RET AND TP53 CONCOMITANT MUTATIONS

A CHALLENGING APPROACH TO A UNIQUE ASSOCIATION OF HIGH TUMOR PREDISPOSING CONDITIONS

M. Calanchini[1,2], A. Fabbri[2], A. Grossman[1], B. Jafar-Mohammadi[1]

Oxford Centre for Diabetes, Endocrinology & Metabolism

[1]Dept. of Endocrinology, OCDEM, Churchill Hospital, University of Oxford
[2]Dept. of Endocrinology, CTO Alesini, University of Rome Tor Vergata

The Authors have no disclosures

CASE REPORT: A 33-year-old woman, with a history of cortisol-secreting adrenocortical carcinoma (ACC) surgically treated aged 4, presented for prenatal screening at 20 weeks of gestation. Ultrasound examination identified that the female fetus had a 3 cm left adrenal lesion (Fig.1).

The patient had a positive family history for medullary thyroid cancer (paternal grandmother had medullary thyroid cancer aged 30) and her father's cousin was diagnosed with ACC and Li-Fraumeni syndrome (Box 1) at 30 years of age.

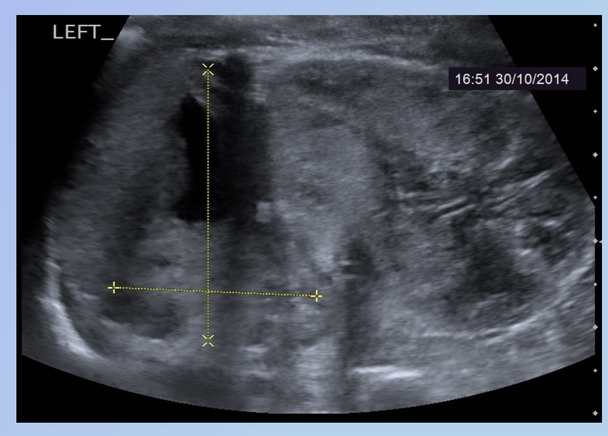

Fig. 1. 3 cm left adrenal mass confirmed on post-natal abdomen US

Box 1. Li-Fraumeni syndrome (LFS)

- LFS is a rare autosomal dominant condition, caused by a germline mutation in the tumor suppressor *TP53* gene
- It is characterized by the development of a very wide range of cancers, often at a young age (Fig. 2)
- High penetrance: around 50% of the individuals carrying mutations in *TP53* will develop cancer by the age of 30 ys, with a lifetime risk of up to 70% in men and 100% in women
- The effectiveness of cancer screening test is unclear

LFS and ACC: ACC is one of the LFS core tumors. About two third (68%) of individuals with TP53 germline mutation develop ACC before age 4 and 90% before age 20

