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 electrolytic imbalance 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 KCI orally and 200 mg/day of Spironolactone, treatment used initially in the National Institute of Endocrinology “C.I. Parhon”. Patient was transferred 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.

TREATMENT

We initiated treatment with Ketoconasole 400 mg, 1 day, then 600 mg, for 2 days, but with inadequate correction of alkalosis and kypokalemia pH was 7.54-7.59, BE 5.7-9.8 mmol/l, K 3.16 mmol/l. The third day patient became septic-(IMRSA Staphylococcus probably) due to central catheter and intrstitial pneumonia-fibrinogen 660 mg/dl, AST 87-160 U/l, ALT 95-103 U/l, GGT 348-365 U/l, total bilirubine 2.44 mg/dl, leucocytes 13400/333, granulocytes 8500/333. 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 tumoral 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 pericellular 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, Immunohistory-Ck7, Ck20, CEA, TF1, ER-negative, MELAN A positive – suggested diffuse hyperplasia of left adrenal gland.

One hour after left adrenalectomy-cortisol was 18.2 mcg/dl, ACTH 42.3 pg/ml, patient needed inotropic 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 mmo/l/Hb was 8.4 g/dl.Ketoconasole 600 mg/di was started again. Patient had fever, delirium, pulmonary railes, so Meronem was initiated for 2 days, then Tigecicline 3 days, then 7 days of Klicacid at home, also Calcium 1 g/day, 1000 UI D3, 0.3mg of 1alpha-calcido/day, hepatic protection, vitamins, basal insulin.

10 days after adrenal resection cortisol was 26.6 mg/dl, K 3.9 mmol/l, Calcium was normal. Mg was 1.57 mg/dl, allowing second operation - resection of lung tumour proved to be typical carcinoma with kl-67 -3%, ACTH, synaptophysin and cromogranine positive.

Hematsitin-eosin staining Carcinoid

Ki 67 staining -3%

ACTH staining

Synaptophysin staining

Cromogranine staining

Thoracic CT-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 APR 2015.

Mild kypokalemia 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 carcinoma 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 carcinoma. Patient’s sister was operated for 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 tonic imbalance, insulinomas, anesthesis, brain atrophy, relative adrenal insufficiency after surgery. There are no guidelines that state the adequate cortisol levels to be reached before operating, nor the duration of Ketoconasole wash-out to prevent adrenal insufficiency.

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