Adrenal

ADRENAL CASE REPORTS III

A Rare Case of Adrenocortical Carcinoma Arising From Ectopic Adrenal Tissue in the Mesentery

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MON-LB042

Background: ACTH independent Cushing's syndrome usually arises from benign or malignant tumors of the adrenal gland. Ectopic adrenal tissue can undergo malignant transformation resulting in the development of adrenocortical carcinoma (ACC) with normal adrenal glands. We present a unique case of ACTH independent Cushing's syndrome from a cortisol and androgen producing ACC arising from the mesentery.

Clinical Case: A 72-year-old woman presented with a 6-month history of progressive weakness, lower extremity edema, worsening hypertension and uncontrolled DM. She had moon facies, hirsutism, multiple bruises, and proximal muscle weakness. Labs revealed hypokalemia (2.6 mmol/L, N 3.5 -5.1 nmol/L), elevated random cortisol (51.3 mcg/dL, Nl- 5-23), suppressed ACTH (<1 pg/mL, Nl-7.2-63.3) abnormal 8 mg dexamethasone suppression test (58.1 mcg/dL, N <1.8 mcg/dL), elevated DHEAS (538mcg/dL, N 10-90 mcg/dL), elevated testosterone (590.2 ng/dL, N <75 ng/dL) and elevated 11-deoxycortisol (4650 ng/dL N-<32 ng/dL). 24 hour urinary free cortisol was 2810mcg/mL (<45mcg/dL). MRI of pituitary was normal. CT scan of abdomen/pelvis showed normal bilateral adrenal glands and innumerable enhancing masses throughout the abdomen with the largest mass near the distal ileum and cecum. Biopsy of right lower abdominal mass revealed adrenocortical morphology with immunohistochemical staining positive for inhibin, synaptophysin and calretinin. Ki-67 index was 10-15%, suggestive of low-grade adrenocortical carcinoma. A CT scan done one and half years prior noted a 4.4 cm soft tissue mass in the right lower mesentery supporting origin of the tumor from the mesentery. Hypercortisolism was controlled with Metyrapone 250 mg BID. Mitotane 1000 mg bid was initiated but patient developed peritoneal carcinomatosis within 1 month. **Conclusions:** Our case is remarkable for the development of a metastatic ACC from an ectopic adrenal tissue with normal bilateral adrenal glands. Ectopic ACC is very rare with only a handful of cases reported in the literature. This is the first reported case of ACC arising from the mesentery. Ectopic adrenal tissue can be found close to the adrenal glands, along the path from gonads to adrenal glands or in association with the gonads. In the setting of ACTH independent Cushing's syndrome with normal adrenal glands, physicians should direct their search to a functioning ectopic adrenocortical tissue. Concomitant DHEAS secretion suggests ectopic ACC. If surgery is not an option due to metastatic disease, a multidisciplinary approach should be adopted to control tumor growth and associated symptoms. In such cases, control of the hypercortisolemia can be achieved with adrenolytic medications such as Metyrapone, Ketoconazole or Mitotane. Adjuvant chemotherapy (Mitotane and combination of cytotoxic drugs) might be considered for metastatic ACC treatment.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Autosomal Dominant Growth Hormone Deficiency Due to a Novel c.178g>A Mutation in the GH1 Gene Is Caused by Alternative Splicing to Produce a Small GH Isoform.

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MON-LB014

Introduction: Growth hormone (GH) plays a vital role in human physiology. Mutations in *GH1* cause isolated growth hormone deficiency (GHD). The most frequent cause of familial growth hormone deficiency is Type II autosomal dominant GHD (isolated GHD type II) due to several heterozygous *GH1* mutations. These mutations have been shown to (a) produce shorter isoforms of GH that do not bind to growth hormone receptors, (b) cause diminished secretion of GH, or (c) result in misfolded GH protein. **Methods:** Genomic DNA from patients with familial GHD was enriched for the coding exons using hybrid capture technology, and *GH1* was sequenced using Next Generation Sequencing technology. The p.A34T mutant protein was expressed in bacteria, and binding to GHR was studied by surface plasmon resonance technology. Computational prediction of transcription indicated that alternative splicing is likely to produce a shorter GH variant with skipping of exon 3 in *GH1*. Mammalian cell-based studies incorporating transfection of whole *GH1* gene containing exons/introns were used to study transcriptional effects. RNA was isolated from cells transfected with WT and mutant *GH1* gene and analyzed by RT PCR using primers in the second and fifth exons of *GH1* that could identify all possible isoforms of *GH1* mRNA. **Results:** GHD was identified in three female siblings aged 3.25-6.33 years (Ht SDS -3.21 to -1.13, peak GH 2.9-6.6 ng/mL); their mother had previously been diagnosed with GHD at age 12.33 years (Ht SDS -3.44, GH peak &lt 2 ng/mL). Sequencing of GH1 identified a novel heterozygous variant (c.178G&gtA; p.Ala34Thr) not found in the Broad ExAc dataset representing &gt60,000 children without the severe childhood-onset disease. Functional studies using whole gene transfection showed that the c.178G&gtA mutation leads to alternate splicing resulting in increased production of the shorter 17.5kD isoform of GH due to exon 3 skipping. Results were confirmed by quantitative RT-PCR as well as GH secretion assays, which showed a lower level of GH production from cells transfected with the GH1 gene containing the c.178G&gtA mutation. The

