CAH was recognized [1]. In those with CAH, the EDS phenotype tend to be more severe that those without [3, 25]. This may be related to the large deletion when classic-like EDS is associated with CAH (in contrast to a point mutation) or indicate an interaction between these diseases beyond the genetic mutations. Perhaps the hormonal abnormalities seen in CAH play a role in the clinical presentation.

The contiguous gene deletion syndrome CAH-X has a prevalence of 8.5% in patients with CAH resulting from 21-hydroxylase deficiency [26]. Recent studies have further determined that there are monoallelic and biallelic forms of CAH-X, with the biallelic form being the least common of them [3]. Of 29 patients with CAH-X, 5 had biallelic CAH-X, like our patient. In this group, 4 were male, all of them had generalized hypermobility, severe hyperextensible skin, and easy bruising, and 2 showed cardiac chamber enlargement [3], as observed in our patient. The distinction of the different underlying recombination or chimera is also relevant because it translates into different CAH-X phenotypes [25]. Because *TNXB* and *CYP21A2* are located in an area of chromosome 6, where there is high recombination, in addition to the presence of pseudogenes (*TNXA* and *CYP21A1P*), it is not surprising that misalignment occurs during meiosis. When *TNXA* and *TNXB* undergo chimeric recombination, *CYP21A2* can be deleted, resulting in CAH-X. To date, 3 chimeric genes have been described. In the first one, called CAH-X CH-1, *CYP21A2* is deleted, and *TNXB* exons 35 through 44 are replaced with *TNXA* producing a non-sense 120-bp deletion (c.11435_11524 + 30del) that leads to a nonfunctional gene causing reduced expression of TN-X, supporting a haploinsufficient behavior [3]. In CAH-X CH-2, *CYP21A2* is deleted, and *TNXB* exons 40 through 44 are replaced by *TNXA*, which features 2 contiguous mutations of c.12150C > G (synonymous) and c.12174 C > G (p.C4058W) that has a more severe EDS phenotype [3, 25]. In CAH-X CH-3, *CYP21A2* is deleted, and *TNXB* exons 41 through 44 are replaced by *TNXA*. Thus far, this chimera has been reported in 1 patient and has unclear significance [25]. As opposed to CAH-X CH1, in CH2 and CH3, TN-X is produced but with an abnormal structure, ultimately impairing its function [3].

Interestingly, the TGF-β is dysregulated in both CAH-X and MEN 1, but in different ways. TN-X has an important role in promoting epithelial-mesenchymal transitions mediated by the TGF-β pathway [22]. In skin fibroblasts obtained from CAH-X patients, TGF-β2, TGF-β3, and SMAD 1, 5, and 8 were found elevated compared with CAH controls [4]. These 2 cytokines (TGF-β2 and TGF-β3) and their downstream proteins, SMADs, are important regulators of cardiac development, which could explain the cardiac abnormalities observed in these patients, including this case. SMADs 2, 3, and 4 are important tumor suppressors [5]. Menin acts as a scaffold protein in the nucleus to regulate the transcription of multiple

genes, including SMAD3, a key protein in the TGF-β signaling pathway. In MEN-1, TGF-β signaling is disrupted because SMAD3 is not able to inhibit cell division, predisposing to proliferation, and tumorigenesis [5]. It seems that alterations in both CAH-X and MEN-1, via altering distinct proteins, lead to modifications in TGF-β signaling pathways. Because TGF-β has been associated with collagen synthesis, this might explain the forehead wrinkles observed in the patient.

The patient presented here has additional clinical features that are not part of CAH-X or MEN1, such as prognathism and prominent supraorbital ridges (had normal IGF-1 level), learning disability, deep-set eyes, mild hypertelorism, convex nasal ridge, broad distal phalanx, drumstick fingers, and possibly mild webbing between the index and middle finger. Differential diagnoses were considered including pachydermoperiostosis (because of the forehand wrinkles at a young age), arthrochalasia EDS, as well as other genetic mutation screening, including *SYNGAP1* and *CUL7*; however, none was positive.

In conclusion, here we report a rare case with an unusual combination of diseases. The complex genetic situation with a large deletion causing continuous gene deletion syndrome (CAH-X), 12% homozygosity because of consanguinity, and an additional heterozygote disease results in a complex clinical picture, where attributing each of the phenotypic abnormality to 1 of the 3 genetic problems (CAH-X, MEN-1, high level of homozygosity) creates significant challenges. We draw the attention of endocrinologists to evaluate for signs of EDS in patients with CAH resulting from 21-hydroxylase deficiency.

Acknowledgment: We are grateful for the help in the diagnostic workup and interpretation of the genetic results to Dr. Anju Sahdev, Barts Health NHS Trust, London, UK and Dr. Márton Doleschall, Semmelweis Medical School, Budapest, Hungary. Written consent was obtained from the patients to include their photographs. Additionally, all potential identifiers on the figures have been removed. For additional information on the genetic studies and pathology report, please email the corresponding author.

Acknowledgments

Financial Support: This work was not supported by any grants.

Additional Information

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Disclosure Summary: None of the authors have conflicts of interest to disclose.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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