Mitigating thyroid cancer risk in multinodular hyperplasia secondary to a 10q23.31 deletion (PTEN Hamartoma Tumour Syndrome)

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INTRODUCTION
The phosphatase and tensin homolog (PTEN) hamartoma tumour syndrome (PHTS) groups related multi-system genetic disorders linked to germline mutations in the PTEN gene, a tumour suppressor gene. Inheritance is autosomal dominant or variants can arise de novo. There is an increased risk of thyroid cancer in PHTS, with some cases arising in childhood. Annual surveillance for thyroid cancer by ultrasound is recommended (1).

CASE REPORT
A 15 year old female was referred to Paediatric Endocrinology by Clinical Genetics for thyroid surveillance given a 10q23.31 deletion involving the PTEN gene. She had significant developmental delay, with severe learning difficulties, a diagnosis of autism spectrum disorder (ASD) and seizures. Her father and brother were known to have the same PTEN deletion (Figure 1).

Figure 1: Pedigree

Our patient was clinically euthyroid and had a normal thyroid examination. She had reached her final adult height (95th centile). Her head circumference plotted on the 50th centile. She did not have any mucocutaneous lesions, lipomas or haemangiomas. She was wheelchair bound and non-verbal. Thyroid function was normal (TSH 0.68 mU/L, 0.34 – 5.6), FT4 14.8 pmol/L (7.5 – 21.1)). A thyroid ultrasound scan revealed bilateral thyroid lesions predominantly cystic in nature, without microcalcification or cervical lymphadenopathy (Figure 2). The patient required a general anaesthetic for fine needle aspiration (FNA), which was performed on the largest lesion (15 mm diameter). Histology was inconclusive and reported mostly colloid.

Figure 2: Thyroid ultrasound scan depicting bilateral thyroid lesions

Table 1: Diagnostic criteria for PHTS (2)

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Breast cancer</td>
<td>Autism spectrum disorder</td>
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<tr>
<td>Endometrial cancer</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>Thyroid cancer (follicular)</td>
<td>Oesophageal glycogenic acanthoses</td>
</tr>
<tr>
<td>GI hamartomas</td>
<td>Lipomas</td>
</tr>
<tr>
<td>Lhermitte-Duclos disease (adult)</td>
<td>Renal cell carcinoma</td>
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<tr>
<td>Macrocephaly</td>
<td>Testicular lipomatosis</td>
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<tr>
<td>Macular pigmentation of the glans penis</td>
<td>Thyroid cancer (papillary or follicular variant of papillary)</td>
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<td>Multiple mucocutaneous lesions</td>
<td>Thyroid structural lesions (e.g. adenoma, multinodular goitre)</td>
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<td></td>
<td>Vascular anomalies</td>
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</tbody>
</table>

Table 1: Diagnostic criteria for PHTS (2)

Application of criteria:
1. Three or more major criteria (one must include macrocephaly, Lhermitte-Duclos disease or GI hamartomas) OR
2. Two major and three minor criteria OR
3. One major and five minor criteria OR
4. Three major or two minor criteria OR
5. Three minor criteria

DISCUSSION
PHTS is associated with an estimated 35% lifetime risk of differentiated thyroid cancer, with case reported as young as 7 years (3). How best to mitigate her risk of thyroid cancer given her diagnosis of PHTS?

The UK cancer genetics group recommend an annual ultrasound scan (USS) from 16 years (or younger as guided by family history) (4). The American Thyroid Association (ATA) recommend benign thyroid nodules be followed by serial USS and undergo repeat FNA if suspicious features develop (5). In this case, the USS appearance was likely to become more florid with time, necessitating repeat FNAs. However, are repeated FNAs feasible and useful for this patient? This patient did not tolerate FNA under sedation and required a general anaesthetic, so the risk versus benefit of repeated general anaesthesic need to be considered. Also FNAs aren’t without complications (including haemorrhage, infection and infection) whilst FNAs can be diagnostic, accuracy in children can vary. The ATA recommend that definitive surgery may be considered for those with benign cytopathology in certain circumstances (5). The family and the multidisciplinary team (MDT) were in agreement that this was the most appropriate way to manage her risk of thyroid cancer.

LEARNING POINTS

- PHTS is characterised by cancer predisposition and neurodevelopmental abnormalities, with huge phenotypic variability.
- Individuals with PHTS carry an estimated 35% lifetime risk of differentiated thyroid cancer.
- An annual thyroid USS from 16 years (younger as guided by family history) is recommended in PHTS.
- Scan characteristics and clinical context should be used rather than FNAs. Application of criteria:
- Such a procedure may not be tolerated by these individuals and the risks versus benefits of repeated general anaesthetic for FNAs need to be considered.
- Thryoidectomy is not routine management, however definitive surgery may be considered for those with benign cytopathology in certain circumstances – an individualised approach is required.

REFERENCES
4. PTEN management guidelines [Internet]. Cancer Genetics Group.