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Papillary Thyroid Cancer in a Patient with Germline TTN Mutation

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Background

- The TTN gene encodes Titin, the largest protein in the body and an essential component of cardiac sarcomeres.
- Mutations in the TTN gene are the most common known cause of dilated cardiomyopathy and can lead to cardiac arrythmias.[1]
- Studies have also suggested a link between TTN mutations and cancer incidence and prognosis.[2]
- Here we present a case of a 60-year-old male with a history of known germline TTN mutation and atrial fibrillation who presented with hyperthyroidism and was ultimately diagnosed with papillary thyroid carcinoma.

Case Presentation

- A 60-year-old male presented with new onset atrial fibrillation and hyperthyroidism.
- His past medical history was significant for germline TTN mutation and recurrent ventricular tachycardia status post implantable cardiac defibrillator placement.
- He had been treated with amiodarone for two and a half years and had stopped the medication eight months prior to presentation.
- Laboratory workup was done (table 1) and an ultrasound of the thyroid gland showed a multinodular goiter with subcentimeter cysts and a right lower lobe nodule.
- A follow-up thyroid ultrasound twelve months later showed a new 11 mm nodule in the left lower lobe (Figure 1) and a stable 5 mm nodule in the right lower lobe (Figure 2).
- Fine needle aspiration of the left nodule was suspicious for follicular neoplasm with suspicious Afirma Genome Sequence Classifier testing (corresponding to ~ 50% risk of malignancy).

Initial Labs	Result (reference range)
Thyroid Stimulating Hormone	<0.01 (0.25-4.50) uIU/mL
Free Thyroxine (T4)	3.45 (0.80-1.80) ng/dL
Free Triiodothyronine (T3)	10.30 (2.30-3.80) pg/mL
Thyroid Stimulating Immunoglobulin	<89 (<140% baseline)
Thyroid Peroxidase Antibody	<9 (0-31) u/mL

Table 1

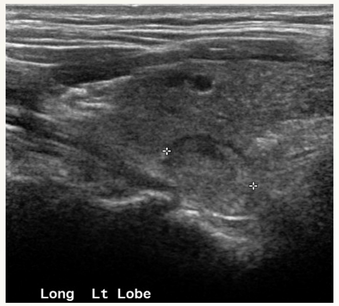

Figure 1: Thyroid ultrasound showing a mixed echogenicity solid nodule in the left lower lobe, measuring 11 x 11 x 15 mm

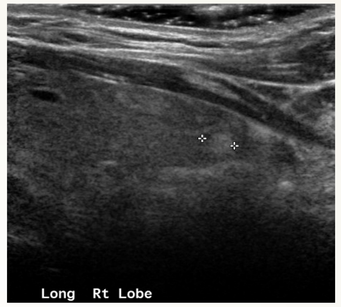

Figure 2: Thyroid ultrasound showing a solid nodule in the right lower lobe, measuring 5 x 7 x 5 mm

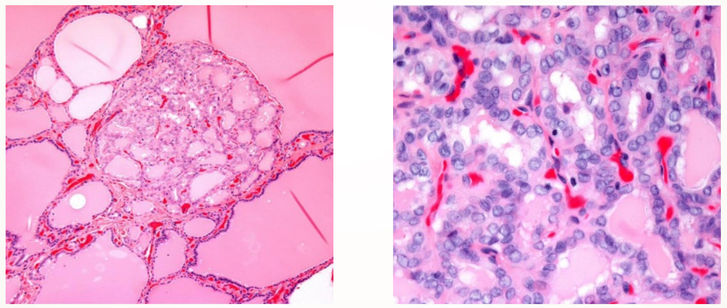

Figure 3: Representative histopathology showing a papillary microcarcinoma[3]

Post Operative Labs	Result (reference range)
Thyroid Stimulating Hormone	1.19 (0.25-4.50) uIU/mL
Free Thyroxine (T4)	1.88 (0.80-1.80) ng/dL
Thyroglobulin	0.2 (2.8-40.9) ng/mL
Thyroglobulin Antibody	11 (0.0-60) u/mL

Table 2

Treatment and Outcome

- His hyperthyroidism was treated with methimazole, which he was able to stop after nine months.
- Six months after discovery of the new left lower lobe thyroid nodule, the patient underwent a total thyroidectomy and pathology showed a 1.5 mm stage I papillary microcarcinoma in the right lower lobe (figures 3 and 4).
- Post operative testing showed improvement and a low thyroglobulin level (table 2).
- His symptoms resolved and he is being treated with levothyroxine.

Discussion

- In this case, a 60-year-old male with a known germline TTN mutation developed atrial fibrillation, hyperthyroidism, and papillary thyroid carcinoma.
- Mutations in the TTN gene may be associated with early onset atrial fibrillation. In one study, a loss of function mutation in a TTN gene was associated with increased odds of atrial fibrillation (OR 1.76 (95% CI 1.04-2.97).[4]
- The patient's hyperthyroidism was presumed to be due to his previous amiodarone use. There are two forms of amiodarone induced hyperthyroidism (AIT). Type I AIT is more likely in the presence of underlying thyroid nodules or latent Graves disease, and typically occurs early after amiodarone is started, and is due to increased thyroid hormone synthesis. Type II AIT is a destructive thyroiditis and is more likely in patients without underlying thyroid disease.
- When amiodarone induced hyperthyroidism (AIT) starts after amiodarone discontinuation, it is more likely to be due to type II AIT.[5] Despite, the timing of his hyperthyroidism, he was treated with methimazole for type I AIT due to his multinodular goiter and responded well.
- Interestingly, this patient was later discovered to have papillary thyroid microcarcinoma. A recent study by Han et al found that TTN is one of the top five mutated genes in thyroid cancer, together with BRAF, NRAS, HRAS, and thyroglobulin.[2] They also found an association between TTN mutations in thyroid cancer and worse prognosis. However, they did not distinguish between germline vs. tumor specific TTN mutations.

References

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