# A familial adrenal incidentaloma story

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## INTRODUCTION

Cushing syndrome (CS) has an incidence estimated to be approximately 10 per 1 million persons. In 10 to 20% of cases, CS is caused by primary adrenal cortisol hypersecretion. However, bilateral macronodular adrenal disease is an extremely rare cause of CS, representing less than 2% of all cases [1].

## CASE REPORT

Primary bilateral macronodular adrenal hyperplasia (PBMAH) was incidentally identified in a 69-year-old woman (Blanca) who developed a biliary colic. She had a 30 years history of hypertension and was treated by three antihypertensive drugs. Concomitantly, one of her four sons (Pablo) was also referred after incidentally discover of a PBMAH. This 50-year-old man has developed one year before severe hypertension needing four antihypertensive drugs. Moreover, two years before, another son (Jaime) was also incidentally diagnosed for PBMAH through an ampulloma cure. This 49-year-old man had no hypertension but severe osteoporosis discovered at the age of 42 after a spontaneous wrist fracture. None of these patients had clinical sign of Cushing's syndrome (**Figure 1**).

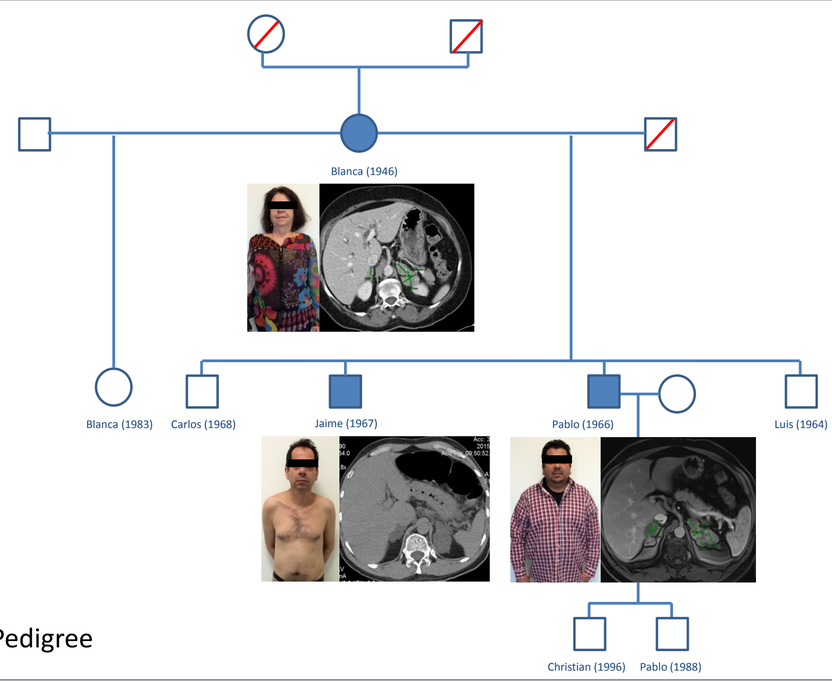



**Figure 1**: Pedigree

## Hormonal evaluation

However, hormonal evaluation showed in all three patients: basal suppressed ACTH, plasma midnight cortisol (sleeping) > 50 ng/ml and no plasma cortisol suppression after 1-mg over-night dexamethasone (DXM) suppression test while urinary free cortisol measurements (CFU) were variable (**Table 1**).

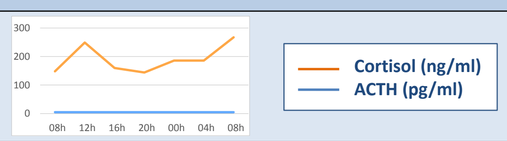
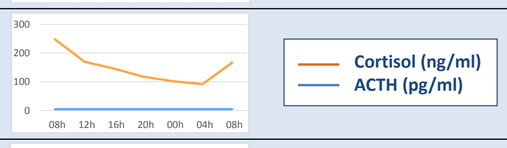
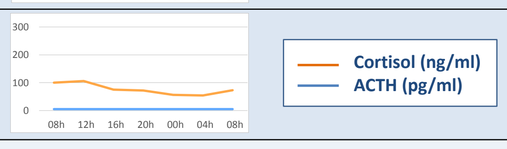
| Patient | Nycthemeral rhythm of the corticotropic axis | Cortisol (ng/ml) after 1 mg DXM at midnight | CFU (µg/24h) (N: 10-110) |
|---|---|---|---|
| Blanca |  | 164 | 39 |
| | | | 44 |
| Pablo |  | 214 | 171 |
| | | | 100 |
| Jaime |  | 184 | 54 |
| | | | 154 |



