

TESTICULAR ADRENAL REST TUMORS ARE NOT ASSOCIATED WITH 21 HYDROXYLASE GENE MUTATIONS OR THERAPY COMPLIANCE IN BOYS WITH CLASSIC FORM OF CAH

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Authors declare no conflict of interest

Introduction

Testicular adrenal cell rest tumors (TART) are common in adult males treated for congenital adrenal hyperplasia (CAH) and contribute to reduced fertility. Their prevalence varies between 6-50%, and the incidence raises during adolescence. Reports about the influence of CYP21A2 gene mutations and compliance to therapy in development of TART are controversial.

Aim

To explore the appearance of TART in a group of 25 male children in the age group 3-18 years who were treated for CAH and who were molecularly characterized.

Methods

Compliance to the treatment was assessed through 17OHP and ACTH values at 4 months intervals. Gene analysis for the CYP21A2 gene was performed using amplification creation restriction site method (ACRS) detecting 11 most frequent mutations. Ultrasound examination of testis was performed at yearly intervals (after the age of 6 years). If positive for TART, it was followed by the MRI. Two adolescent boys with palpable testicular tumor and significant ultrasound findings underwent biopsy of the testes. Regular and immunostaining of the slides obtained from testicular biopsies was performed.

Results

TART was palpable in 2 boys. On ultrasonography, it was present in 6 children (24%) at the age 7-16 years (14.2 years average). Four had a classical salt wasting form, two had simple virilizing form of CAH. Molecular analysis confirmed homozygous I2S mutation in 3 patients, homozygous Q318X mutation in one, homozygous I127 mutation in one, and homozygous P30L mutation in one. One patient was compound heterozygote I2S/Q318X (Table 1). Ultrasonographic examination revealed tumors located around rete testis and consecutively decreased amount of the normal testicular tissue. Repeated examination revealed progression of the tumor (Fig 1). MRI confirmed TART, and clarified the distribution of the tumors (Fig 2). Histology was diagnostic of TART in two patients (Fig3) although Leydig cell tumor was suspected in one. Three of the patients had non-compliance, however in remaining 3, 17 OHP and ACTH were constantly within the normal range. Surprisingly, one of the boys with TART developed mixed phenotypic leukemia at the age of 16 years. We found no similar case in the literature.

Increase of the dose of hydrocortisone or dexamethasone did not decrease the size of tumors in our patients.

Discussion

The issue of testicular adrenal rest tumors detected in male children with congenital adrenal hyperplasia are addressed more frequently during the last decades. The hypothesis that existing adrenal cells in the testis of all male children undergo hypertrophy when exposed to stimulating factors (increased levels of ACTH in CAH patients) does not hold completely, since several studies present compliant and well regulated patients with large TART. Progression of TART causes fibrosis of the testis and consecutive sterility. In 10% of patients risk of malignancy has been documented. Although some authors suggest higher doses of dexamethasone to reduce TART in early stages, results with this approach are not commonly favorable due to the side effects. No guidelines for diagnosis, follow up and treatment are available for TART in children since this condition appears in late adolescence and adulthood. However, our group of patients is younger than most of the previously reported.

Conclusions

- TART is not rare in boys with salt wasting or simple virilizing form of CAH.
- It is not associated with the genotype or the therapeutic compliance.
- Systematic testicular ultrasonography in male children with CAH since early childhood at yearly intervals provides timely diagnosis of TART.
- Search for better treatment of TART in order to improve fertility is warranted.

Table 1. Patients with CAH and testicular adrenal rest tumor

Patient	Age (years)	Type of CAH	Genotype	17OHP (nmol/l) at diagnosis	Compliance	Ultra-sound (testis)	MRI	Histology
1. *	14	SW	Q318/Q318	>75	Variable	+	+	TART*
2.	13	SW	I2SM/I2SM	>75	NC	+	+	TART
3.	14	SW	I2SM/I2SM	>75	Variable	+	NA	NA
4.	15	SW	I2SM/Q318X	>75	Compliant	+	+	TART
5.	13	SV	P30L/P30L	>75	Compliant	+	+	NA
6.	7	SV	I172N/I172N	>75	Compliant	±	NA	NA

* Patient who developed mixed type leukemia, I2SM -intron 2 splicing mutation, NC- noncompliant,

