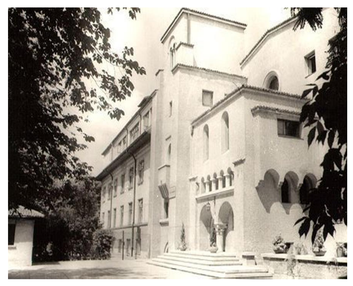
Cushing's Syndrome due to Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) Clinical and Hormonal Characterisation



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INTRODUCTION: PBMAH is a rare cause of Cushing's syndrome (CS), less than 2% of endogenous CS [1,2]. CS due to PBMAH is classified as ACTH-independent CS, but cortisol secretion in PBMAH may be mediated by locally produced ACTH, in a paracrine or autocrine fashion [3]. PBMAH can be due to the aberrant hormone receptors expression [4] or it can have a genetic origin. Mutations in PKA pathway, APC, menin or FH can favor the development of PBMAH. Inactivating mutations in ARMC5, a novel tumor suppressor gene, were recently described, in up to 50% of PBMAH cases [1].

OBJECTIVE and METHODS: To describe a series of patients with CS due to PBMAH. Case series using hormonal and imaging evaluation. Cortisol stimulation testing to detect the presence of aberrant adrenal receptors using a modified version of the Lacroix protocol.

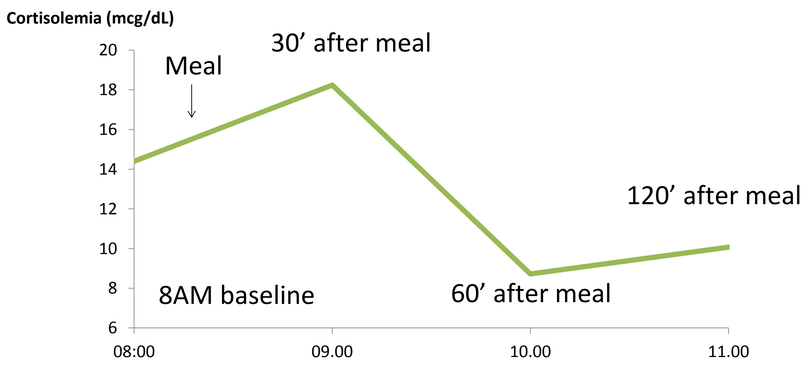
PATIENT 1, female, 66 years

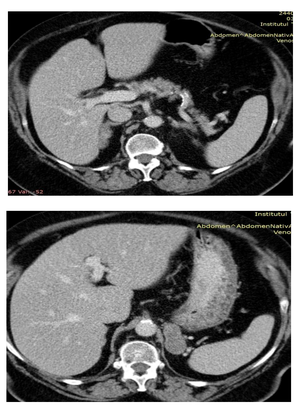
- **Sep. 2011:** clinical suspicion of CS, morbid obesity

Cushingoid features	BMI (kg/m²)	HT	Diabetes mellitus	Osteoporosis
Yes	45.54	Yes	Yes	Nk

8 AM Cortisol (mcg/dL)	Overnight 1 mg DEX (N< 1.8)	LDDST (2x2 mg)	UFC (x ULN)	ACTH (pg/mL)
12.78	5.96	4.88	0.7	2.56

- **Jul. 2015:** Refused adrenalectomy. Lost to follow-up. Contacted by phone, re-assesed by cortisol measurement postprandially, for food induced CS

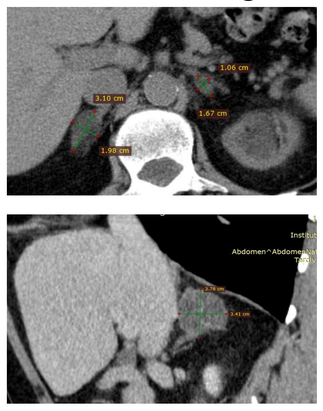




- Patient refused adrenalectomy and was again lost to follow-up

PATIENT 2, male, 61 years

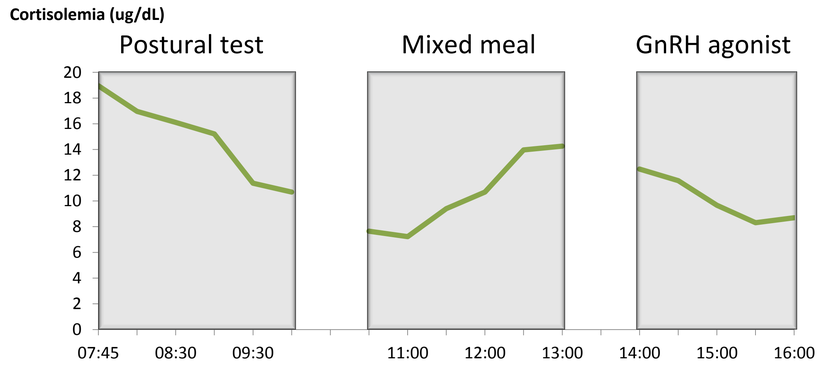
- **Nov. 2015:** diagnosed incidentally (CT scans) with PBMAH



Cushingoid features	BMI (kg/m²)	HT	DM	Osteoporosis
No	24.8	No	No	No

8 AM Cortisol (mcg/dL)	Overnight 1 mg DEX (N< 1.8)	LDDST (2x2)	UFC (x ULN)	ACTH (pg/mL)
9.86	2.75	1.8 (at dg) 4.8 (Sep 17)	0.6	7.21

Cortisolemia (ug/dL)



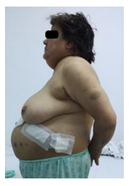
- **Active follow-up:**
30 months – no change

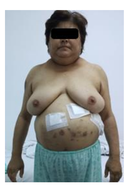
PATIENT 3, female, 50 years

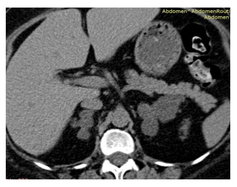
- **May 2017:** high suspicion of CS

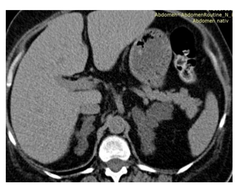
Cushingoid features	BMI (kg/m²)	HTN	Diabetes mellitus
Yes	30	Stage 3	Yes (HbA1c 11.6%) 140 UI insulin/day Retinopathy, neuropathy, CKD stage 4

8 AM Cortisol (ug/dL)	LDDST (2x2 mg) (N< 1.8)	UFC (x ULN)	ACTH (pg/mL)
27.17	29.38	0.86	1.63









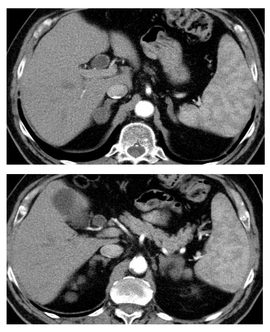
- **May 2017**: Metyrapone 750 mg/day 8 AM cortisol 21.3 mcg/dL
2 days after Metyrapone cessation 8 AM cortisol 41.7 mcg/dL
Insulin ↑ 410 U/day, glycemia ~ 250 mg/dL
- **Jun. 2017:** left laparoscopic adrenalectomy: 8 AM cortisol 17 mcg/dL, no improvement in glycemic control
Post-adrenalectomy: Metyrapone 1000 mg/day: 8 AM cortisol 7.9 mcg/dL, insulin 96 U/day, glycemia 137-253 mg/dL, HbA1c 6.1%
- **Jul 2017:** right open adrenalectomy, glycemia 94 mg/dL, 4 days postop septic shock, resuscitated cardiac arrest, exitus

