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

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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.

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

- 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

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

<table>
<thead>
<tr>
<th>RISK</th>
<th>RET codon mutation</th>
<th>Recommended age to begin annual screening for MTC</th>
<th>Recommended timing of thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>918</td>
<td>Not applicable</td>
<td>In the first months to year of life</td>
</tr>
<tr>
<td>High</td>
<td>634, 883</td>
<td>Three years</td>
<td>At or before age 5 yr</td>
</tr>
<tr>
<td>Moderate</td>
<td>568, 609, 611, 618, 620, 630, 666, 768, 804, 891, 912</td>
<td>Five years</td>
<td>Childhood or young adulthood</td>
</tr>
</tbody>
</table>

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 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

Wells SA Jr et al. Thyroid 2015

Recommended age to begin annual screening for MTC: 1. 5 years (Tab. 1)


discussion concludings:

- 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 tumor 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.