CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 16 (2015) 64–66

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Running in the family: A rare diagnosis of familial papillary thyroid cancer

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ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form
10 September 2015
Accepted 15 September 2015
Available online 21 September 2015

SUMMARY

INTRODUCTION: Whilst inherited medullary thyroid cancer has been extensively reported, familial non-medullary thyroid cancer is a rare and less well described clinical entity. Familial forms of the disease demonstrate more aggressive features than sporadic non-medullary thyroid cancer.
PRESENTATION OF CASE: A 54 year old lady was referred with globus on a background of a longstanding goitre. Three first degree relatives had a history of non-medullary thyroid carcinoma. Investigations revealed a papillary thyroid carcinoma and the patient proceeded to total thyroidectomy and ipsilateral Level VI neck dissection, followed by adjuvant radioiodine ablation.
DISCUSSION: Familial papillary thyroid carcinoma syndrome is defined as three or more first degree relatives diagnosed with the disease in the absence of other known associated syndromes. It is often associated with the presence of benign thyroid disorders, and is characterised by the early onset of multi-focal bilateral locally advanced tumours.
CONCLUSION: Familial papillary thyroid cancer is a rare clinical entity but should be considered where ≥3 first degree relatives are diagnosed with non-medullary thyroid cancer. It is necessary to exclude other familial tumour syndromes to make the diagnosis. It demonstrates more aggressive features with higher rates of local recurrence than its sporadic counterpart, and therefore mandates more aggressive management than might otherwise be indicated. Screening of first degree relatives should be considered.
SUMMARY: The case of a 54 year old female diagnosed with familial non-medullary thyroid carcinoma is reported.

1. Introduction

Familial thyroid cancer is conventionally divided into either medullary or non-medullary types [1]. Inherited medullary thyroid cancer has been extensively reported, either in isolation or in the setting of MEN2 syndrome.

In contrast, familial non-medullary thyroid cancer is a rare and less well described clinical entity [1]. It is a heterogeneous disease incorporating both syndromic-associated tumours and non-syndromic tumours [1]. The first group encompasses familial adenomatous polyposis (FAP), PTEN-hamartoma syndrome (Cowden's disease), Werner syndrome and the Carney complex, where thyroid cancer is not the primary tumour [1]. The second group has been defined as the presence of three or more first degree relatives with a well differentiated thyroid cancer, in the absence of another familial tumour syndrome [1]. The form of inheritance is believed to be autosomal dominant with incomplete penetrance and variable expression. Although only recently becoming elucidated, a number of subtypes have been described associated with various gene loci; these include pure familial papillary thyroid cancer, familial papillary thyroid cancer with multinodular goitre, and papillary thyroid cancer associated with renal papillary neoplasia [1].

Familial forms of the disease demonstrate more aggressive features such as early onset, multi-focality, lymphatic and vascular invasion with associated extra-thyroidal extension and extensive lymph node metastatic disease when compared to sporadic tumours [1–4]. Interestingly, it does not appear to be associated with known BRAF mutations which occur in sporadic papillary thyroid carcinoma. It is associated with a reduction in disease-free survival although overall survival appears to be unaltered [2,4,5]. Multi-modality treatment is advocated, encompassing a total thyroidectomy and ipsilateral Level VI neck dissection as well

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http://dx.doi.org/10.1016/j.ijscr.2015.09.018

Table 1
Syndromic FNMTC: inheritance and genetic loci [1].

Syndrome	Histologic type	Gene loci	Gene mutation
FAP	PTC	5q21	APC tumour suppressor gene
Cowden syndrome	FTC, PTC, C cell hyperplasia	10q23.2	PTEN tumour suppressor gene
Carney complex	FTC, PTC	2p16, 17q22–24	PRKAR1-*x*
Werner syndrome	FTC, PTC, ATC	8p11–p12	WRN

PTC, papillary thyroid carcinoma. FTC, follicular thyroid carcinoma. ATC, anaplastic thyroid cancer.

as radioactive iodine ablation and suppressive thyroid hormone therapy [6].

There is no consensus regarding familial screening. A thyroid ultrasound of unaffected adult relatives on an annual basis has been recommended by some authors while others suggest that routine physical examination in an outpatient setting is sufficient [6].

This case is important because it raises awareness of a rare disease which is not commonly encountered in clinical practice. It encourages clinicians to consider familial papillary thyroid cancer as a differential diagnosis when multiple family members are affected.

2. Presentation of case

A 54 year old lady was referred complaining of an intermittent choking sensation. She had no associated stridor, dyspnoea or dysphagia. She had no clinical symptoms suggestive of hyper or hypothyroidism. Her background history was significant for the presence of a longstanding goitre. Her medical history was otherwise non-contributory and she took no regular medications.

The patient reported that three first degree relatives had a history of well differentiated thyroid carcinoma. Her mother was diagnosed with thyroid carcinoma in her 30 s and underwent a total thyroidectomy. Accurate histological diagnosis of her thyroid was not established. Her mother also underwent a right nephrectomy for a renal cell carcinoma. Her sister was diagnosed with a papillary thyroid carcinoma aged 38 years. She underwent a total thyroidectomy and adjuvant radioactive iodine ablation. She remains disease free 2 years later. She also underwent a left nephrectomy for a non-functioning kidney secondary to vesicoureteric reflux. Her second sister was diagnosed aged 48 years and had a background history of a multinodular goitre. She underwent a total thyroidectomy for a papillary thyroid carcinoma and adjuvant radioactive iodine ablation. She subsequently developed a local recurrence nine years after her initial diagnosis and underwent further surgical resection. A number of other malignancies were diagnosed within the family but these were not consistent with any identifiable syndrome.

