Rare disease

Insular thyroid carcinoma in a Filipino woman

Mark Anthony S. Sandoval, Elizabeth Paz-Pacheco

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

Correspondence to Mark Anthony S. Sandoval, markanthony_sandoval@yahoo.com

Summary

A 30-year-old Filipino woman presented with goitre of 4 years' duration. The right thyroid lobe was enlarged with no palpable lymph nodes. She had no thyrotoxic signs and symptoms.

Free thyroxine and thyrotropin were normal. Ultrasound revealed a cystic nodule on the right lobe. Fine needle aspiration biopsy was consistent with colloid nodule.

She underwent right lobectomy with extended isthmusectomy. Microscopic examination of the 6.5 cm mass showed well-defined, round, nests of tumour cells surrounded by a rim of collagen. Mitotic figures and necrosis were absent. There was capsular invasion. Immunohistochemical staining was positive for thyroglobulin and negative for calcitonin. These findings gave the diagnosis of insular thyroid carcinoma.

She underwent complete thyroidectomy with central node dissection. Five weeks after, she received 3700 MBq of radioactive iodine 131. Post-treatment, whole body scan revealed functioning thyroid tissue limited to the thyroid bed. The patient is on regular follow-up 2 years after diagnosis with no evidence of disease.

BACKGROUND

Insular carcinoma is a rare type of thyroid cancer. Diagnosis rests on the recognition of its distinct histological architecture. It is morphologically in between the well-differentiated carcinomas (papillary and follicular) and the undifferentiated carcinoma (anaplastic). It also has a prognosis intermediate between the two. Treatment is the same for the well-differentiated forms but initial aggressive treatment and close follow-up are recommended.

CASE PRESENTATION

The patient is a 30-year-old Filipino woman who had an anterior neck mass of 4 years' duration. The mass initially started as a small nodule about the size of a marble and slowly increased in size. There were no associated hyperthyroid symptoms, such as palpitations, weight loss, tremors, fatigue, heat intolerance, irritability, increased sweating or hyperdefecation. There were also no obstructive symptoms such as dysphagia and dyspnoea. She did not experience hoarseness. She consulted because of the progressive increase in size of the mass.

Pertinent in the medical history is acute hepatitis A infection, which she contracted at age 13 years. There is no history of neck irradiation. There is no family history of goitre or cancer. The patient has no vices.

Physical examination revealed an 8×8 cm doughy, non-tender mass on the right thyroid lobe. Heart rate, blood pressure and body temperature were normal. There was no exophthalmos, thinning hair, palpable cervical lymph nodes nor stridor. She had no tremors and reflexes were normal. The rest of the physical examination findings were unremarkable.

INVESTIGATIONS

Initial laboratory evaluation showed normal thyroid function. Free T4 was 18.7 pmol/l (normal range: 11–24) while

thyroid stimulating hormone (TSH) was 1.1 µIU/l (normal range: 0.3–3.8). Thyroid ultrasound done 1 year after the patient noted the anterior neck mass showed a right thyroid lobe measuring 3.4×1.5×1.8 cm, which contained a 1.6×1.6 cm cystic structure. The left thyroid lobe did not have any focal lesions and was normal in size measuring 3.1×1.1×1.4 cm. Fine needle aspiration of the nodule was initially interpreted as 'cytologic findings consistent with a colloid nodule.' However, a review of the specimen after the final histological diagnosis was made showed atypical cells. Complete blood count, serum calcium and albumin, and prothrombin and partial thromboplastin times were also normal.

DIFFERENTIAL DIAGNOSIS

Initial assessment was non-toxic single thyroid nodule (colloid nodule by fine needle aspiration biopsy; International Classification of Diseases (ICD) 10 code E04.1).

TREATMENT

She underwent right thyroid lobectomy with extended isthmusectomy. Intraoperative findings revealed an 8×7 cm well-encapsulated firm mass on the right thyroid lobe. There were no nodules palpated on the left thyroid lobes. No enlarged lymph nodes were seen. Frozen section was not performed.

There were no postoperative complications such as hypocalcaemia, hoarseness, bleeding or infection.

Gross pathological examination of the surgical specimen revealed a 100 g thyroid consisting of a 7×6×5 cm right lobe. The whole right lobe contains a well-delineated 6.5×5.5×4.0 cm ovoid yellow-brown doughy mass with a whitish rubbery centre.

Histopathological examination of the mass showed large, well-defined, round nests of uniform-looking tumour cells (figures 1–3). The nests are surrounded by a thin rim of

Figure 1 Scanning photomicrograph showing the round nests of tumour cells ('insulae') separated by hyalinised collagen and artifactual clefts. Note the microfollicle formation ($\times 40$ magnification).

Figure 2 Low power magnification showing a monotonous population of tumour cells. Note the artifactual clefts on the upper right corner, which are actually capillaries. To the left and the left bottom corner are microfollicles ($\times 100$ magnification).

