Papillary thyroid carcinoma in a mother and child evolving after the manifestation of Graves' disease

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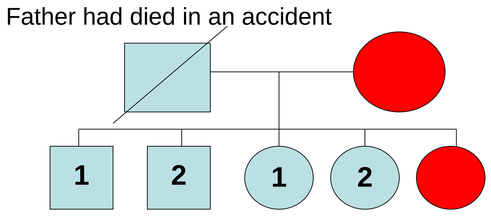
OBJECTIVES

Large familial papillary thyroid carcinoma (PTC) in childhood has been described only in single cases, mainly in the context of rare syndromes (e.g APC-associated-syndrome, PTEN-hamartoma syndromes). Small PTC in Graves' disease (GD) has been described in adults[1], but not in familial cases including young children. PTC in GD seems to be more aggressive[2]. We investigated the association of large metastatic PTC in a 10 years old girl and her mother evolving rapidly in both of them after the manifestation of GD. A genetic basis for the non-syndromic familial GD and PTC in a background with a high prevalence of PTC in adults GD was suspected.

Patient History



2 Brothers:
- euthyroid
- normal ultrasound

Sister 1:
- euthyroid
- cystic lesion with calcification in left lobe

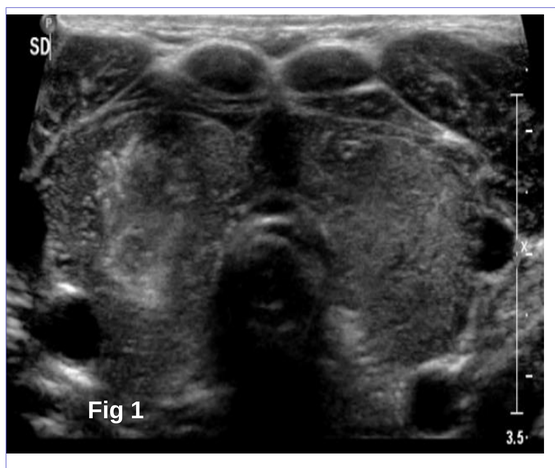
Sister 2:
- euthyroid
- cystic lesion in right lobe

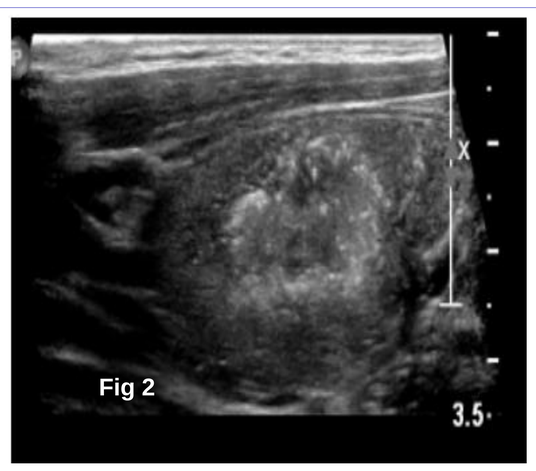
<u>The mother:</u>
Manifestation **Graves' disease** (TSH-R AB positive) 2014: initiation of antithyroid drug treatment with carbimazole

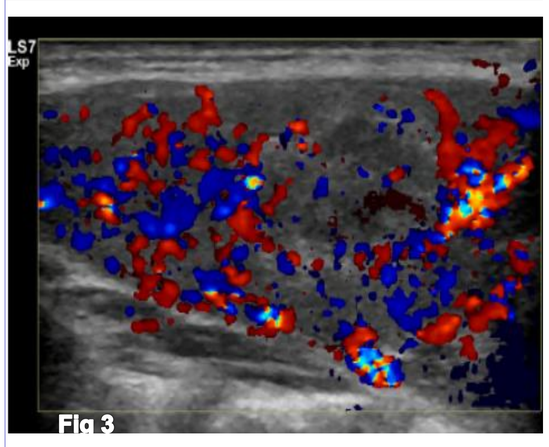
<u>3 months later:</u>
detection of a large nodule, **PTC**, one LN metastasis,
→ ablative thyroid surgery, radioiodine treatment