SPR based receptor binding assay and cell proliferation assay using bacterially expressed proteins showed that once produced, the GH protein with the A34T mutation behaves similar to WT GH protein. All these results confirm that the cause of GHD due to the c.178G&gtA mutation in *GH1* is due to altered transcription leading to the production of the shorter 17.5 kD isoform of GH protein and not due to the amino acid change A34T that is caused by the mutation. **Conclusion:** The presence of a heterozygous GH1 variant (c.178G&gtA, p.Ala34Thr) in four individuals with GHD suggests that this is a novel cause of IGHD type II. Production of the smaller 17.5 kD GH isoform results in reduced overall GH secretion and loss of binding to GHR due to competition with the normal GH protein, explaining the dominant-negative phenotype.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Is Late Diagnosis of Postsurgical Hypoparathyroidism the Rule, Not the Exception?

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SAT-LB71

Background The most prevalent etiology for hypoparathyroidism is postsurgical. In the literature, years or even decades of delay for the diagnosis have been reported, with sometimes extremely low calcium levels and dramatic clinical manifestations including heart failure and seizures requiring treatment in the emergency room or intensive care unit. Often,,typical" hypocalcemic symptoms are absent in these patients.

Methods In this retrospective Austrian single-center cohort at the Medical University of Graz, we identified patients with low parathyroid hormone concentration (<25 pg/ml) and hypocalcemia using the hospital information system during 2004 and 2014. The time between neck surgery and the first reported diagnosis of postsurgical hypoparathyroidism and/or available low calcium levels was collected.

Results We identified a total of 119 patients treated between 2004 and 2014 at our institution. Most patients were women (78%), the average age was 61 ± 17 years. 12% had nonsurgical etiologies (ie. AIRE or 22q11 mutations), and 88% had postsurgical hypoparathyroidism (n=105). The median time between surgery and diagnosis of hypoparathyroidism was 5.5 years (range 0 -67 years). Only a third of all patients was diagnosed within the first year after surgery. Paresthesia and tetany were present in most patients at diagnosis, but in extreme hypocalcemia, other,,nonclassic" symptoms including severe heart failure, dyspnea and seizures appeared to be more prevalent.

Conclusion Our data suggest that diagnosis of permanent postoperative hypoparathyroidism is often delayed, as in our Austrian retrospective cohort the time lag between surgery and diagnosis or onset of hypoparathyroidism was often years or even decades. Whether this is truly a delayed occurrence of the disease or a delayed diagnosis of a condition already present for years or a combination of both can not be answered with our data, but certainly merits more intense research in the future.

Healthcare Delivery and Education

EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

Application of Lean Six-Sigma DMAIC Tool for Improvement and Sustainability of Diabetes Management in Outpatient Clinics.

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MON-LB301

Application of Lean Six-Sigma DMAIC tool for improvement and sustainability of diabetes management in outpatient clinics.

DMAIC: Define, Measure, Analyze, Improve, Control.LSL: Lower specified limit.USL: Upper specified limit.

Lean Six Sigma DMAIC is quality improvement methodology used for strategic business management. Frequent applications of this methodology in healthcare include improvement of patient satisfaction, reduction of emergency department waiting times, prescription error reduction and monetary recovery by reducing waste.

Patients with a HgbA1c testing frequency of >6 months have poorer glycemic control. The American Diabetes Association recommends HgbA1c test quarterly in patients whose therapy has changed or who are not meeting glycemic goals and at least two times a year in patients who are meeting treatment goals.

We hypothesized that the Lean Six-Sigma DMAIC tools can be used in the outpatient clinic setting to improve frequency of HgbA1c testing in patients with diabetes mellitus.

At baseline, 19% of our patients with diabetes mellitus had HgbA1c tested infrequently, defined as more than 6 months. This high percentage is a concern as it could lead to poor diabetes control. The aim was to increase percentage of patients having an HgbA1c tested between 3 to 6 months before an appointment in our clinic, to a goal of 90%. Target population included all patients with diabetes mellitus seen in outpatient endocrinology clinic.

A baseline analysis of existing processes was done through brainstorming with the clinic staff using a fish bone diagram. Lack of follow up and HgbA1c testing orders were some of the modifiable factors identified. The new processes implemented include nurse driven standing medical orders for HgbA1c testing and pre-visit planning. Control phase included regular audits to sustain the improvements.

The percentage of patients with a HgbA1c testing within 3-6 months of appointment improved from a baseline of 76.7% (LSL:70%, USL:94%) to 92.2% (LSL:88%, USL:93.7%). The improvement was noticeable within 1 month of new process implementation and continues to sustain. The mean had an absolute improvement of 15.5%. The variation from the mean decreased from 25% at baseline to 6% at the end of the control phase. The reduction in variation made our future results more predictable.