Vascular Proliferation of the Thyroid: Potential Histopathological Pitfalls as a Consequence of Fine Needle Aspiration

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Keywords

Thyroid · Neovascularisation · Angiogenesis · Vascular proliferation · Histologic alterations · Fine needle aspiration biopsy · Haemangioma · Angiosarcoma

Abstract

Objective: Fine needle aspiration biopsy (FNAB) can cause reactive histopathological changes, commonly including haemorrhage and granulation tissue. The literature describing vascular proliferation after FNAB is sparse. We aimed to describe neovascularisation in thyroid gland specimens as a consequence of FNAB. **Study Design:** We analysed all thyroid histopathological specimens from the Fimlab Laboratories collected between 2010 and 2013 for neovascularisation and distortions in the accompanying tissue. We evaluated HE-stained slides and CD31-, podoplanin-, and Ki-67-immunostained slides. **Results:** We observed vascular proliferation in 64 out of 787 specimens (8.1%). In these patients, the mean age was 62 years, 43 were female and 21 were male. Previous FNAB data were available in 49 cases (76.6%). In 51 cases (79.7%), the neovascularisation occupied less than 5% of the thyroid gland area. The vessel dilatation was moderate in 28 cases (43.8%) and low in 20 cases (31.3%). In tumours, neovessels were detected within the tumour and in the surrounding tissue. **Conclusions:** Post-FNAB tissue samples in-

clude dilated newly formed vessels, which pathologists should differentiate from rare thyroid vascular tumours. The proposed mechanism is a traumatically induced haemorrhage followed by haematoma and thrombosis that resolves by recanalisation. A knowledge of tissue alteration is needed to avoid misdiagnoses.

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Introduction

Fine needle aspiration biopsy (FNAB) of the thyroid gland is a well-established, safe, and rapid method for the management of thyroid nodules [1, 2]. Thyroid FNAB is useful for selecting patients who need surgical treatment [3, 4]. Clinical complications of FNAB include haematoma formation and acute airway obstruction, which are fortunately uncommon [5, 6].

Previous studies have characterised FNAB needle tract-related histopathological changes in various organs, including lymph nodes, salivary glands, parathyroid glands, and breast [7–10]. The most common change is

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infarction or necrosis [11–13]. Dissemination of malignant cells during FNAB is rare, as was reviewed by Polyzos and Anastasilakis [14].

In 1994, LiVolsi and Merino [15] described worrisome histologic alterations following fine needle aspiration of the thyroid (WHAFFT). Several subsequent studies confirmed their observations [16–19]. Thyroid FNAB-related histopathological changes often include haemorrhage, fibrosis, granulation tissue, and necrosis [15–21]. Necrosis and infarction of the thyroid gland had already been described before the WHAFFT concept, mainly as case reports and case series [22, 23].

Vascular changes as a consequence of FNAB have been infrequently described [15–17, 24, 25]. They include haemangioma-like vascular proliferation, angiosarcoma-like proliferation, papillary endothelial hyperplasia, and thrombosis with recanalisation [16, 17, 20]. Notably, thyroid vascular tumours such as haemangioma and angiosarcoma are remarkably rare [26].

The present study aimed at describing the frequency and histopathological characteristics of vascular proliferation in histopathological specimens from the thyroid gland, and its possible relation to previous FNAB. Here, we present a detailed analysis of 64 cases covering a 4-year period.

Materials and Methods

The study was conducted at the Department of Pathology, Fimlab Laboratories, Tampere University Hospital, and was approved by the local ethical committee. We reviewed all total thyroidectomy and thyroid lobectomy samples obtained between January 2010 and December 2013 ($n = 787$) for vascular proliferation. The surgical specimens were routinely fixed in 10% formalin and processed into paraffin blocks. The tumour cases were totally blocked. In goitre cases, all nodules were sampled and there was a minimum

of 3 blocks per lobe. Sections of 4 μm were stained with haematoxylin and eosin (HE). We performed additional immunostainings with primary antibodies detecting the endothelium (CD31, dilution 1:400, clone JC70A; DAKO Denmark, Glostrup, Denmark), lymphatic endothelium (podoplanin, dilution 1:200, clone D2–40; DAKO Denmark), and proliferation (Ki-67, clone MIB-1, dilution 1:200; DAKO Denmark). We used a fully automated immunostaining system (Bondmax; Leica Biosystems Newcastle Ltd, Newcastle-upon-Tyne, UK).

Neovascularisation was further analysed for localisation within the thyroid gland, the total area and the dimension of the vessels, as well as endothelial characteristics. Also, we evaluated the presence of haemorrhage, thrombosis, fibrin deposits, oedema, fibrosis, necrosis, granulation tissue, and cystic degeneration in the tissue around the neovessels.

