histological features.[10] Patients with ectopic tumours following complete surgical resection were reportedly free of recurrence for a period of 6–24 months. In April 2018, our patient was disease free, 26 months after neck dissection and 23 months after chemoradiation treatment.

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Parasitic nodules of thyroid: some insights into the origin and early evolution

Sir,
Parasitic nodule (PN) of the thyroid, also known as sequestered, detached or accessory thyroid nodule, is a peripheral nodule of goitre that is anatomically separate from the main thyroid gland. Spontaneous detachment of thyroid tissue may occur in nodular goitre, Hashimoto's thyroiditis (HT), and Graves' disease. Alternatively, PN may represent concurrent hyperplastic changes in accessory thyroid tissue, i.e., portions of thyroid which did not fuse with the main gland during embryological development. Less than 100 cases of PN have been described in the literature, with the largest series reported by Rodriguez and Rosai.[1] Most PNs are single, located separate but close to the thyroid gland (<1 cm). Size can vary from a few millimeters to 6.5 cm.[1] Sometimes a fibrovascular pedicle connecting to the main thyroid can be discovered after careful dissection at surgery. The main practical significance is that PN needs to be differentiated from nodal metastasis of thyroid cancer.

It is believed that the main mechanism of PN formation is the mechanical action of neck muscles, which may separate the portion of goitrous thyroid extending through the fascia.[2] As a result, histological appearance of PN usually mirrors that of the main thyroid, frequently showing changes compatible with nodular goitre, HT or Graves' disease. The variable size of PNs suggests that in some cases large-sized nodules can separate from the thyroid, while in other situations subcentimetre nodules may detach early and undergo further growth in size supported by autonomous vascularisation. PNs can obtain blood supply from the thyroid via a thin fibrovascular pedicle, or from the surrounding soft tissues.

Recently, we reviewed a large series of neoplastic and non-neoplastic thyroid surgical specimens enrolled in the biomarkers project[3] and could identify 10 PNs sized 3–20 mm. This series of detached nodules along with the corresponding main thyroid gland was analysed in order to determine common histological features associated with the formation of PNs. Diagnostic criteria were as per recommendations of

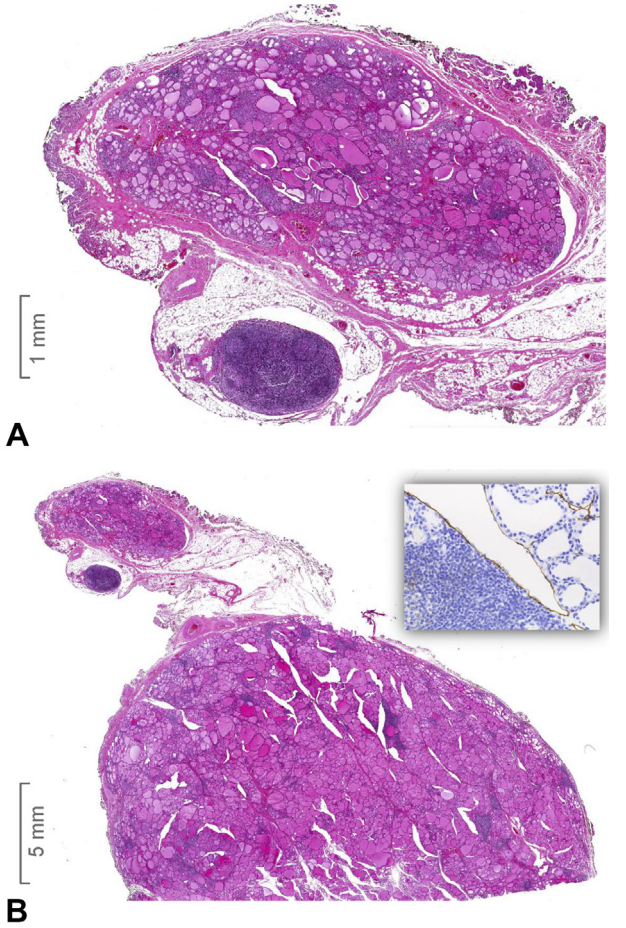

Fig. 1 Representative microscopic appearance of thyroid parasitic nodule. (A) A nodule of thyroid tissue enclosed by a thin capsule (H&E); note the perivascular location and intranodular vessel providing blood supply. (B) Parasitic nodule is located at a distance from the main thyroid (H&E); the latter shows signs of Hashimoto's thyroiditis, stromal septation by thin fibrous bands, and tissue clefting. Note that essentially similar features are found in the nodule in A. Inset: Cracking space lined by endothelium decorated by D2-40 immunostaining.

