Original Article

# Vanishing tumors of thyroid: histological variations after fine needle aspiration

**Parisha Bhatia[1], Ahmed Deniwar[1], Hossam Eldin Mohamed[1], Andrew Sholl[2], Fadi Murad[1], Rizwan Aslam[3], Emad Kandil[1,3]**

[1]Department of Surgery, [2]Department of Pathology, [3]Department of Otolaryngology, Tulane University School of Medicine, New Orleans, LA 70112, USA

*Contributions:* (I) Conception and design: P Bhatia, E Kandil; (II) Administrative support: R Aslam, E Kandil; (III) Provision of study materials or patients: A Sholl; (IV) Collection and assembly of data: P Bhatia, A Deniwar, HE Mohammad, F Murad; (V) Data analysis and interpretation: P Bhatia, R Aslam, E Kandil; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Emad Kandil, MD, FACS. 1430 Tulane Avenue, SL 22, New Orleans, LA 70112, USA. Email: ekandil@tulane.edu.

**Background:** Fine needle aspiration (FNA) can lead to changes that extensively replace cytological confirmed thyroid lesions. These lesions, so called "vanishing tumors" can be diagnostically challenging to pathologists and therapeutically challenging for endocrinologists and surgeons. We performed a retrospective analysis to identify these tumors.

**Methods:** Data of 656 patients referred for thyroid surgery was reviewed. Patients with suspicious lesions on neck ultrasound (US) underwent FNA. We compared FNA cytological and surgical pathological findings to identify vanishing tumors. FNA-induced changes such as cystic degeneration, hemorrhage, calcification, cholesterol crystals, fibrosis and granulation tissue were identified.

**Results:** Seventeen patients (2.5%) were identified with vanishing tumors. FNA cytology was indeterminate in seven (41.1%) and benign in ten (58.8%) patients. Surgical pathology in all nodules showed regressive changes partially or entirely replacing the tumor. The mean size of vanishing tumors was 2.4±1.5 cm in greatest dimension. Seven nodules (41.1%) were entirely replaced while remaining ten nodules showed partial replacement of tumors. Three (17.6%) nodules had focal areas of optically clear nuclei suspicious of papillary thyroid carcinoma (PTC); one showed an additional focus of follicular neoplasm (FN) of uncertain malignant potential.

**Conclusions:** FNA-induced changes can lead to obliteration of nodules rendering pathological diagnosis with no evidence of confirmed lesions. Pathologists and surgeons should be aware of this challenging scenario.

**Keywords:** Biopsy fine needle; cytodiagnosis; infarction; pathology; thyroid neoplasms

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## Introduction

Fine needle aspiration (FNA) cytology is considered the gold standard in the diagnosis of thyroid nodules that may require surgical excision. The advent of FNA has led to a decreased number of unnecessary surgeries performed for benign thyroid tumors; however, malignant nodules can be missed in a minority of cases (1,2). The reported sensitivity of thyroid FNA results is 65–99% while its specificity is 72–100% (3-5). A standard protocol followed after detection of a thyroid nodule on palpation is to perform a thyroid ultrasound (US). According to the revised guidelines of the American Thyroid Association (ATA), thyroid US is being increasingly used for nodules >1 cm in size. Nodules presenting with US features suspicious of malignancy, such as presence of micro-calcification,

hypo-echogenicity, "taller-than-wide" shape and increased vascularity, are subsequently examined by FNA biopsy to detect the presence and type of cancer cells (6). However, 15–20% of the nodules are deemed indeterminate on cytological results (7). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) uses three categories that fall in the "grey zone" between benign and malignant cytology: follicular lesion of undetermined significance/atypia of undetermined significance (FLUS/AUS), suspicion for follicular neoplasm (FN)/Hürthle cell neoplasm, and suspicious for malignancy, the sensitivity of which is variable according to different investigators (7-11). The definite diagnosis of these nodules is provided by histological examination following surgical excision of the tumor.

Interestingly, FNA performed on these nodules can (infrequently) lead to reactive changes that are observed 20–40 days after initial FNA. These changes are expressed in the form of atypical nuclei, hemorrhagic cysts, fibrosis, cystic degeneration, necrosis, and squamous metaplasia on specimen histopathology after the patient undergoes surgical excision (12-14). Following FNA, these changes can partially or extensively replace thyroid tumor tissue, obscuring the final diagnosis of the previously biopsy-proven tumor. Consequently, changes in histological features may lead to an altered diagnosis that finally renders the nodule negative for malignancy on surgical pathology. These lesions are called vanishing tumors and are of great clinical concern to surgeons. This scenario influences treatment and can lead to an ambiguous management strategy by clinicians. In the literature, vanishing tumors of the prostate have been reported for the past few years, the incidence of which is on a decline (15,16). The vanishing tumor phenomenon has been recently described in thyroid gland by some authors (17,18).

In this study, we conducted a retrospective analysis of patients that were referred to our institution for thyroid disorders and management. We then identified the number of patients diagnosed with vanishing tumors by evaluating their surgical pathological reports.

