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

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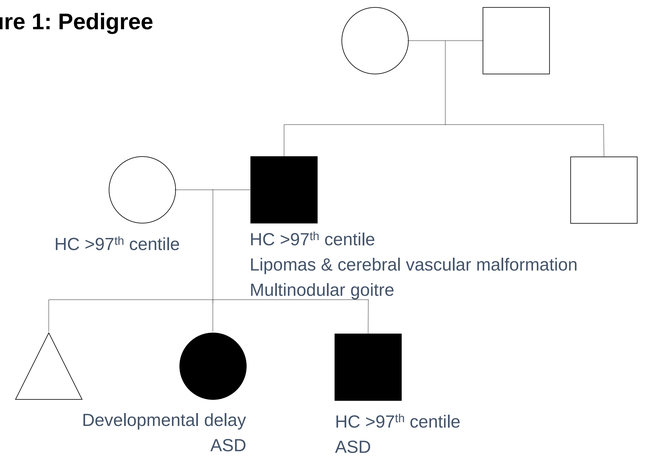
INTRODUCTION

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

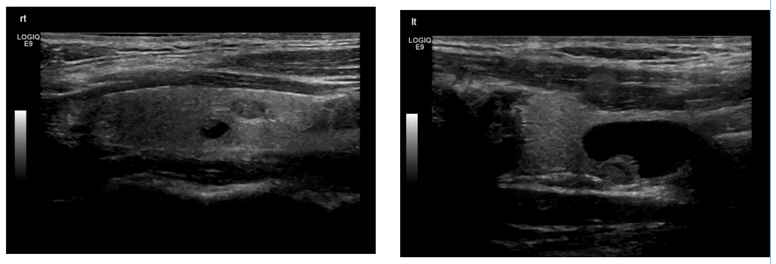
A 15 year old female was referred to Paediatric Endocrinology by Clinical Genetics for thyroid surveillance given a 10q23.31 deletion involving the *PTEN* gene. She had significant developmental delay, with severe learning difficulties, a diagnosis of autism spectrum disorder (ASD) and seizures. Her 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 (9-25th 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



Annual ultrasound surveillance with likely FNAs versus definitive surgery was discussed at the oncology thyroid MDT. Following an in-depth discussion with the family, the patient, who was not Gillick competent, underwent a prophylactic total thyroidectomy aged 16 years. She was commenced on lifelong levothyroxine. Histology reported multinodular hyperplasia. The patient was subsequently diagnosed with PHTS (PTEN pathogenic variant plus three minor criteria) (Table 1).

Table 1: Diagnostic criteria for PHTS (2)

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

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
Operational diagnosis in a family where one individual meets revised PHTS clinical diagnostic criteria or has a PTEN pathogenic/ likely pathogenic variant:
1. Any two major criteria with or without minor criteria OR
2. One major and two minor criteria OR
3. 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 anaesthetics need to be considered. Also FNAs aren't without complications (including haemorrhage, fibrosis and infection) and 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 nodule size to identify nodules that warrant FNA.**
- **Such a procedure may not be easily tolerated in these individuals and the risks versus benefits of repeated general anaesthetic for FNAs need to be considered.**
- **Thyroidectomy is not routine management, however definitive surgery may be considered for those with benign cytopathology in certain circumstances – an individualised approach is required.**

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