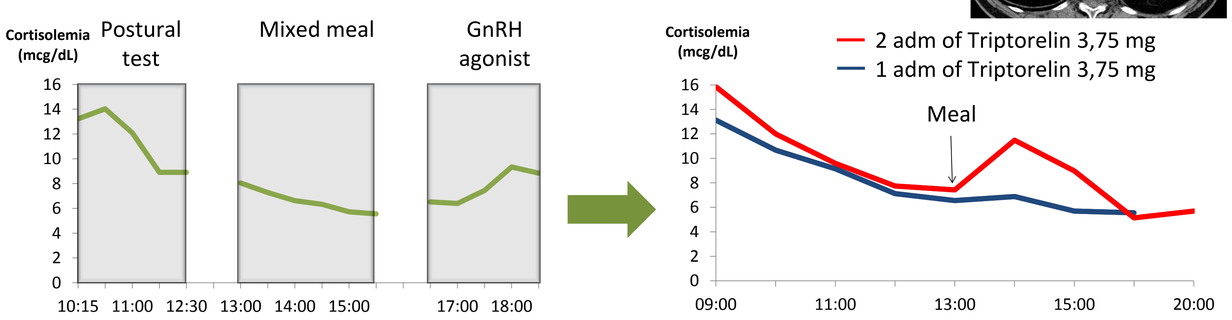
PATIENT 4, male, 62 years

- **Jan. 2018:** metabolic syndrome

Cushingoid features	BMI (kg/m²)	HT	DM	Osteoporosis
No	29	Yes	Yes	Yes

8 AM cortisol	Overnight 1 mg DEX (N< 1.8)	LDDST (2x2)	UFC (x ULN)	ACTH (pg/mL)
-	3.37	2.75	0.23	7.94





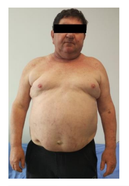
- active follow-up by day cortisol curve

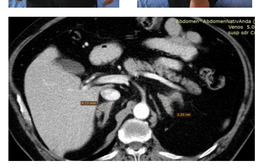
PATIENT 5, male, 62 years

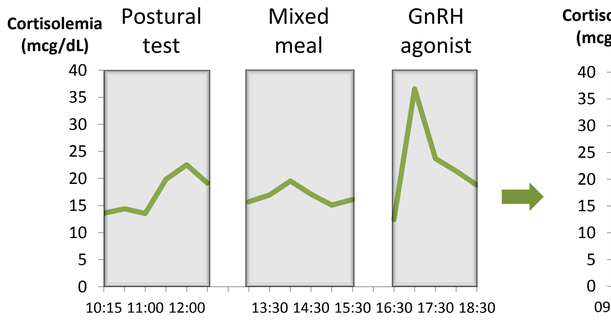
- **Mar 2018:** CS features: round red face, abdominal obesity

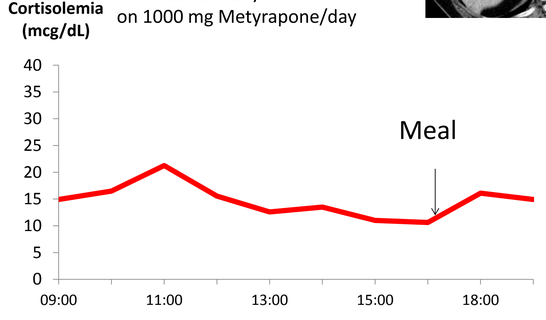
Cushingoid features	BMI (kg/m²)	HT	DM	Osteoporosis
Yes	36.31	Yes	Yes	Nk

8 AM cortisol (mcg/dL)	Overnight 1mg DEX (N < 1.8)	LDDST (2x2)	UFC (x ULN)	ACTH (pg/mL)
12.1	11.26	8.91	3.01	5.11









- Adrenalectomy delayed (dual antiplatelet TX for coronary angioplasty; on metyrapone

CONCLUSIONS: Clinical presentation in PBMAH is variable, from asymptomatic incidentalomas to severe CS. Screening for CS in patients at higher risk is warranted.
UFC was within reference range in subclinical/mild CS, while DXM suppression testing and ACTH were diagnostic.
Biochemical dynamic testing for aberrant adrenal receptors has therapeutic implications and should be performed.
Management should be individualized, with targeted medical therapy where appropriate and/or with steroidogenesis inhibitors. Unilateral adrenalectomy may be curative [5].

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2. Albiger NM, Regazzo D, Rubin B *et al.* A multicenter experience on the prevalence of ARMC5 mutations in patients with primary bilateral macronodular adrenal hyperplasia: from genetic characterization to clinical phenotype. *Endocrine* 2017;**55**:959–68.
3. Louiset E, Duparc C, Young J *et al.* Intraadrenal Corticotropin in Bilateral Macronodular Adrenal Hyperplasia. *N Engl J Med* 2013;**369**:2115–25.
4. Lacroix A. ACTH-independent macronodular adrenal hyperplasia. *Best Pract Res Clin Endocrinol Metab* 2009;**23**:245–59.
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Adrenal and steroids
Serban Radian
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