Fig 2. Ultrasound of the testis confirming TART

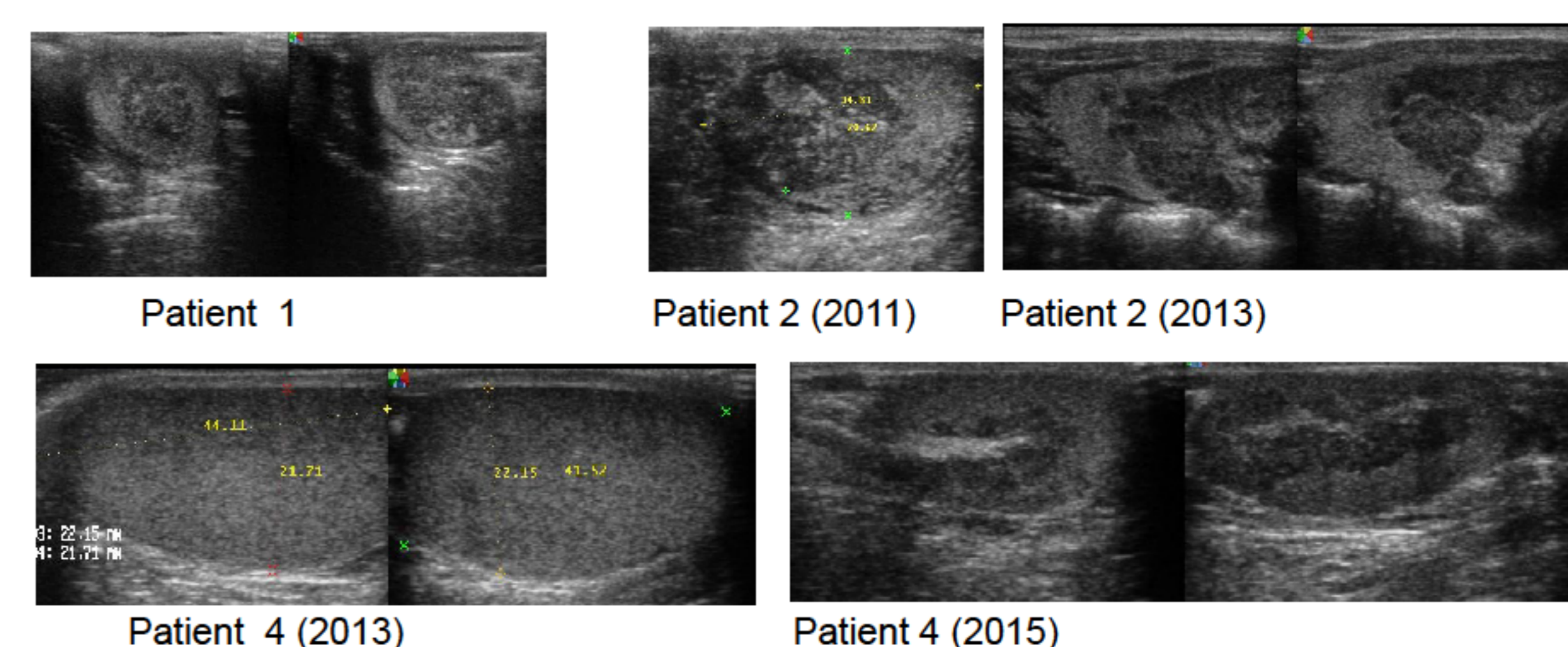


Fig 3. MRI of the testis confirming TART

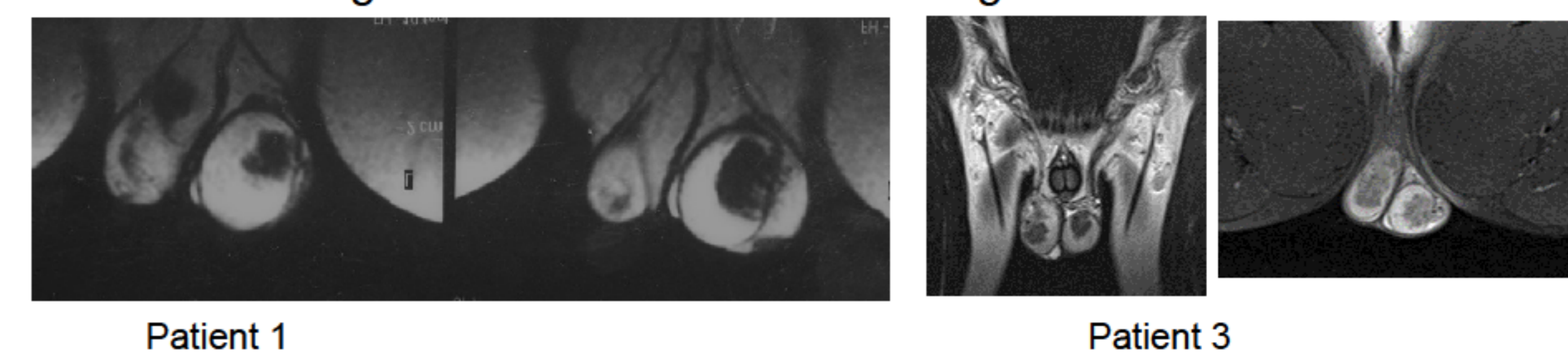