We used IBM SPSS (version 21.0) for statistical analysis. Significant associations were defined using the χ^2 test.

Results

Out of 787 thyroid specimens, vascular proliferation was found in 64 cases (8.1%). The study population consisted of 43 females and 21 males aged 21–88 years (mean age 62 years). The histopathological diagnoses were papillary carcinoma in 6 cases, follicular carcinoma in 7 cases, follicular adenoma in 25 cases, and nodular goitre in 26 cases. In addition to these main diagnoses, Hashimoto thyroiditis was diagnosed in 16 cases. Oncocytic metaplasia was found in 28 cases, with oncocytic tumour variants that included oncocytic papillary carcinoma in 3 cases, oncocytic follicular carcinoma in 4 cases, and oncocytic follicular adenoma in 15 cases.

Data on the preceding FNAB date and diagnosis were available in 49 cases (76.6%). The frequency of FNAB availability and the distribution of the main diagnoses were comparable between the studied cases and the rest of the department specimens.

Fig. 1. Histopathological and immunohistochemical characteristics of vascular proliferation. **a** Dilated thin-walled capillaries surrounded by haemorrhage and cystic degeneration in nodular goitre. HE stain. Original magnification $\times 40$. **b** Dilated, mainly blood-filled capillaries in a fibrin-rich haemorrhagic area in nodular goitre. HE stain. Original magnification $\times 40$. **c** The case of follicular adenoma: dilated vessels with fibrin-rich walls represent arteriole/venule levels. HE stain. Original magnification $\times 20$. **d** Area of oedema, haemorrhage, and onion-like fibrin deposits surrounding dilated capillaries in follicular adenoma. HE stain. Original magnification $\times 20$. **e** Clusters of dilated capillaries in a haemorrhagic area in an oncocytic variant of follicular adenoma. HE stain. Original magnification $\times 40$. **f** A thrombotic vessel in the vicinity of papillary carcinoma. HE stain. Original magnification $\times 100$.

g Thick-walled, fibrin-rich, CD31-positive vessels in follicular carcinoma. CD31 immunohistochemistry. Original magnification $\times 40$. **h** Numerous irregular venules or arterioles revealed CD31 positivity in nodular goitre. CD31 immunohistochemistry. Original magnification $\times 40$. **i** Dilated irregular capillaries showed features of branching in another goitre case. CD31 immunohistochemistry. Original magnification $\times 100$. **j** Irregular thickened walls of newly formed vessels in a goitre case. CD31 immunohistochemistry. Original magnification $\times 200$. **k** No lymphatic vessels were found in vessel-rich areas. Podoplanin immunohistochemistry. Original magnification $\times 100$. **l** Proliferation activity as detected with Ki-67 antibody was sparse in newly formed vessels. Ki-67 immunohistochemistry. Original magnification $\times 100$.

(For figure see next page.)

Radiologists performed ultrasound-guided FNABs with 22-G needles. In 40.8% of the cases, FNAB was taken less than 2 months before surgery, and in total the FNAB time frame ranged from 1 month to 2 years. The dilatation of neovessels correlated with the FNAB time span, but no statistical difference was found for the total vessel area. In 9 cases, FNAB was repeatedly taken twice and in

1 case was taken 3 times. The data were unavailable in 15 cases (23.4%) because information was not available for FNABs obtained in private clinics or other regions.

The observed vessels were capillaries, venules, and arterioles. The vessel shapes were irregular and dilated, and they were mainly clustered (Fig. 1a–f). The endothelium was positive for pan-endothelial marker CD31 (Fig. 1g–

Fig. 2. Co-presence of haemorrhage, oedema, fibrin deposits, and cystic degeneration with vascular proliferation in the presented study.

j), but negative with lymphatic endothelium marker podoplanin (Fig. 1k) [27]. We did not find mitoses or nuclear atypia in the endothelium. No proliferation activity was detected with Ki-67 in the endothelium and the tissue surrounding vascular structures (Fig. 1l).

The newly formed vessels were characterised by dilatation, branching, and sprouting with local endothelial irregularities. The neovessel areas varied among the cases. The area reached 80% of the thyroid gland tissue sections in only 1 case. In 51 cases (79.7%), the neovascularisation occupied less than 5% of the thyroid gland area. In all cases without FNAB data, the area was <5% and accompanying changes were limited. It is noteworthy that in 34.7% with FNAB data available, the neovascularised area was $\geq 5\%$ ($p = 0.008$). According to the main diagnoses, in 21 out of 24 nodular goitres, the area was less than 5%.

