# A challenging case of paraneoplastic Cushing syndrome-case report- ECE 2015

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## INTRODUCTION

Paraneoplastic Cushing syndrome represents 5-10% of all Cushing syndrome and has a severe prognosis due to severe metabolic imbalance, denutrition, associated infections and progression of tumoral underlying pathology.

## CLINICAL CASE

A 67 years old woman presented with mental confusion, progressive weight loss, severe edema and kypokalemia, without typical features of Cushing or hyperpigmentation. Patient's behaviour altered in the last 5 months,she was nasty with her daughter,bickering, while diabetes and hypertension aggravated in the last 3 months.

The electrolitic imballance was severe- K 1,65 mmol/l, inspite of multiple attempts to correct it with 150 mmol/day KCl on peripheral i.v.line, 40 mmol/day of KCl orally and 200 mg/day of Spironolactone, treatment used initially in the National Institute of Endocrinology “C.I. Parhon”. Patient was transffered in the I.C.U. of Central Military Emergency Hospital “Dr.Carol Davila”for the weekend, in order to obtain a better control using a central i.v. catheter .

## Laboratory work and imaging

One month prior to admittance patient had hypercortisolism, with normal hepatic citolytic enzymes, normal TSH, free T4 and calcitonin values.

Investigations at admittance revealed paraneoplastic Cushing's with ACTH 82,5 pg/ml, cortisol levels more than 63 mcg/dl, UFC 2866 mcg/24 h(21-111);DHEA-sulfate 230,5 mcg/24h, 2 mg Dexametazone supression test showed unsupressed cortisol 59,17 mcg/dl, ACTH 123,8 pg/ml.

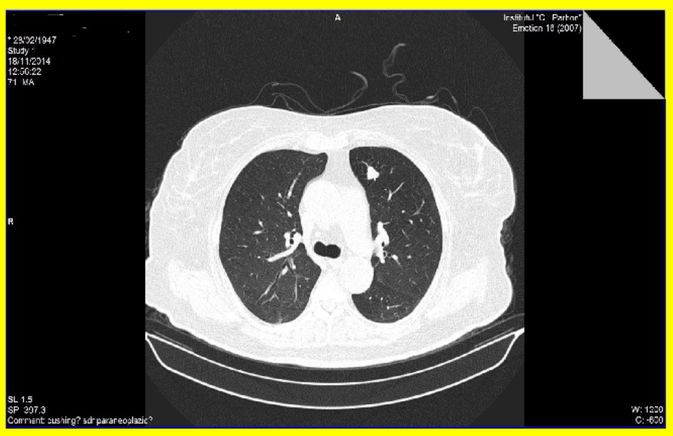
Patient associated also empty sella syndrome with thyreotrop and gonadotrophic insufficiency,normal prolactin and IGF-1,normal mineralocorticoid hormones,catecolamines, serotonin and 5HIAA, slightly enlarged cromogranine A-148 ng/ml(upper limit 125 ng/ml).

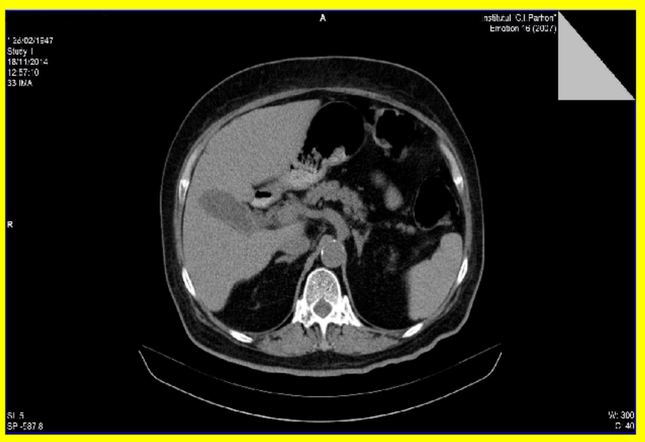
Patient had also left breast tumour, Helicobacter pylori gastritis, polinodular goiter, denutrition and hepatic dysfunction.