**Table 1:** Circadian rhythm of the corticotropic axis, plasma cortisol after 1-mg over-night dexamethasone suppression test and urinary free cortisol measurements (CFU)

In order to investigate cortisol responses to various stimuli independently from any ACTH variation, patients were given dexamethasone before a series of tests for illegitimate adrenocortical receptors detection. The tests were performed as previously described by Reznik et al [2]. Results are expressed as percentage variation from basal, calculated as follows:

[(peak cortisol – basal cortisol)/(basal cortisol)] x 100 %

Response is positive when percentage is > 25%. Results are shown in **Table 2**.

| Test | Dependance mode | Tested Receptors | Response (%) | | |
|---|---|---|---|---|---|
| | | | Blanca | Pablo | Jaime |
| Supine-to-upright posture test | Catecholamine<br>Angiotensine II | β-adrenergic<br>AT1, V2, V3 | **86 %** | **48 %** | **41 %** |
| Meal | Food intake | GIP | 10 % | 6 % | **45 %** |
| TRH, GHRH, LHRH, CRF | Hypothalamic-releasing hormones | TRH, GhRH, GnRH, TSH, GH, LH/hCG, FSH | 6% | 11 % | **45 %** |
| Terlipressine | Vasopressin | V1a, V1b, V3 | **196%** | **128 %** | **171 %** |
| Glucagon | Unknown | Glucagon | 11 % | 7 % | 0 % |
| Metoclopramide | Serotinine | 5-HT4, 5HT7 | 28% | 3 % | **67 %** |
| Synacthen® | ACTH | ACTH | **96%** | **166 %** | **52 %** |

**Table 2:** Results of clinical screening for illegitimate membrane adrenal receptors

## Evolution

The mother underwent surgical resection of the most voluminous adrenal gland **(Figure 1A, 1B)** and of the biliary duct tumor **(Figure 3A, 3B)**, while Pablo had a bilateral adrenalectomy **(Figure 1C, 1D)**.

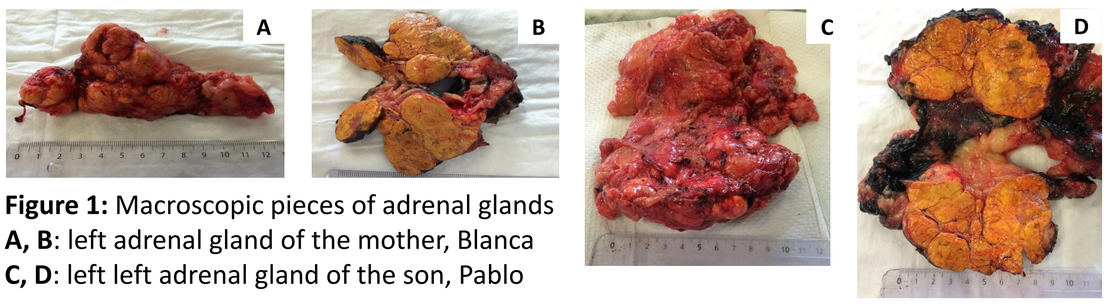



**Figure 1:** Macroscopic pieces of adrenal glands
**A, B**: left adrenal gland of the mother, Blanca
**C, D**: left left adrenal gland of the son, Pablo

Histology confirmed the macronodular adrenal hyperplasia (**Figure 2**).

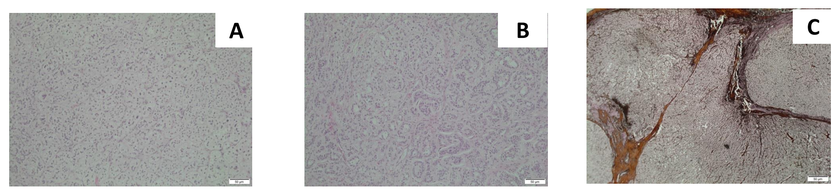



**Figure 2** : Hematoxyllin and eosin coloration of the adrenal gland of the mother **(A)** and the son **(B)** showed epithelioid cells. Reticuline staining highlighted the septa between de different adrenal macroadenomas **(C)**.