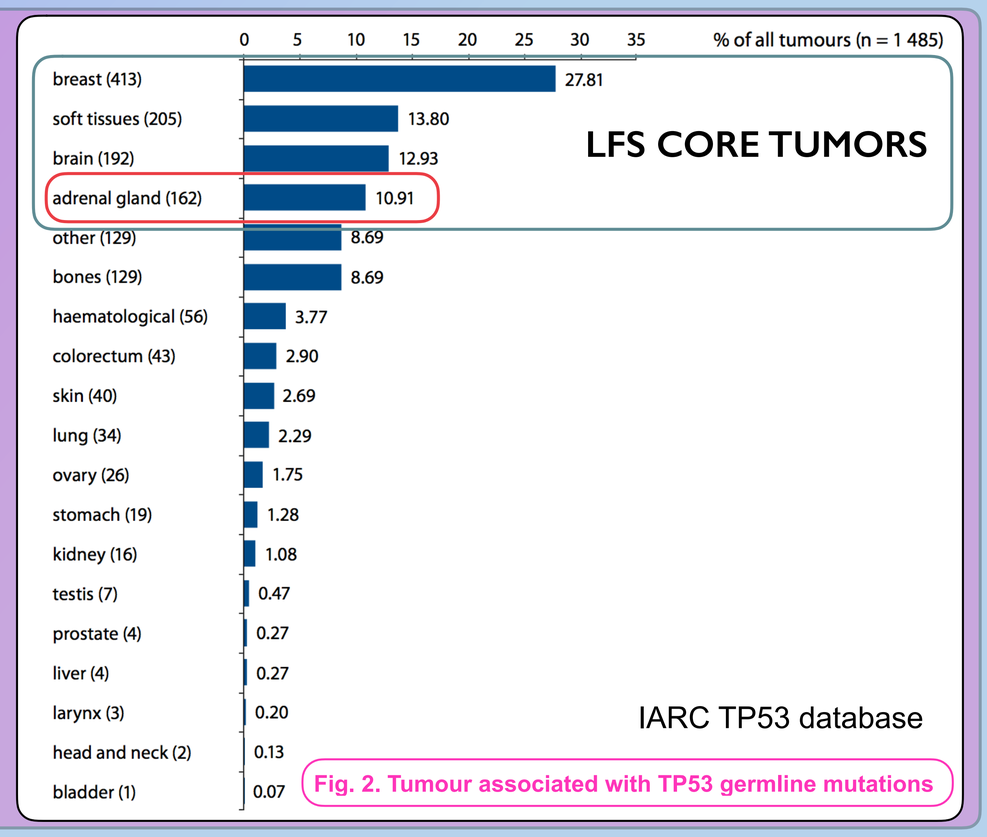

Fig. 2. Tumour associated with TP53 germline mutations

- Mother's plasma calcitonin and PTH, and urine metanephrines were within normal limits. The rest of the pregnancy and delivery were uneventful
- Two months post-partum her daughter's CT confirmed an unchanged adrenal mass with predominantly low attenuation (Fig. 2)
- No evidence of cathecholamine excess, and neither increased urinary steroid metabolites, androgen precursors or glucocorticoids were identified
- Aged 2 months her daughter underwent an adrenalectomy, but no histological features of malignancy were reported

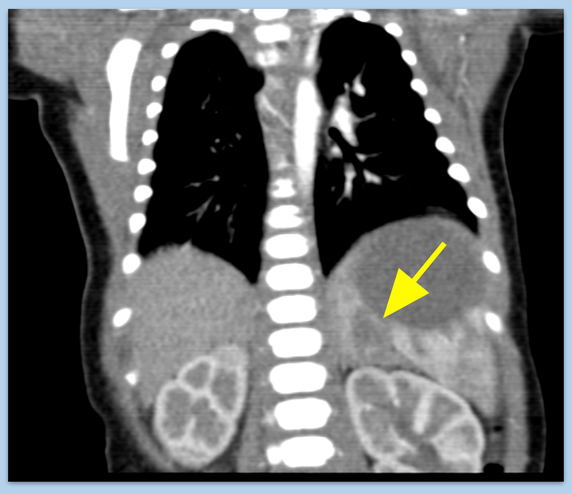

Fig. 2. 2 months post-partum abdomen CT showed unchanged adrenal mass

GENETIC TESTING confirmed that the mother was *RET* (Val 804 Met) and p53 (Arg158His) mutation-positive.

The mother wished her daughter only to be tested for the *RET* mutation, and the same *RET* mutation was found

Tab. 1 Timing of thyroidectomy in carriers of a mutation in the *RET* gene

RISK	*RET codon mutation*	Recommended age to begin annual screening for MTC	Recommended timing of thyroidectomy
Highest	918	Not applicable	In the first months to year of life
High	634, 883	Three years	At or before age 5 yr
Moderate	533, 609, 611, 618, 620, 630, 666, 768, 804, 891, 912	Five years	Childhood or young adulthood

Wells SA Jr et al. Thyroid 2015

- The mother underwent prophylactic thyroidectomy
- She is under adult screening surveillance for a wide range of cancers, including annual breast MRI

The daughter's suggested management was:

- Thyroidectomy before age 5 years (Tab. 1)
- Clinical examination, abdomen ultrasound and hormone evaluation every 6 months, in particular aiming for earlier detection of ACC
- Avoidance of ionizing radiation
- Discuss again with parents advantages and disadvantages of testing for p53 mutation

DISCUSSION AND CONCLUSIONS:

- ACC is one of the LFS core tumors. Due to its characteristic association with LFS, discovery of an ACC, especially in a child, is an absolute indication for researching TP53 mutations
- The *RET* Val 804 Met mutation is correlated with the MEN2 Familial Medullary Thyroid Cancer phenotype and with low tumor aggressiveness
- This is the first case of a concomitant carriage of *RET* and *p53* mutations, both rare and high tumour predisposing conditions
- Due to this unique association and the multiple possible tumour manifestations, a safe (ideally with zero dose of radiation), effective and appropriate (taking into account the psychological effect) screening programme is mandatory

55ESPE 41--P1

Adrenal

matilde calanchini

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER

PosterSessionOnline.com