Table 1 Characteristics of patients with 10 parasitic thyroid nodules

Case	Age	Sex	Surgery	Histopathological diagnosis	Background condition	Side	Gross report	Nodule size, mm	Adjacent vessel	Tissue clefting[a]	Chronic thyroiditis[a]	Stromal septation[a]
1	26	F	Lobectomy	FA Onco + HT	HT	Right	Lymph node	11 + 6	−/+[b]	+	+	−
2	35	F	TTx	Graves + PmC	Graves	Left	Unremarkable	6.5	+	+	+	+
3	55	F	TTx	PTC + HT	HT	Right	Unremarkable	3	+	+	+	+
4	33	F	Lobectomy	HT + PTmC	HT	Left	Unremarkable	3 + 5	+	+	+	+
5	61	F	Lobectomy	PTC + MNG	MNG	Left	Separated mass	20	−	−	−	−
6	52	F	Lobectomy	FA	HT	Right	Unremarkable	5	+	+	+	+
7	15	F	TTx	Graves	Graves	N/A	Lymph node	10	+	+	+	−
8	50	M	TTx	Graves	Graves	Right	Unremarkable	5	+	+	+	+

FA Onco, oncocytic follicular adenoma; HT, Hashimoto's thyroiditis; MNG, multinodular goitre; N/A, not available; PTC, papillary thyroid carcinoma; PTmC, papillary thyroid microcarcinoma; TTx, total thyroidectomy.
[a] Main thyroid.
[b] Corresponds to 11 mm (−) and 6 mm (+) nodules from the same case.

Rosai *et al.*, i.e., no evidence of lymph node structures, PN should be in the same fascial plane as thyroid gland and exhibit a similar histological appearance as the main gland.[4] In addition, presence of intranodular artery (Fig. 1A) was required, as per our own considerations. Peri-isthmic nodules (usually submillimetre) were excluded because this anatomical region is known to be a common ground for ectopic thyroid tissue.

Ten cases of PN from one male and seven female patients, mean age 40.9 years (Table 1), were retrieved from the archive of the Department of Pathology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Mean size of PN was 7.5 mm; most of the nodules were not detected during a gross examination; however, two PNs were labelled by a surgeon as lymph nodes and another one as 'separated mass' in multinodular goitre. Half of the patients were operated on for thyroid tumours (Table 1). Background conditions predisposing to formation of PNs were HT ($n = 4$), Graves' disease ($n = 3$), and nodular goitre ($n = 1$). All PNs displayed a histopathological appearance identical to the background condition of the main thyroid gland (Fig. 1B). There was no histological evidence of malignancy in PNs, such as papillary pattern of growth or papillary carcinoma-type nuclei. We found that several microscopic features, including perivascular location, tissue clefting, and stromal septation, were consistently associated with the formation of PNs (Table 1, Fig. 1). These findings confirm that mechanical action plays a major role in the origin of PNs.

We suppose that contraction of cervical muscles is important for detachment of large PNs and their further descent or migration in the neck. More delicate mechanical

