

A Man with Abdominal Pain: Enough Evidence for Surgery?

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CASE

A 53-year-old man experienced periodic abdominal discomfort and decreased capacity to work. His primary physician ordered a broad range of laboratory tests as part of the initial workup. The results revealed a greatly increased adrenocorticotrophic hormone (ACTH)⁷ of >1250 pg/mL (>278 pmol/L), reference interval <46 pg/mL (<10.2 pmol/L). Cortisol was within the reference interval. Repeat measurements 4 weeks later confirmed the increased ACTH. Investigators rapidly excluded two well-known conditions associated with increased ACTH concentrations: Cushing disease (ACTH-producing pituitary tumor) and Addison disease (adrenal insufficiency) (1,2). An investigation for an ectopic source of ACTH was begun (3).

Over the next 18 months the patient underwent a plethora of imaging studies. A series of conventional studies failed to provide an explanation for the increased ACTH and ultimately a positron emission tomography/computed tomography (PET/CT) scan using a relatively new radiotracer, ⁶⁸Ga-labeled 1,4,7, 10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-D-Phe¹-Tyr³-octreotide (⁶⁸Ga-DOTATOC), was performed (4). A 3.3-cm area in the head of the pancreas with an increased uptake of radiotracer was observed (Fig. 1). In light of the persistently increased ACTH, this finding raised the suspicion of a pancreatic ACTH-secreting neuroendocrine tumor, a rare ectopic source of ACTH (3). Although MRI and conventional CT evaluations did not confirm the presence of a tumor, the patient was offered immediate surgical treatment. The patient declined the offer and subsequently sought second and third opinions at medical facilities in 2 different countries. In both facilities, a neuroendocrine tumor was deemed the likely cause of his problems, and surgery was again suggested. Wishing minimally invasive treatment, the patient contacted the Interventional Centre at our hospital, which offers laparoscopic resection of the pancreas.

Pre-operative investigations with MRI, optimized multiphase CT, and ¹¹¹In-labeled diethylenetriamine pentaacetic acid octreotide (¹¹¹In-DTPA-octreotide) single-photon emission computed tomography/CT (SPECT/CT), a well-established protocol for visualizing neuroendocrine tumors (4), failed to identify the supposed tumor. The data from the previously positive ⁶⁸Ga-DOTATOC PET/CT were requested for reinvestigation, and surgery was postponed.

Laboratory results at our hospital were comparable with the earlier results. ACTH, measured in a morning sample on the Immulite 2000 platform (Siemens Healthcare Diagnostics), was highly increased at 923 pg/mL (203 pmol/L). Cortisol, measured concurrently on the Modular E platform (Roche Diagnostics), was normal at 16.9 $\mu\text{g/dL}$ (467 nmol/L) [reference interval for morning samples 8-25 $\mu\text{g/dL}$ (220-690 nmol/L)]. Results for other hormones, electrolytes, and tumor markers (neuron-specific enolase, chromogranin A, serotonin metabolites) were unremarkable. An endocrinologist could not find convincing clinical evidence of pathology in the pituitary-adrenal axis (specifically, no hyperpigmentation of the skin) to support the laboratory findings. He suggested that the persistently increased ACTH could be a laboratory artifact.

Four laboratories in Norway currently offer analysis of ACTH; however, troubleshooting was complicated because all the laboratories use the same commercial assay. To investigate potential heterophilic antibody interference, we routinely add aggregated murine monoclonal MAK33 (Roche Biochemicals) to samples and reassay. Unfortunately, the addition of aggregated MAK33, even in high concentrations, had no effect on the ACTH result.

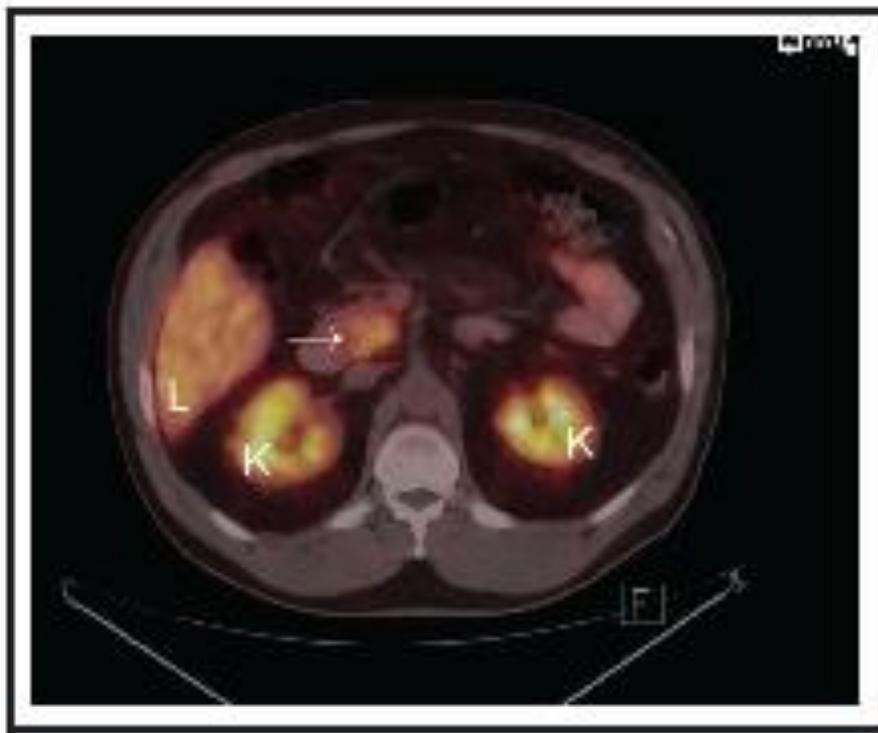


Fig. 1. ^{68}Ga -DOTATOC PET/CT scan from June 2009 showing increased uptake of radiotracer in the processus uncinatus of the pancreas (arrow), with a maximum standardized uptake value (SUV_{max}) of 9. Physiological accumulation in the liver (L) and kidneys (K).

References

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Questions to Consider
• Why did the endocrinologist specifically look for hyperpigmentation of the skin?
• In a patient with a greatly increased ACTH, what would be the expected electrolyte disturbance(s)?
• What are 3 potential problems associated with ACTH measurement?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the August 2012 issue of *Clinical Chemistry*. To view the case and comments online, go to <http://www.clinchem.org/content/vol58/issue8> and follow the link to the Clinical Case Study and Commentaries.

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