We differentiated the vessel dilatation into 3 grades, which were high grade in 16 cases (25.0%), moderate grade in 28 cases (43.8%), and low grade in 20 cases (31.3%). The accompanying inflammatory infiltrates of Hashimoto thyroiditis did not influence the vessel characteristics, dilatation, or total area. In fact, the neovessels were not localised in the inflammatory areas.

We found vascular changes within the tumour in 92.0% of adenomas and 61.5% of carcinomas ($p < 0.001$).

The surrounding tissue harboured vascular changes less often, but still with remarkable frequency. Similarly, in nodular goitres, we found neovascularisation within the nodules.

In the majority of the cases in which we observed haemorrhage (90.6%), oedema (84.4%), fibrin deposits (79.7%), and cystic degeneration (65.6%), the FNABs were taken less than 2 months before surgery. Figure 2 shows clustering of the changes.

Surprisingly, we found thrombosis only in 4 cases (6.3%; Fig. 1f) and necrosis in 3 cases (4.7%). Necrotic lesions did not correspond to areas with oncocytic metaplasia. We observed fibrosis in 32.8% of the cases.

Discussion

The thyroid gland is a highly vascularised organ [28]. Vascular endothelial growth factor levels are also high in the thyroid tissue [29]. The diagnostics of thyroid vascular lesions are not straightforward. The heterogeneous disease spectrum consists of reactive lesions like benign endothelial proliferation, benign haemangiomas, and extremely rare malignant angiosarcomas [26]. Table 1 represents a literature review of thyroid haemangiomas. Outside the endemic alpine area, angiosarcomas and malignant haemangioendotheliomas are uncommon [44, 45]. Table 2 summarises various non-tumourous vascular lesions, which are not related to FNAB [46–49].

Several studies have described the relation of FNAB and vascular proliferation [15–19, 24, 25, 50] (Table 3). In the WHAFFT concept article, however, only dilated vessels were mentioned [15]. Erzös et al. [16] found vascular proliferation and thrombosis in 45% of thyroids that were aspirated, but they did not find these changes in non-aspirated cases. In contrast, Bolat et al. [18] reported vascular changes in only 2.7% of studied thyroids. In another series, 10 out of 102 thyroids showed vascular changes, led by thrombosis and recanalisation in 5 cases [17]. It is noteworthy that, in contrast to our data, all the cases of vascular changes were associated with necrosis. Our own necrosis cases were not accompanied by neovascularisation [21].

Interestingly, Pandit and Phulpagar [17] also showed angiosarcoma-like alterations in a specimen 147 days after FNAB. Erzös et al. [16] did not report nuclear pleomorphism and mitotic figures, which is consistent with our results. In some cases, plump endothelial cells and endothelial hyperplasia mimic vascular tumours [7, 26].

Table 1. Thyroid gland haemangiomas

First author [Ref.]	Pathological diagnosis	Size, cm	Sex	Age, years	FNA history	Histologically verified
Pickleman [30]	Primary haemangioma/haemangioma NOS	7.5 × 3 × 2	M	56	No	Yes
Pendse [31]	Primary haemangioma	6 × 3.5	M	53	Yes	Yes
Kumar [32]	Primary haemangioma	4 × 4	M	53	No	Yes
Ríos [33]	Cavernous haemangioma	5 × 4	F	48	No	Yes
Ríos [33]	Cavernous haemangioma	5 × 3	F	63	No	Yes
Kano [34]	Cavernous haemangioma	5.5 × 3.0 × 2.0	M	21	No	Yes
Hassan [35]	Epithelioid haemangioendothelioma	5.0 × 8.0 × 4.0	F	73	–	Yes
Lee [36]	Cavernous haemangioma	17.0 × 16.5	M	66	No	Yes
Datta [37]	Cavernous haemangioma	4.9 × 4.4	M	25	No	Yes
Ciralik [38]	Cavernous haemangioma	7 × 6 × 6	M	64	No	Yes
Sakai [39]	Cavernous haemangioma	5.2 × 4.8 × 3.5	F	71	No	Yes
Michalopoulos [40]	Cavernous haemangioma	3.7	M	78	No	Yes
Gutzeit [41]	Cavernous haemangioma	4	F	84	No	Yes
Maciel [42]	Cavernous haemangioma	22 × 21 × 17	F	80	No	Yes
Dasgupta [43]	Cavernous haemangioma	4.5 × 4	M	38	No	Yes