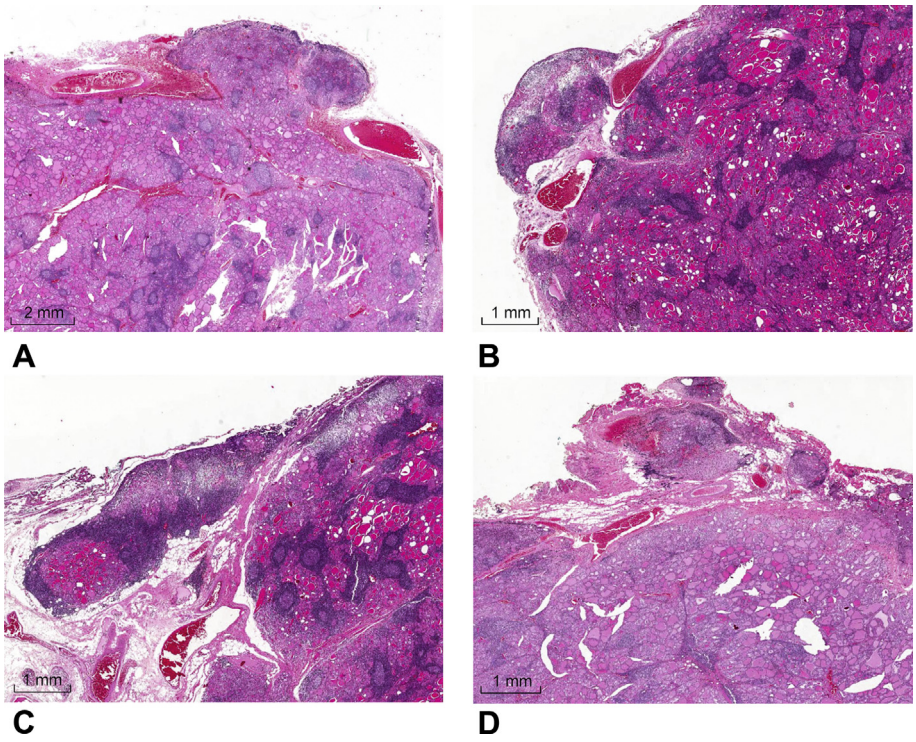

Fig. 2 Evolving detachment of thyroid tissue in Hashimoto's thyroiditis (H&E). (A,B) A small nodule of thyroid tissue protrudes between vessels. (C,D) Separated nodules immediately adjacent to the thyroid gland. Detaching nodules are either connected to the capsule (A, wide base; B, narrow strip) or lie beyond it (C,D). (A−D) Main thyroid with Hashimoto's thyroiditis and (A,D) tissue clefting. (A−D) Blood vessels in the vicinity of the nodules are well appreciated. (C) Note that detached nodule may contain abundant lymphoid component mimicking lymph node.

oscillations may play a role in budding of small nodules. This suggestion was prompted by the finding that the majority of PNs in our series (7/10) were located in close proximity to small arteries on the gland surface (Fig. 1). We reviewed additional archival cases of HT ($n = 32$) without apparent PNs with special attention to microscopic changes around the superficial vascular network. It was found that small nodules of thyroid tissue may protrude between or around blood vessels (Fig. 2A,B) and later evolve into completely detached nodules lying beyond the thyroid capsule (Fig. 2C,D). Such microscopically detached small nodules are mainly lacking their own artery and therefore have a high chance of regressing, however acquisition of autonomous vascularisation may promote growth of true PN, which becomes grossly separated.

In addition, the vast majority of cases in our series of PNs showed histological signs of chronic lymphocytic thyroiditis (7/8 patients) with moderate-to-marked inflammatory infiltrate and formation of lymphoid follicles in the main thyroid. This was seen in all cases of clinically confirmed HT and Graves' disease. Five of these seven cases demonstrated apparent septation of parenchyma ranging from thin fibrous bands to evident nodularity, which can be considered as another predisposing factor to margination and detachment of PNs.

We also noted prominent tissue clefting (Fig. 1B) in the main thyroid of seven patients. Such phenomenon, alternatively known as retraction clefts, cracking spaces, or separation artifact, is well documented in HT. Di Tommaso *et al.* showed that the cracking spaces in HT are mainly lymphatic vessels and represent a characteristic feature of autoimmune thyroid diseases.[5] We performed immunohistochemical staining with the anti-D2-40 antibody (Nichirei Bioscience, Japan) on paraffin sections of thyroids associated with PNs using a Dako Autostainer Link 48 (Dako, USA). It was confirmed that a surface of the cracking spaces is lined by D2-40 positive endothelium of lymphatics (Fig. 1B, inset). Tissue clefting, in the same manner as parenchymal septation, is a definitive mechanical factor facilitating formation and detachment of PNs.

In conclusion, we identified previously unreported histological features predisposing to the formation of PNs of the thyroid. It appears that constant pulsation of pericapsular blood vessels coupled with parenchymal septation and tissue clefting in HT and Graves' disease or nodularity in multinodular goitre are early events associated with the detachment of small marginally-located thyroid nodules. Further growth and migration of PNs is dependent on the acquisition of autonomous vascularisation and mechanical action of neck muscles.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

APPENDIX A. SUPPLEMENTARY DATA

Virtual slides are available for this article:

Case 2 https://nagasaki.pathpresenter.net/publicdisplay/DisplayCase/2b6a8e21-7dbc-4505-8632-92d5991db5e5.

Case 5 https://nagasaki.pathpresenter.net/publicdisplay/DisplayCase/91fd9bbd-16d2-43b0-97f7-ac6f84a8e52d.

Case 7 https://nagasaki.pathpresenter.net/publicdisplay/DisplayCase/6abfdfec-591c-4735-a561-cdead121c35d.

Budding of parasitic nodule https://nagasaki.pathpresenter.net/publicdisplay/DisplayCase/2f255084-fa5b-463f-88fb-83942059033b.

D2-40 expression in HT with tissue clefting https://nagasaki.pathpresenter.net/publicdisplay/DisplayCase/2177FD67-283B-43AF-B16D-0F97B7CD7079.

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