The biliary duct tumor of the mother was an exceedingly rare tumor that closely mimics hepatocellular carcinoma: an hepatoid adenocarcinoma. The diagnosis could be made by immunochemistry (positive immuno-staining for HepPar 1) after exclusion of other diagnoses (negative immuno-staining for CD56, Chromogranin, Synaptophysin, CD10, CD117, S-100 protein, Vimentin, PLAP, CK7, CK19) (**Figure 3**). HepPar 1 antibody is directed to an hepatocyte mitochondrial membrane associated-antigen. Bile ducts and liver originate from the same endodermal tissue.

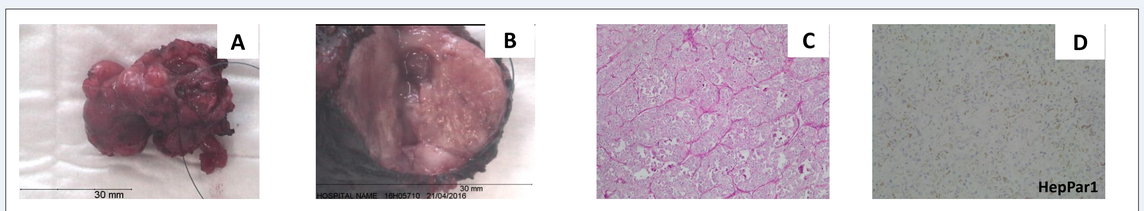



**Figure 3**: Macroscopic piece of the biliary duct tumor **(A, B)**. Hematoxyllin and eosin coloration **(C)**. HepPar 1 staining **(D)**.

## DISCUSSION

In this case, the bilateral nature of the adrenocortical tumors and the familial form of the disease suggests a genetic origin. PBMAH is often genetically determined and several genes have been identified, *ARMC5* being the last one[3]. A model of tumor suppressor gene has been proposed for *ARMC5* alterations **(Figure 4)**[4].

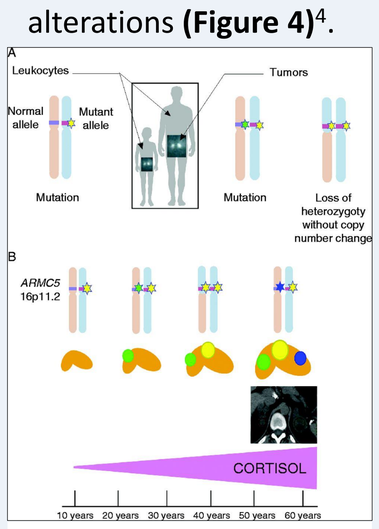



**Figure 4**: Model of *bi-allelic* inactivation of a tumor suppressor gene in PBMAH development. A first germline inactivating mutation is followed by a somatic secondary hit on the other allele

Genetic testing targeted on *ARMC5* gene is still in progress in this family. However, the associated-tumors phenotype exhibited by this family does not enter into the spectrum of the described malignancy predisposing syndromes: absence of hyperparathyroidism and biliary duct tumor association [4].

Moreover, illegitimate receptor expression observed in the majority of PBMAH is until now not clearly explained. This aberrant receptor expression could be due to a cell dedifferentiation favored by a decrease of apoptosis in *ARMC5* mutated cells. It is interesting to note that the biliary duct tumor of our patient expressed hepatocellular markers indicating, also, a cell dedifferentiation.

## CONCLUSION

This case is remarkable for several reasons:

- at our knowledge, it is the first described case of PBMAH associated to a digestive tumor
- it illustrates well the phenotype variability within one family with a rare genetic cause of Cushing's syndrome as well as the presence of different type of aberrant receptors in the same family
- it highlights the importance of a complete clinical characterization to permit phenotype-genotype correlations
- the comparison of genetic profiles of the adrenal and digestive tumor tissues (germline and somatic mutations) could also give new data for a better knowledge of this disease

## REFERENCES

1. J. Newell-Price et al. Endocr Rev 1998; 19: 647-72
2. Y. Reznik et al. Clinical Endocrinology 2004; 61, 311-19
3. G. Assié et al. NEJM 2013;22:2105-14
4. L Drougat et al (2015) 173, M121–M131 EJE 2015;173,121-131