**Imaging techniques:99m Tc Tektrotyd** scintigraphy showed uptake at 10 minute in left breast and jejunal loop;Upper and lower endoscopy, echoendoscopy- revealed no tumours;Bronchoscopy-no visible tumour; after procedure-syncope that lasted 2 minutes;Thyroid ultrasound-macronodule of 15/18/22 mm located in the lower part of left lobe-15/18/22 mm, with low peripheral vascularisation, uptakes iodine at CT scan and has a peripheral calcification.

Thoracic CT revealed pulmonary tumor located in Fowler segment of left superior lung lobe.

Abdominal CT-minimally enlarged right adrenal gland, with nodule 0.88/0.88 cm; enlarged left adrenal gland, with nodule of 1,03/1.24 cm.





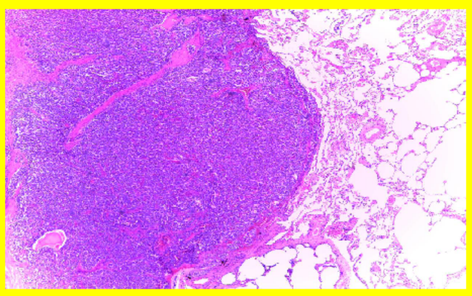
## TREATMENT

We initiated treatment with Ketoconasole 400 mg, 1 day, then 600 mg, for 2 days, but with inadequate correction of alcalosis and kypokalemia-pH was 7,54-7,59, BE 5,7-9,8mmol/l, K 3,16 mmol/l.The third day patient became septic-(MRSA Stafilococcus probably) due to central catheter and interstitial pneumonia-fibrinogen 660 mg/dl, AST 87-160 UI/l, ALT 95-103 UI/L, GGT 348-365 UI/l, total bilirubine 2,44 mg/dl, leucocytes 13400/mm3, granulocytes 8500/mm3.Cortisol levels were 26,3-29,2 mcg/dl and Ketoconasole was increased to 1200 mg/day,also associating Tavanic 500 mg initially, then Tigecycline 100 mg/day.The high values of ALT and AST were due to sepsis and did not increase after doubling Ketoconasole dosage.After 1 day of high dose Ketoconasole, K was 4,7 mmol/l, allowing introduction of Mifepristone 200 mg/day.The seventh day after Mifepristone was introduced, cortisol levels were 18,7 mcg/dl(4,2-38,4) , allowing surgery.Due to denutrition, pulmonary sepsis, lack of localisation of tumour-lung/thyroid/ileum?, recent syncope, severe brain atrophy with cognitive impairment, we decided to perform left adrenal gland resection. The adrenal resection was difficult due to diffuse bleeding and lack of tissue elasticity.Hepatic biopsy showed periportal fibrosis, but no necrosis of hepatocytes, probably due to use of toxic substances at work;Left adrenal was 7/3/1.5 cm in diameters, with focal hemorrhage.Imunochemistry-Ck7, Ck20, CEA, TF1, ER-negative, MELAN A positive –suggesterd diffuse hyperplasia of left adrenal gland.

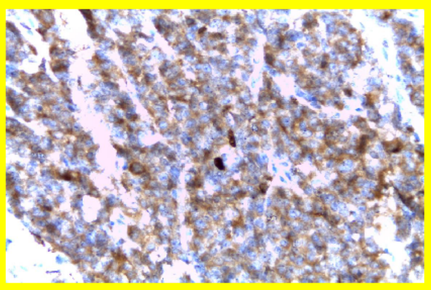
**One hour after left adrenalectomy-**cortisol was18,2 mcg/dl, ACTH 42,3 pg/ml , patient needed inotrop support with Noradrenaline , hydrocortisone 75 mg 1 day, 50 mg the second day.

The third day cortisol desupressed to 51,25 mcg/dl,ACTH 43 pg/ml(3-66),K decreased to 2,9 mmol/l,Hb was 8,4 g/dl.Ketoconazole 600 mg/zi was started again. Patient had fever, delirium, pulmonary rales, so Meronem was initiated for 2 days, then Tigecicline 3 days., then 7 days of Klacid at home, also Calcium 1 g/day, 1000 UI D3, 0.5mcg of 1alfa-calcidol/day, hepatic protection, vitamins, basal insulin.

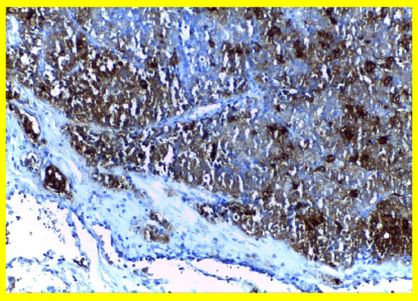
10 days after adrenal resection cortisol was 26,6 mcg/dl, K 3,9 mmol/l, Calcium was normal, Mg was 1,57 mg/dl, allowing second opperation-**resection of lung tumour-** proved to be typical carcinoid with **ki-67 3%, ACTH,synaptophysin and cromogranine positive.**



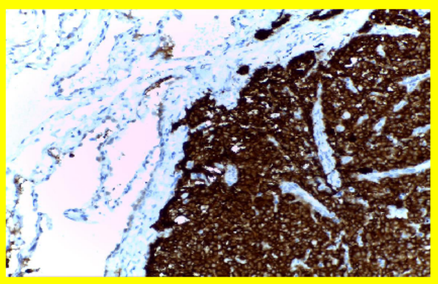
Hematoxillin-eosin staining-Carcinoid



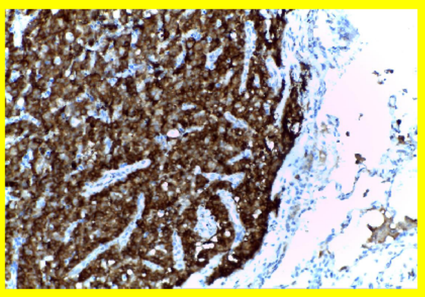
Ki-67 staining-3%



ACTH staining



Synaptophysin staining



Cromogranine stainig

1day after carcinoid resection; ACTH 5,95 pg/ml(3-66), cortisol 17,38 mcg/dl- done at „C.I.Parhon”Institute
12 days after carcinoid resection:ACTH 16,56 pg/ml(7,2-63);Cortisol 10,72 mcg/dl(6,2-19,4)
22days: lost 8kg, ACTH 19,1pg/ml, normal ALT and AST, GGT236UI/l,Mg 1,39mg/dl,Ca 9,96 mg/dl
47 days:lost 15 Kg, ACTH 16,5 pg/ml; cortisol 9 mcg/dl, Mg low even with supplementation
78 days:GGT 259 Ui/l(5-36), Mg 1, 45 mg/dl, K 3,83 mmol/l, glucose 142 mg/dl,cortisol 20,87 mcg/dl, TSH 2 microUi/ml
3 months:basal cortisol 11,2 mcg/dl, (6,2-19,4), basal ACTH 17,46pg/ml(3-88), cortisol 24 EET-3,24 mcg/dl,cortisol during supression test with Dexamethasone1 mg overnight-0.48 mcg/dl,PTH 12,32 pg/ml(15-165),low 25OH–D 12,8 ng/ml(30-100), UFC 40,3 mcg/24 h(21-111)

ThoracicCT-left breast tumor of 0.76/1,21 cm, right adrenal-stationary;portal vein 14.5 mm;patient performed FNAB of left thyroid nodule on 20 APR2015.

Mild kypokaliemia and hypomagnesemia ,even with oral supplementation, sartan therapy and normal levels of cortisol and ACTH, persisted after surgery,probably due to severe deficit of intracellular compartment , even at 3 months after carcinoid resection.Patient does not remember the 2 months prior to surgery, even if cognitive impairment is mild now.

This case was difficult due to metabolic challenges, multiple associated pathology, lack of SSTR2 and SSTR5 receptors with negative scan, mild elevation of cromogranine A levels despite a typical bronchial carcinoid . Patient's sister was operated for adrenal adenoma confirmed on histology exam, her daughter had papillary thyroid cancer, but no MEN association was proven in this family.

**Patient needed more than 30 days of hospital admittance in two different hospitals and five clinics in order to obtain a good clinical result.The vital risk was high due to sepsis denutrition,metabolic and ionic imballance, hepatic lesions, anesthesia, brain atrophy, relative adrenal insufficiency after surgery.There are no guidelines that state the adequate cortiso levels to be reached before opperating, nor the duration of Ketoconasole wash-out to prevent adrenal insufficiency.**

**She still needs to do a breast biopsy in the nearest future.**

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