Figure 3 High power magnification showing small monotonous cells with nuclei with clumped chromatin and inconspicuous nucleoli and scanty cytoplasm ($\times 400$ magnification).

Figure 4 Scanning photomicrograph showing the tumour on the right invading the capsule on the left ($\times 40$ magnification).

Figure 5 Immunohistochemical staining for thyroglobulin was positive confirming that the tumour cells are follicle cell-derived ($\times 100$ magnification).

Figure 6 Immunohistochemical staining for calcitonin was negative ruling out medullary thyroid carcinoma ($\times 100$ magnification).

hyalinised collagen and are separated by clefts. Interspersed among the cell nests are microfollicles containing colloid. The individual tumour cells are monomorphous and small. The nuclei have well-defined chromatin and inconspicuous nucleoli. The cytoplasm is scant. There were no mitotic figures seen. Necrosis was absent. However, the mass was noted to be infiltrating its capsule encroaching onto the surrounding normal thyroid tissue (figure 4). Immunohistochemical staining was positive for thyroglobulin (figure 5) and negative for calcitonin (figure 6). The histopathological findings were interpreted as insular thyroid carcinoma.

On follow-up, the patient was advised to undergo repeat surgery for complete thyroidectomy and central node dissection.

Intraoperative findings during the second surgery revealed a 4×4 cm left thyroid lobe, which did not contain any nodules. There were no grossly enlarged lymph nodes. The histopathological analysis of the specimen revealed multinodular colloid goitre on the left thyroid lobe with no residual tumour seen. Fragments of skeletal muscle, parathyroid gland and thymic tissue were seen in the excised specimen.

No postoperative complications developed.

OUTCOME AND FOLLOW-UP

Five weeks after the complete thyroidectomy, the patient received 3700 MBq (equivalent to 100 mCi) of radioactive iodine 131. Whole body iodine-131 scan done after administration of the therapeutic radioactive iodine revealed functional thyroid tissue remnants limited to the thyroid bed. There were no distant metastases seen.

The patient is maintained on levothyroxine 2.2 µg per kg body weight per day, which was started after the therapeutic administration of iodine-131. The thyroglobulin level taken 3 months after radioactive iodine treatment was low at 0.2 ng/ml indicating the absence of residual or recurrent disease. Levothyroxine was withheld for 3 weeks prior to the measurement of serum thyroglobulin levels.

Administration of recombinant human TSH (rhTSH) was offered to this patient but she chose to just temporarily withhold levothyroxine prior to iodine-131 treatment and thyroglobulin determination.

The patient is on regular follow-up and is still clinically well 2 years after the diagnosis with no evidence of loco-regional or distant metastases.

DISCUSSION

When is thyroid carcinoma labelled ‘insular carcinoma’?

Insular thyroid carcinoma is a histological diagnosis. Thus, surgical excision and submission of the specimen for histological analysis is required to come up with the diagnosis.

The descriptive term ‘insular’ means relating to or forming an island. The name of this tumour is actually derived from its histological pattern with nests of tumour cells appearing as islands. The following are the histological features of this tumour^{4 8}:

Predominant pattern solid, but microfollicles may be encountered. Lacks papillary or follicular growth patterns. Cells: monomorphous and small. Cytoplasm: scant and

eosinophilic. Nuclei: smooth to slightly irregular nuclear membranes, clumped chromatin and inconspicuous nucleoli. Mitosis. Infiltrative growth. Necrosis.

All of these features are seen in this case, except mitosis and necrosis.

The tumour cells in insular carcinoma are also derived from the follicle cell. Insular thyroid carcinoma is said to be a form of poorly differentiated thyroid carcinoma. It is morphologically in between the differentiated thyroid carcinomas (papillary and follicular) on one hand and undifferentiated thyroid carcinoma (anaplastic) on the other.¹⁰

Thyroid carcinomas are considered differentiated when there is a well-developed glandular architectural pattern. Papillary carcinoma shows finger-like projections (papillae) while follicular carcinoma shows a layer of cells (follicle) surrounding colloid material. In insular carcinoma, there is no definite glandular architecture. The histological appearance is reminiscent of the embryonic thyroid with attempts at glandular formation as shown by the presence of microfollicles. On the other extreme, there is no architectural organisation of the cells in anaplastic carcinoma.¹⁰

The well-differentiated and poorly differentiated forms express thyroglobulin while anaplastic carcinoma does not. This has practical significance since immunostaining for thyroglobulin will differentiate insular carcinoma from other tumours of similar appearance like medullary thyroid carcinoma.¹⁰ For this case, immunohistochemical analysis was positive for thyroglobulin and negative for calcitonin (figures 5 and 6). This confirms that the tumour cells are of follicle cell origin and not derived from parafollicular or C cells—the latter giving rise to medullary thyroid carcinoma.

There are clinical and histological features that need to be considered that have clinical prognostic significance. Age, presence of at least 3 mitoses per 10 high power fields (HPFs) and presence of necrosis have been shown to be correlated with poorer survival. Volante and co-workers have come up with a scoring system that gives a numerical score for each of these prognostic features. Presence of necrosis carries the biggest weight with a score of 3, while age and presence of at least 3 mitoses per 10 HPFs carry 1 score each. A higher total score portends a poorer survival rate.¹¹

Our case was only 30-years-old when diagnosed. There were no mitoses or necrosis seen on histological examination; thus, her score is 0. The survival of those with a score of 0–1 is similar for those with papillary and follicular carcinoma.¹¹

How common is it?

Published literature have shown that insular carcinoma represents only 3.0–6.2 % of all thyroid tumours.^{1 6}

In the Philippine General Hospital, a review of 1500 thyroidectomy specimens over 3 years (2005–2007) revealed one other definite case of insular carcinoma with lymph node metastases and two suspected cases for which immunostaining was recommended. Of the two suspected cases, one was found to be medullary carcinoma clinically on the basis of an elevated serum calcitonin. The other suspected case was labelled as a poorly differentiated carcinoma in the cervical lymph nodes for which immunostain for neuron-specific enolase, thyroglobulin, cytokeratin and thyroid transcription factor-1 (TF-1) was suggested but was not done.

There is no published case report or case series of insular thyroid carcinoma in the Philippines based on the Philippine Index Medicus from 1917 up to 2007.

How is insular carcinoma different from other thyroid cancers in terms of clinical behaviour?

Diagnosing insular carcinoma correctly is of clinical significance because this tumour behaves differently compared to the more frequently encountered well-differentiated thyroid carcinoma.³

Insular carcinoma has been shown to have more frequent lymph node metastasis compared to follicular carcinoma, and has more frequent distant metastasis than both papillary and follicular carcinomas.⁹

Comparison of the survival rates of well-differentiated carcinoma (papillary and follicular) and those of poorly differentiated carcinoma (trabecular, insular and solid patterns) showed that the latter group had poorer survival rates.^{9–11} The insular histotype represented half of the cases in the poorly differentiated group. Based on a Kaplan-Meier estimate of survival, 80% of patients with well-differentiated carcinomas would still be alive after 240 months (20 years), while 60% would remain alive for the poorly differentiated carcinoma group after that same time period. In contrast, no patient is expected to survive more than 30 months in anaplastic carcinoma.¹¹

Therefore, insular thyroid carcinoma is intermediate between the differentiated carcinomas and undifferentiated carcinoma both in terms of the degree of morphological differentiation and clinical prognosis.¹¹

Is insular carcinoma managed differently from the other thyroid cancers?

To date, there are no clinical trials addressing this question mainly because this is a rare disease entity. Insular thyroid carcinoma is treated in the same way as the differentiated carcinomas with the suggestion that there would be aggressive initial treatment and closer follow-up. However, it is not yet known whether this current practice is indeed the optimal treatment regimen.⁹

Five weeks after the completion thyroidectomy, our patient received 3700 MBq (equivalent to 100 mCi) of RAI-131. Whole body iodine-131 scan done after the administration of the therapeutic RAI revealed functional thyroid tissue remnants limited to the thyroid bed. There were no distant metastases seen.

Metastases are expected to take up iodine-131.^{5–12} Therefore, physicians can use the whole body iodine-131 scan to check for distant spread. In the series by Justin and co-workers, there were four patients with histologically confirmed insular carcinoma in whom metastases were localised postoperatively with iodine-131. These metastases were confirmed by performing a radiographic procedure (x-ray or CT scan).

The patient was maintained on levothyroxine 2.2 µg per kg body weight per day, which was started after the therapeutic administration of iodine-131. Thyroglobulin level taken 3 months after RAI treatment was low at 0.2 ng/ml indicating the absence of residual or recurrent disease. Levothyroxine was withheld for 3 weeks prior to the measurement of serum thyroglobulin levels.

Bombardier *et al* suggested that administration of rhTSH can be used in patients with insular carcinoma because of its

clinical aggressiveness so that there will be no need to stop intake of levothyroxine prior to RAI treatment or monitoring of thyroglobulin levels.² In the Philippines, rhTSH is not readily available and is expensive. Administration of rhTSH was offered to this patient but she chose to just temporarily withhold levothyroxine prior to iodine-131 treatment and thyroglobulin determination.

The patient is on regular follow-up and is still clinically well 2 years after the diagnosis with no evidence of loco-regional or distant metastases.

Learning points

- ▶ This rare thyroid malignancy is diagnosed based on a distinct histological pattern.
- ▶ It is morphologically in between the differentiated thyroid carcinomas (papillary and follicular) and undifferentiated (anaplastic) carcinoma.
- ▶ This tumour behaves differently compared to the differentiated thyroid cancers in the sense that loco-regional and distant metastases occur more frequently and that long-term survival is somewhat poorer.
- ▶ The clinical behaviour and prognosis is still more favourable than that of anaplastic carcinoma.

Competing interests None.

Patient consent Obtained.

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