On examination she had a multi-nodular goitre with a dominant nodule on the right side with no associated lymphadenopathy. She proceeded to have a thyroid ultrasound and FNAC of a 1.2 cm focal nodule with internal microcalcifications. The resulting cytology was reported as Thy 5, showing features consistent with papillary thyroid carcinoma. Preoperative TFTs demonstrated a hypothyroid picture with an elevated TSH (7.67) and decreased free T4 (10.8). Serology performed a number of years prior to referral showed a negative anti-thyroglobulin antibody and an anti-microsomal antibody titre of 6400.

She proceeded to a total thyroidectomy and ipsilateral Level VI central nodal dissection. The revised American Thyroid Association guidelines recommend central neck dissection for patients with papillary thyroid cancer (Level B) as a large proportion of patients who are clinically and radiologically node negative may harbour occult regional LN metastases. Although she had a small tumour we felt that her strong family history rendered her high risk. This intervention lasted 2½ h, with no immediate post-operative complications. She was discharged 3 days from admission. The final histology demonstrated a multi-focal papillary thyroid carcinoma (8 mm focus in the right lobe and a second 1 mm focus in the left lobe) occurring on a background of Hashimoto's thyroiditis. There was no extra-thyroidal extension. Five Level VI lymph nodes were benign (pT1a(m)N0M0). Following discussion at the multidisciplinary thyroid conference, she was referred for consideration of radioiodine ablation due to the multifocal nature of disease. However, due to her low risk status and a thyroglobulin of <0.1 it was decided to omit this.

Initial follow up was at 2 weeks post discharge, and thereafter at 2, 3 and 6 month intervals. She suffered no long term complications and required minimal titration of her levothyroxine dose. TFTs on most recent review (22 months post op) were normal, with normal calcium and PTH.

In light of the strong family history of disparate malignancies the possibility of a familial tumour syndrome was considered. However, with histology confirmed in two first-degree relatives, and no distinct pattern of other malignancy consistent with a familial tumour syndrome, the final diagnosis of familial papillary thyroid cancer was made.

No genetic testing was undertaken due to the lack of a distinct identifiable syndrome.

3. Discussion

The case for a familial disposition to non-medullary thyroid carcinoma has only recently emerged and therefore the literature is limited. The first case of familial follicular thyroid carcinoma was reported in 1955, when identical twins in Kansas City underwent a total thyroidectomy and radical neck dissection [7]. A further description was found in 1975 when a 9 year old boy, with no prior environmental exposure and his mother were diagnosed [8].

Familial papillary thyroid carcinoma syndrome is defined as when three or more first degree relatives are diagnosed with the disease in the absence of other known associated syndromes. Statistically when two members of a family are diagnosed this may be as a result of sporadic tumours but when three or more members of a kindred or where men or children are involved is more

Table 2
Non-syndromic FNMTC: inheritance and genetic loci [1].

Histologic type	Inheritance	Gene loci	Candidate genes
PTC with papillary RCC	Unknown	1q21	Unknown
Familial MNG with PTC	Autosomal dominant	14q	Unknown
Familial PTC	Unknown	2q21	Unknown
Familial thyroid carcinoma with oxyphilia	Autosomal dominant	19p13.2	Unknown/TCO/T1MM44

RCC, renal cell carcinoma. MNG, multinodular goitre.

suggestive of a familial disposition. It is often associated with the presence of benign thyroid disorders, such as lymphocytic thyroiditis, multinodular hyperplasia and multiple adenomatous nodules [2,4,9,10].

It is characterised by the early onset of multi-focal bilateral locally advanced tumours. The identification of even micro-papillary tumours within this group is associated with a 71% risk of multi-focal disease, a 43% risk of vascular invasion and a 57% rate of lymph node metastasis, all statistically significantly higher than in sporadic papillary micro-carcinoma [11]. Despite the presence of adverse prognostic features, overall survival does not appear to be affected. This may be due to the fact that mortality from differentiated thyroid carcinoma remains low.

The role for screening remains controversial. It has been suggested for individuals with two affected family members a clinical history, examination and cervical ultrasound should be performed. However, the literature remains limited due to the small number of reported cases with short follow-up. This stems from the low prevalence of the disease and the difficulty in identifying appropriate cases. As the underlying genetic mutation has not been identified, widespread genetic testing is not available (Tables 1 and 2).

4. Conclusion

- Familial papillary thyroid cancer is a rare clinical entity, but should be considered where three or more first degree relatives are diagnosed with non-medullary thyroid cancer.
- It is necessary to exclude other familial tumour syndromes, where non-medullary thyroid cancer is not the primary malignancy.
- It is believed to be inherited in an autosomal dominant mode with incomplete penetrance and variable expression.
- Familial papillary thyroid cancer demonstrates more aggressive features with higher rates of local recurrence than the sporadic counterpart. Therefore it mandates more aggressive management than might otherwise be indicated.
- Screening of first-degree relatives should be considered.

Conflicts of interest

None declared.

Funding

None.

Ethical approval

Not applicable.

Consent

Written and signed consent obtained from patient to publish case report.

Author's contribution

L. O'Connell, R.S. Prichard, E. O'Reilly, E.W. McDermott—identification and write up of case.

S. Skehan, D. Gibbons—review of radiology and pathology pertaining to the case.

E.W. McDermott—operating surgeon.

Guarantor

L. O'Connell, R.S. Prichard, E. O'Reilly.

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