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

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Abstract

The contiguous gene deletion syndrome of congenital adrenal hyperplasia and Ehlers-Danlos syndrome, named CAH-X, is a rare entity that occurs due to a deletion of a chromosomal area containing two neighboring genes, TNXB and CYP21A. Here we describe a patient from a consanguineous family where 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 CAH 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 exon 35-44 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.

Keywords: Congenital Adrenal Hyperplasia, Ehlers-Danlos Syndrome, Contiguous Gene Deletion Syndrome, Multiple Endocrine Neoplasia type 1, Adrenal myelolipoma, Neuroendocrine tumor
Introduction

Salt-wasting congenital adrenal hyperplasia (CAH) and classic-like Ehlers-Danlos Syndrome (EDS) were initially linked more than 20 years ago. 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 be detected even when one allele is affected. CYP21A2 (OMIM 201910), the gene mutated in salt-wasting CAH due to 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 due to 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, 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 two syndromes, we found that both CAH-X and MEN-1 can disrupt the transforming growth factor-beta (TGF-β) signaling pathway, however in different ways.

Case Presentation

A 33-year-old man with a history of learning disability, salt-wasting CAH, and MEN-1 syndrome due to 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 (4’5”), wrinkled forehead, teeth malocclusion, mild prognathism, short fingers & toes, hyperextensible and loose joints, soft and velvety skin (Figure 1. A-D). His parents were first cousins. His father died at age 56 from liver cancer. Out 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 MRI (Figure 2A-B), and a normal IGF-1 (Table 2). Additionally, he had primary hypogonadism with small, soft testicles of 8-10 mL bilaterally, a 1.6 cm enhancing pancreatic mass, and replacement of the normal adrenal tissue with large bilateral (left 5.7 x 10.6 cm and right 8.5 x 3.7 cm) lipomatous lesions resembling myelolipomas (Figure 2C-D). A DEXA scan reported Z-scores consistent with low bone mineral density for his age (lumbar spine -2.9, femoral neck -1.8, and distal 1/3 forearm -1.7). A bladder diverticulum, typical of Ehlers-Danlos syndrome, was incidentally found (Figure 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), while 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 exon 35-44 of the TNXB gene. Due to the consanguinity and learning disability, a chromosomal microarray analysis was performed using the Cytoscan HD platform (Affymetrix) containing 2,699,550 markers 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 six neuroendocrine tumors, from 0.5-1.8 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 (Figure 3A and C). The mitotic activity ranged from 0-1/10 high power
field. Lympho-vascular 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 (Figure 3D), and two tumors did not stain with any of the four hormones insulin, glucagon, somatostatin, or gastrin. The distal pancreatectomy tumor was staged as pT1[m6]NX. The non-neoplastic pancreas showed a range of abnormalities, including islet cell hyperplasia, dysplastic islets, microadenomatosis, rare ductulo-insular complexes, and peliosis in islets (Figure 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, his gastrin and chromogranin A levels normalized. He is on cabergoline 0.25 mg biweekly for prolactinoma, hydrocortisone 20 mg in AM and 10 mg in PM 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 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 classical-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 due to 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 NET in the setting of MEN-1 after gastrinomas, occurring in about 18% of patients. Diffuse endocrine hyperplasia, dysplasia and microadenomas are also features of MEN-1. 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, as seen in this case. This patient’s hypoglycemia was likely due to 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 20-70% of MEN-1 patients. 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.

Glucagonomas are seen in 1-6% of patients with MEN-1. Despite positive glucagon immunostaining in one 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 non-functioning pancreatic NET that
stained positive for glucagon, which can occur in about 24-52% of the surgical specimens of MEN-1 patients.\textsuperscript{11–13}

MEN-1 syndrome most often is due to heterozygous loss-of-function mutations in the \textit{MEN1} tumor suppressor gene (OMIM 613733), located in chromosome 11q13, and encoding a protein called Menin.\textsuperscript{14,15} His \textit{MEN1} mutation c.784-9G>A, affects intron 4 and has been described in 1.9% of 1,133 reported \textit{MEN1} independent kindreds.\textsuperscript{16} Pardi et al. found 12 out of 54 probands (22%) with this specific mutation.\textsuperscript{15} Phenotypically all of them developed primary hyperparathyroidism, 3 had pituitary tumors, and 10 gastro-entero-pancreatic tumors, consistent with this patient presentation.

Salt-wasting CAH is an autosomal recessive disease caused by mutations in \textit{CYP21A2} in about 95% of the cases.\textsuperscript{17} His short stature seems secondary to excessive androgen exposure early in life due to 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 is not available, but adrenal rest tumors can be present even in small testicles.\textsuperscript{18} Therefore, the patient developed hypogonadism for two reasons, 1) hyperprolactinemia and 2) damaged testis due to 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 CT, 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.\textsuperscript{19–21}

Classic EDS is an autosomal dominant disease caused by mutations in the \textit{COLA5A1} (OMIM 130000) or \textit{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. It is involved processes related to cell adhesion, migration and stabilization of collagen fibers, including type I, III, V, VII, and IX. 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*. In 2001, five additional cases were described, demonstrating a form of EDS with an autosomal recessive pattern of inheritance. Our patient presented joint hypermobility, hyperextensible, soft and velvety skin, all known features of classic-like EDS. 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.

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. In those with CAH, the EDS phenotype tend to be more severe that those without. 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 due to 21-hydroxylase deficiency. 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. Out of 29 patients with CAH-X, 5 had bi-allelic CAH-X, like our patient. In this group, four were male, all of them had generalized hypermobility, severe hyperextensible skin, easy bruising, and two showed cardiac chamber enlargement, as observed in our patient. The distinction of the different underlying recombination or chimera is also relevant, as it translates into different CAH-X phenotypes. 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, three chimeric genes have been described. In the first one, called CAH-X CH-1, \(CYP21A2\) is deleted, and \(TNXB\) exons 35-44 are replaced with \(TNXA\) producing a non-sense 120bp deletion (c.11435_11524+30 del) that leads to a non-functional gene causing reduced expression of TN-X, supporting a haploinsufficient behavior. In CAH-X CH-2, \(CYP21A2\) is deleted, and \(TNXB\) exons 40-44 are replaced by \(TNXA\), which features two contiguous mutations of c.12150C>G (synonymous) and c.12174 C>G (p.C4058W) that has a more severe EDS phenotype. In CAH-X CH-3, \(CYP21A2\) is deleted, and \(TNXB\) exons 41-44 are replaced by \(TNXA\). Thus far, this chimera has been reported in one patient and has unclear significance. As opposed to CAH-X CH1, in CH2 and CH3, TN-X is produced but with an abnormal structure, ultimately impairing its function.

Interestingly, the transforming growth factor beta (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. In skin fibroblasts obtained from CAH-X patients, TGF-β2, TGF-β3, and SMAD 1, 5, 8 were found elevated compared to CAH controls. These two 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. 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 as SMAD3 is not able to inhibit cell division, predisposing to proliferation, and tumorigenesis. It seems that alterations in both CAH-X and MEN-1, via altering distinct proteins, lead to modifications in TGF-β signaling pathways. As 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 setting eyes, mild hypertelorism, convex nasal ridge, broad distal phalanx, drum stick
fingers, and possibly mild webbing between the index and middle finger. Differential diagnoses were considered including pachydermoperiostosis (due to the forehand wrinkles at a young age), arthrochalasia EDS as well as other genetic mutation screening, including SYNGAP1 and CUL7; however, none were 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 due to consanguinity, and an additional heterozygote disease results in a complex clinical picture, where attributing each of the phenotypic abnormality to one of the three 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 due to 21-hydroxylase deficiency.

Written consent was obtained from the patients to include their photographs. Additionally, all potential identifiers on the figures have been removed.
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Disclosure Summary

None of the authors have conflicts of interest to disclose.
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Figure 1 (A-D): Clinical Features, short stature 135 cm (4’5”) compared to his brother (Panel A), wrinkled forehead, prognathism, jaw malocclusion (Panel B) short fingers, hyperextensible and loose joints (Panel C and D).

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

Figure 3 (A-F). NET forming small nests and follicles (HE stain) (Panel A). Tumor in Panel A with faint insulin positivity in the cytoplasm of tumor cells (Panel B). NET with trabecular architecture (HE stain) (Panel C). Tumor in Panel C with strong glucagon positivity in tumor cells (Panel D). Islet cell hyperplasia with islets of varying size highlighted by chromogranin stain (Panel E). Ductal insular complexes (HE stain) (Panel F).
Table 1. Cortisol, 17 OH progesterone and Aldosterone levels during synachten stimulation test.

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

*Hydrocortisone was held for 24 hours prior to the test
| Hormone                        | Patient result     | Reference Range           |
|-------------------------------|--------------------|---------------------------|
| Plasma Renin Activity         | 14.1               | 0.167-5.380 ng/mL/hr      |
| ACTH                          | 27.8 (4:32 pm)     | 1.6-13.9 pmol/L           |
|                               | 220.7 (11:07 am)   |                           |
| 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*                      | 307                | 0-55 pmol/L               |
| Glucagon*                     | 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*                      | 47                 | 70-100 mg/dL              |
| C-peptide*                    | 0.68               | 0.37-1.47 nmol/L          |
| Insulin*                      | 7.76               | 2.6-24.9 U/mL             |
| Proinsulin*                   | 46.1               | 0-10.0 pmol/L             |
| Calcium                       | 2.75               | 2.15-2.55 nmol/L          |
| Parathyroid Hormone           | 11.4               | 1.6-6.9 pmol/L            |
| Insulin Growth Factor -I      | 11.5               | 82-242 ng/mL              |
| Growth Hormone                | 2.8                | 0-10 µg/L                 |
| Prolactin                     | 88.4               | 4-15.2 ng/mL              |

*Pre-Pancreatic Surgery