<u>The patient</u>:
Manifestation **Graves' disease** (TSH-R AB positive) 2015:
• loss of 10 kg BW
• tachycardia
• prominent eyes
initiation of antithyroid drug treatment with carbimazole

<u>3 months later:</u>
detection of a large nodule, **PTC**, one LN metastasis,
→ ablative thyroid surgery, radioiodine treatment







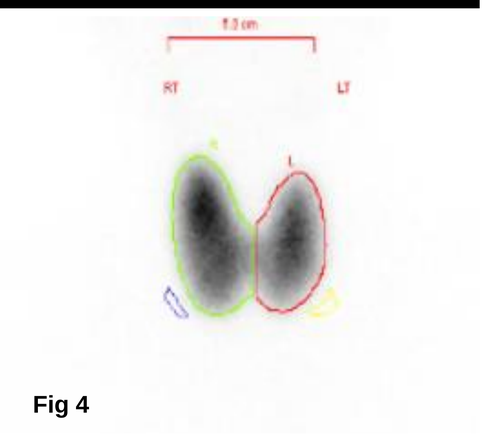
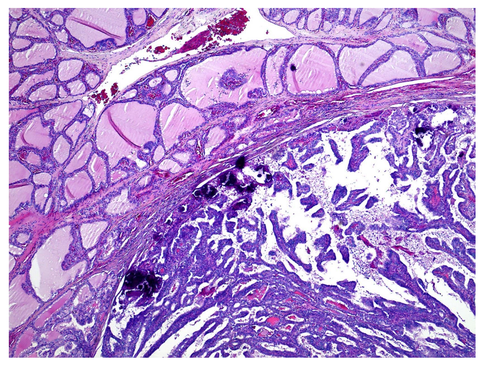


Figure 1 and Figure 2 : Ultrasound studies of the visible nodule
Figure 3: Doppler ultrasound study
Figure 4: ^{99} Technitium uptake study

Results

<u>Imaging studies</u>:
The ultrasound studies revealed a 1,2 x 2,3 cm large nodule in the right lobe and the thyroid with an echostructure compatible with autoimmune thyroid disease and increased perfusion. **(Fig 1/2/3)** Scintigraphy revealed an increased uptake **(Fig 4)**, thus the nodule was not visible.

<u>Histopathology</u>:
16 mm PTC with several lymph node metastases (pT1bpN1b(9/10)R0L0V0) in a thyroid with chronic interstitial inflammation



<u>Genetic studies</u>:
No somatic variants were found for APC 1-16; DDR2 15; DICER1 1-28; EGFR 18-21; ERBB2 5,6,15,20,23,29; FGFR1,3, 7, 13, 17, 18; HRAS 2-4; KIT 9-11, 13, 17, 18; KRAS 2-4; MET 3, 8, 11, 14, 19; NRAS 2; PDGFR 12, 14, 18; PIK3CA 3, 5, 10, 16, 21; PRKAR1A 1-11, PTEN 1-9; RAF/11; RET 0, 11, 13-16; TP53 4-9;

Variants:
1. BRAF-Mutation (V600E)
2. TSH-R Exon 1 mutation: rs2239610 c.154C>A p.Pro52Thr
3. TSH-R Exon 10 variant: c1377G>A; p.=Ala) no AA change

Family Member	Exon 1 rs2239610 c.154C>A p.Pro52Thr
Patient	CA
Mother	CA
Brother 1	AA
Brother 2	CA
Sister 1	CA
Sister 2	CA

Conclusions

A rare association of GD and PTC in a mother and her daughter was associated with BRAF V600E in the tumor tissue. A TSH-receptor variant in Exon 1 was found also in the two sisters with cystic abnormalities in ultrasound studies. Since a high prevalence of PTC associated with GD is known in the ethnic background[3] of the family, a further genetic work-up has been initiated, to find out if this rare association could be caused by a genetic predisposition in thyroid structure or function.
Alternatively an expression of a microRNA caused by an increase in proliferation[4], by a genetic variant of the immune system, an environmental factor or the antithyroid drug treatment may have triggered the development of the PTC.

References

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55ESPE 916--P1
Thyroid
Annette grueters
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS