CASE REPORT

Insular carcinoma arising on a background of follicular carcinoma, thyrolipomatosis and amyloid goitre

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Accepted 17 May 2017

SUMMARY

A 67-year-old man was referred with a history of a right-sided neck lump and dysphonia, secondary to a lesion in the thyroid gland. After undergoing a total thyroidectomy, he was found to have an exceedingly rare combination of follicular carcinoma, insular carcinoma, thyrolipomatosis and an amyloid goitre in his thyroid gland. He subsequently underwent further radioactive iodine ablation and has been in remission. He was also later incidentally diagnosed with systemic amyloidosis, which explained the amyloid deposition in his thyroid gland.

BACKGROUND

Diffuse thyrolipomatosis is an extremely rare condition characterised by diffuse infiltration of the thyroid stroma by mature adipose tissue.[1 2] Fewer than 15 cases have been reported in the literature since its first description by Dhayagude in 1942.[3] It has been associated with systemic amyloidosis, where the fat deposition produces an 'amyloid goitre.'[4] To date, only two cases have been associated with carcinomas, both being the papillary subtype.[1 5]

Insular carcinoma (also known as poorly differentiated thyroid carcinoma, PDTC) is an uncommon subtype of thyroid cancer that lies both morphologically and behaviourally between well-differentiated and undifferentiated/anaplastic carcinomas.[6 7] They make up about 1.8%–15% of all thyroid carcinomas, and are generally poorly understood due to their rarity.[8 9]

Here, we describe the first known case of a PDTC arising completely within a follicular carcinoma, on a background of diffuse thyrolipomatosis with amyloid deposition, likely secondary to Amyloid A (AA) amyloidosis. Neither of these tumours has been associated with diffuse thyrolipomatosis.

CASE PRESENTATION

A 67-year-old man was referred to the otolaryngology service with a 2-week history of dysphonia and right-sided neck lump. This was discovered incidentally while the patient was admitted to hospital for dyspnoea secondary to bronchiectasis. The man was otherwise asymptomatic and had no signs of thoracic inlet obstruction. The patient suffered from chronic renal impairment, which was thought to be secondary to hypertension.

INVESTIGATIONS

An ultrasound of the neck showed a 42×42×37 mm homogeneous nodule in the right thyroid lobe. The thyroid gland was enlarged, with an estimated volume of 186 mL. There were no microcalcifications on the ultrasound scan. A CT scan of the neck again demonstrated this lesion, which was hyperdense with central hypodensity. There was diffuse fatty conversion of the thyroid parenchyma (figure 1). There was no cervical, mediastinal or hilar lymphadenopathy on the CT scan. A fine needle aspiration biopsy of the nodule was non-diagnostic. The thyroid function tests were within normal limits.

Due to the suspicious radiological appearance of the nodule on CT and ultrasound, a right hemithyroidectomy was performed to obtain a histological diagnosis, with a view of proceeding to a staged completion thyroidectomy pending histological confirmation of malignancy. Intraoperatively, the right thyroid lesion was found to have central necrosis. The lesion was not invading the recurrent laryngeal nerve or trachea.

The histological examination of the right hemithyroid showed a 45×40×35 mm nodule. The lesion was consistent with a follicular carcinoma, showing signs of lymphovascular invasion. Within

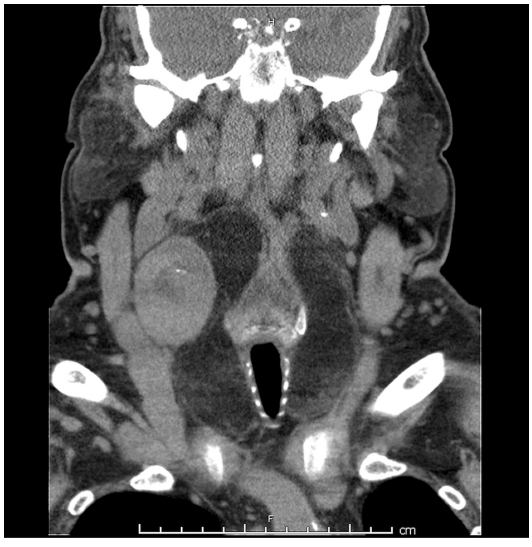

Figure 1 Coronal section of the patient's neck CT scan, demonstrating the large fatty goitre and a solid lesion in the right lobe of the thyroid.

To cite: Loh TL, Latis S, Ali RB, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-219747

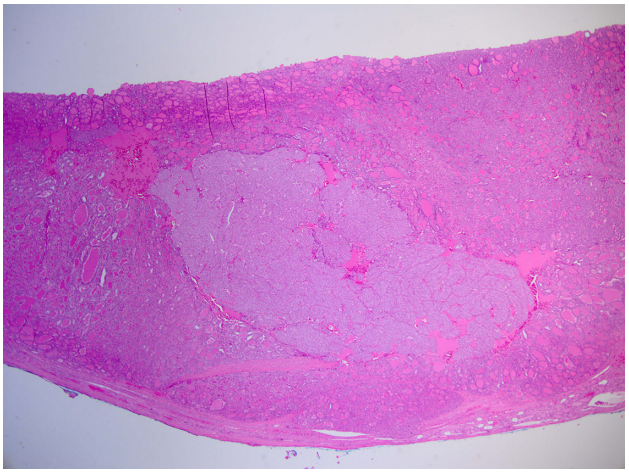

Figure 2 Insular carcinoma completely surrounded by follicular carcinoma.

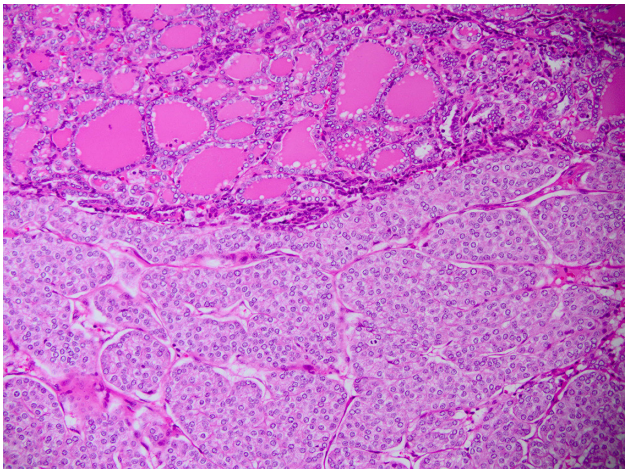

Figure 4 Close-up of both insular (bottom) and follicular (top) carcinomas.

the follicular neoplasm, there was also a patchy distribution of solid nests, islands and trabeculae punctuated by variable numbers of small abortive follicles (figures 2–4). The tumour cells within these areas stained positive for HBME-1 and thyroid transcription factor-1 (TTF-1). Chromogranin, synaptophysin and carcinoembryonic antigen (CEA) staining were all negative. There were no signs of extrathyroidal extension. Based on the AJCC guidelines (seventh edition), this was in keeping with a pT2 N0 insular/PDTC arising within the follicular carcinoma.[10]

Outside of the thyroid nodule, the thyroid gland showed follicles within a stroma that had diffuse adipose tissue infiltration, that is, thyrolipomatosis. Moreover, there was also abnormal amyloid deposition within the perifollicular areas (figure 5). Further staining of this favoured AA-type amyloidosis over the amyloid light-chain (AL) type. Investigations for chronic inflammatory conditions were negative.

TREATMENT

A subsequent completion left hemithyroidectomy was performed after the histological diagnosis of malignancy, largely due to the high-risk histological features identified on the initial hemithyroidectomy. There were also diffuse thyrolipomatosis and amyloid deposition but no signs of malignancy in the left thyroid lobe. The immediate postoperative recovery was complicated by post-thyroidectomy hypocalcaemia, which stabilised with calcium supplementation. Due to the intermediate-high risk for recurrence in PDTC, the patient then completed a course of adjuvant I-131 radioablative therapy (3623 mBq) 1 month after the completion thyroidectomy. He was also commenced on thyroid stimulating hormone (TSH) suppression therapy—thyroxine doses were titrated against thyroid-stimulating hormone levels, aiming for a TSH level of less than 0.1 for 10 years.[11]

OUTCOME AND FOLLOW-UP

After the therapy, surveillance was performed clinically and also with thyroglobulin monitoring. There have been no signs of recurrence at 1 year from the initial surgery. Incidentally, he had a renal biopsy 3 months after the thyroidectomy due to a deterioration of his renal function. The biopsy was consistent with AA amyloid nephropathy. No chronic inflammatory disease has been found on screening investigations to date.

DISCUSSION

According to the Turin criteria, PDTC is recognised by the presence of (1) a solid/trabecular/insular growth pattern, (2) absence of conventional nuclear features of papillary carcinoma, and

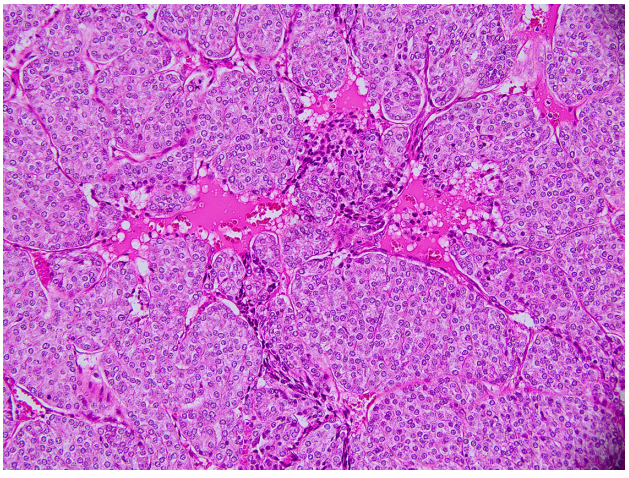

Figure 3 Close-up of insular carcinoma, showing high mitotic activity and an insular growth pattern.