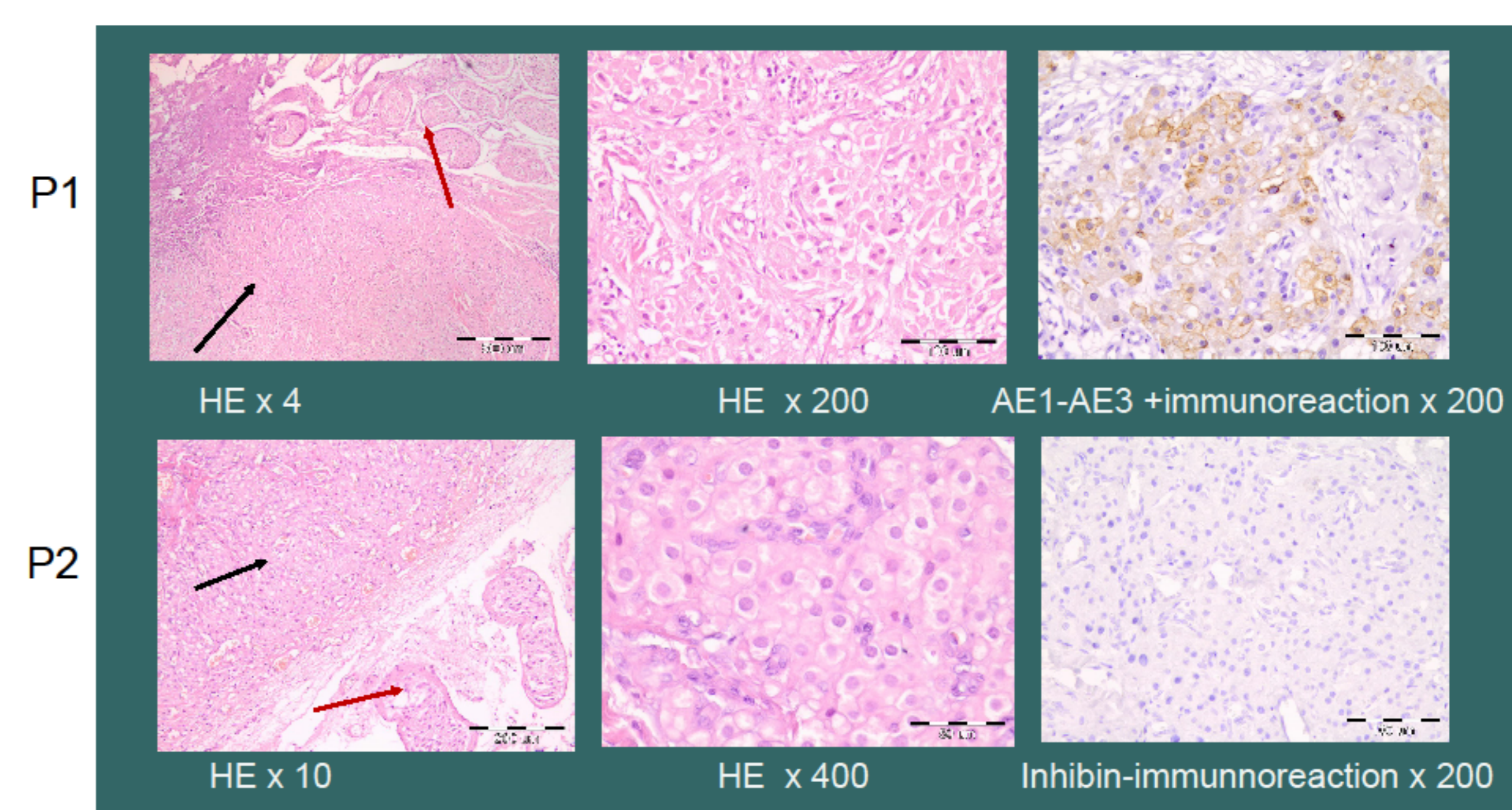


Fig 4. Histology



P1- Patient 1, P2 -Patient 2, black arrow-adrenal tissue, red arrow-testicular tissue

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