Table 2. Non-tumourous vascular changes not related to FNA

First author [Ref.]	Pathological diagnosis of vascular lesion	Cases, <i>n</i>	Co-existing thyroid pathology	FNA history, <i>n</i> (%)
Tse [46]	Capsular intravascular endothelial hyperplasia	3	Follicular carcinoma (<i>n</i> = 2) Papillary carcinoma (<i>n</i> = 1)	1 (33%)
Schmitz [47]	Florid capsular and pericapsular papillary endothelial proliferation	1	Poorly differentiated carcinoma	1 (100%)
Sapino [48]	Intranodular reactive endothelial hyperplasia	11	Adenomatous goitre	1 (9%)
Baloch [49]	Intravascular Kaposi's-like spindle cell proliferation	3	Follicular carcinoma (<i>n</i> = 3) including oncocytic variant (<i>n</i> = 2)	1 (33%)

Due to its high vascularity, the thyroid gland is susceptible to haematoma [16, 24]. The proposed mechanism of neovascularisation is a needle-induced haemorrhage followed by a haematoma and thrombosis that resolves by recanalisation and vessel formation (Fig. 3). Additionally, Pandit and Phulpagar [17] suggested that, besides vascular proliferation, fibroblastic proliferation is also caused by needle trauma. Traumatization by palpation and surgery is a less probable explanation [24]. Sapino et al. [48] described spontaneous haemorrhage in long-standing goitre nodules. This observation is in agreement with our results, as FNAB history was negative/unavailable in 15 cases in our series. Sharma and Krishnanand [19] inves-

tigated the role of the FNAB technique in the aetiology of vascular proliferation, finding a 21-G needle to be less traumatic than other options. The numerous and multiple needle passes increase vascular proliferation development and capsular pseudoinvasion [15, 20] that interferes with follicular adenoma versus carcinoma diagnostics. In our personal experience, the neovascularisation did not interfere with the measurements of nodule/tumour size.

In the literature, the needle tract effect after repeated thyroid FNAB has also been described in cytological specimens. In a study by Recavarren et al. [51], 16 cases of Bethesda atypia of undetermined significance (AUS/FLUS) in repeated FNAB were found. They revealed 2

Table 3. Vascular proliferation after thyroid FNAB: review of the literature

First author [Ref.]	All cases, <i>n</i>	Total vascular change cases, <i>n</i> (%)	Vascular proliferation, <i>n</i> (%)	Vascular thrombosis, <i>n</i> (%)	Papillary endothelial hyperplasia, <i>n</i> (%)	Plump endothelial cells, <i>n</i> (%)
Ersöz [16]	20	9 (45)	9 (45) ^a	9 (45) ^a	n.d.	n.d.
Pandit [17]	265	10 (3.8)	2 (0.7)	5 (4.9)	3 (2.9)	n.d.
Tsang [24]	2	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)
Sharma [19]	100	23 (23)	4 (4)	20 (20)	4 (4)	1 (1)
Bolat [18]	150	14 (9)	4 (2.7)	10 (6.7)	n.d.	n.d.
Ramraje [50]	2	2 (100)	1 (50)	0	1 (50)	1 (50)
Baloch [25]	250	n.d.	n.d.	n.d.	n.d.	n.d.
LiVolsi [15]	300	n.d.	n.d.	n.d.	n.d.	n.d.

n.d., not determined. ^a Reported as vascular proliferation and/or vascular thrombosis.

Fig. 3. Mechanism of vascular proliferation development.

samples with atypical stromal, endothelial, and follicular cells embedded in blood or blood clots, probably induced by previous FNABs. In our opinion, the revision of previous slides is necessary to avoid diagnostic inaccuracies. The cases may nevertheless be categorised into the AUS/FLUS heterogeneous group [52].

Core-needle biopsy (CNB) provides an alternative diagnostic method in non-diagnostic and AUS/FLUS cases [53]. However, thyroid CNB is not widely used in clinical practice. The most common clinical complication is haematoma formation [54, 55]. We suspect that the CNB procedure can cause similar and even worse histopathological alterations than the FNAB procedure.

In conclusion, post-FNAB changes are often accompanied by dilated newly formed vessels. Proper histopath-

ological diagnostics requires the knowledge of reactive post-FNAB tissue alterations and patient history of FNAB in order to avoid misdiagnosis. Pathologists should differentiate reactive vascular changes from rare thyroid vascular tumours. In the clinical practice, a differential diagnosis with angiosarcoma is of paramount importance. However, a secondary haemangioma caused by the organisation of a haematoma is almost impossible to distinguish from a real haemangioma [26]. Nevertheless, the phenomenon of neovessels is quite rare in thyroid gland specimens.

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Ethics Statement

The study was approved by Tampere University Hospital Ethical Committee and informed consent from each individual was not requested. The handling of the tissue blocks/slides was approved by the Finnish Medical Authority Organisation Valvira.

Disclosure Statement

The authors have no conflicts of interest to declare.

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