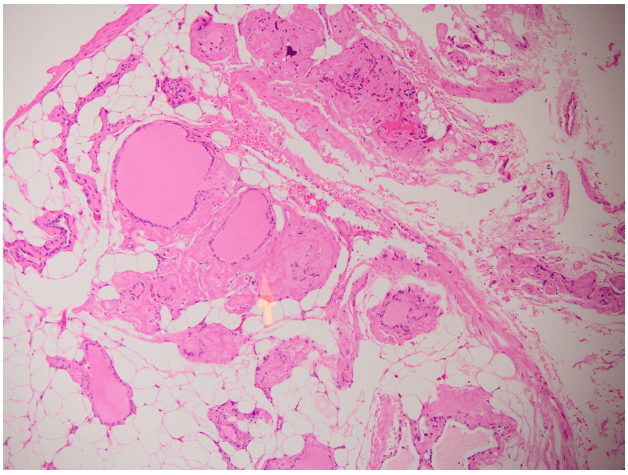

Figure 5 H+E stained section of the thyroid parenchyma not involved by cancer. Diffuse adipose infiltration of the parenchyma is seen. The yellow arrow shows amyloid protein deposition.

(3) presence of convoluted nuclei, mitotic activity or necrosis.[12] PDTC has generally been associated with poorer outcomes than well-differentiated carcinomas, with a 5-year disease-specific mortality rate ranging from 17% to 34% in the literature.[8 12–14] PDTCs that do not produce thyroglobulin or take up radioiodine have a worse prognosis.[15] These tumours are known to arise de novo or from pre-existing follicular and papillary carcinomas, although little is known about the specific boundaries and relationships between well differentiated and PDTC.[12] In this case, the complete nesting of the PDTC within the follicular carcinoma would suggest dedifferentiation of the follicular neoplasm into PDTC. Unfortunately, we were unable to obtain further immunohistochemical analysis to further substantiate this.

Amyloid deposition in the thyroid gland is a known phenomenon, commonly seen in medullary thyroid carcinoma.[16] This usually occurs when the excess calcitonin produced by the neoplastic C cells aggregates into insoluble fibrils. Rarely, systemic calcitonin amyloidosis has been reported in medullary thyroid carcinoma.[17] Systemic amyloidosis is more commonly seen in excess production of immunoglobulin light chains (AL amyloid) in plasma cell neoplasms, or less frequently, an excess of acute-phase proteins (serum amyloid A associated, or AA amyloid). Rarely, the excess of acute-phase proteins that causes AA amyloidosis is associated with malignancies, typically renal cell carcinoma and Hodgkin's lymphoma. However, AA amyloidosis has been described in a wide variety of other carcinomas, such as that of the bladder, uterus and the oesophagus.[18] In this patient's case, it is possible that the AA amyloidosis could have arisen as a result of the chronic inflammation precipitated by the thyroid malignancy.

The mechanism of fatty infiltration of the thyroid gland in systemic amyloidosis is unclear. Based on observations in other solid organs, Schröder *et al* had suggested that ischaemia due to capillary destruction by amyloid deposition triggers metaplasia of stromal fibroblasts, causing a fatty change.[19] In this case, the presence of an invasive neoplasm may have further contributed to this via vascular invasion. Apart from the thyroid carcinoma, there were no other inflammatory or infective conditions found on investigation. It is uncertain whether the thyroid cancer may have precipitated the AA amyloidosis and thyrolipomatosis. Interestingly, despite the multiple pathologies in this case, the oncological outcome was good.

Learning points

- Suspicious thyroid nodules should be investigated promptly with a combination of clinical examination, imaging and, when indicated, biopsies.
- Poorly differentiated thyroid carcinoma is an aggressive type of thyroid cancer that can arise from follicular carcinoma.
- Thyrolipomatosis is a rare condition that can occur in amyloidosis and can present as a goitre—its mechanism of pathogenesis is unknown but may be related to hypoxia, and in this case, possibly malignancy.
- The presence of amyloid in the thyroid gland, on a background of undiagnosed chronic renal impairment, should raise suspicion for systemic amyloidosis

Contributors TLL: drafting and primary author of manuscript. HP, SL, RBA: revision and editing of manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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