## Materials and methods

We retrospectively evaluated the data of 656 patients who were referred for surgical intervention to our institution from April 2008 to July 2015. All patients underwent pre-surgical US examination of the neck to look for suspicious features of malignancy. According to ATA guidelines, thyroid nodules presenting with these features were referred for US-guided FNA biopsy, performed on patients meeting the criteria for the same. All of these patients underwent at least one FNA that was performed at our institution and had a cytological diagnosis. Repeat FNA was performed if the cytology was non-diagnostic. However, expert opinions were involved wherever necessary. Patients were then directed to subsequent lobectomy/thyroidectomy according to their cytological results and/or symptomatic disease due to nodular size. The aspiration cytology and specimen pathology were read by expert cytopathologists. Subsequently, the surgical pathological reports for all the patients were reviewed. Our criteria was set on inclusion of nodules that had (I) suspicious features of malignancy on US; (II) nodules with positive FNA diagnosis and (III) surgical specimens showing FNA-induced degenerative changes or were rendered negative of tumor after a biopsy-proven diagnosis. FNA-induced reactive changes such as cystic degeneration, hemorrhage, calcification, cholesterol crystals, fibrosis and granulation tissue were looked for in specimen pathology. After selection of patients, the FNA cytological and surgical pathological results were compared to identify nodules displaying a vanishing tumor phenomenon. Nodules for which cytological and pathological results provided a definitive diagnosis of the nature of the tumor, without any reactive changes, were not included in the analysis.

All data was collected under desired variables and was arranged using Microsoft Excel. Statistical analysis was performed using standard Microsoft Excel calculations.

## Results

A retrospective data on a total of 656 patients was reviewed from the years 2012–2015. Of all the patients referred for surgical intervention, seventeen patients (2.5%) were identified with vanishing tumors. Females contributed to a larger proportion (88.2%) of these tumors as compared to males. The mean age of the patients was 49.5±16.1 years. Patients were selected for surgical intervention according to clinical observations, suspicious features of neck US and FNA results. FNA-proven results were observed to be TBSRTC indeterminate in seven (41.1%) and benign in ten (58.8%) patients. Furthermore, results of preoperative FNA cytology were compared with surgical pathology of the included cases.

Following surgical intervention, specimen pathology revealed widespread replacement of all tumors by FNA-induced reactive changes. The size of vanishing tumors

 

was 2.46±1.5 cm in greatest dimension. The lesions were reported to have diverse features such as hemorrhagic cysts, fibrosis, squamous metaplasia, and necrosis. Some of these nodules were entirely replaced by these reactive changes, making the final diagnosis difficult to interpret. Additionally, peripherally compressed parenchyma in these nodules assisted with the final diagnosis. Overall, there were seven tumors that were entirely replaced by reactive changes (case 1–5, 7, 16). Of these tumors, the FNA cytology was benign in five, FLUS in one and suspicious for malignancy in one. On specimen pathology, the nodules with benign cytology on FNA showed extensive changes such as cholesterol granulomas, fibrosis and regional squamous metaplasia and nodules completely filled with hemorrhage in two. There were no discrete lesions identifiable on specimen pathology. The final diagnosis of these nodules was determined by thin rim of compressed peripheral parenchyma. Furthermore, the nodule with FNA diagnosis of FLUS (case 3) also showed extensive regressive changes consistent with a diagnosis of reactive changes secondary to prior FNA. This nodule had small focal area of intra-capsular invasion within the fibrous tissue with the final diagnosis of FN. Additionally, deeper sections of this surgical specimen also revealed a single micro-focus suspicious for papillary thyroid carcinoma (PTC) arising in an atypical FN. The residual tumor cells of PTC were embedded deeply within the nodule to diagnose PTC arising in atypical FN.

The remaining ten nodules showed partial replacement of tumors by regressive changes (case 6, 8–15, 17). These lesions had FNA diagnosis of indeterminate in five (FLUS in three, FN in one and suspicious for malignancy in one) and benign in five nodules. For partial replacement, there were multiple foci of regressive changes replacing more than one nodule in the form of hemorrhage, fibrosis, siderosis, dystrophic calcification, and squamous metaplasia within the same nodule with tumor tissue. For cytological benign nodules, hemorrhagic cysts and the parenchyma within the same nodule helped to detect the nature of the tumor. These nodules were provided with the final diagnosis of nodular hyperplasia with regressive changes consistent with reaction to needle aspiration. On extensive review of the specimen with cytological benign result (case 6), residual tumor cells consistent with a diagnosis of PTC were seen arising in the background of a follicular tumor which showed extensive cystic degeneration. The specimen (case 14) with a diagnosis of FN on cytology (right lobe) underwent Afirma Gene Expression Classifier (GEC) test which provided a diagnosis of "suspicious", however, pathology revealed multiple cystic hemorrhagic nodules ranging from 1.6–2.7 cm on the right side. There was intra-capsular extension of the follicular adenomatous tissue with degenerative changes on deeper sections. The patient also had FNAC performed on the left lobe that detected AUS; however, surgical pathology did not reveal any malignant tissue in the entire gland.

Furthermore, we observed three nodules (case 7, 10 and 12) that presented with focal areas of optically clear nucleoplasm suspicious of PTC; however, no malignant cells were detected. These lesions had FNA-cytology as benign in one and FLUS in two. One of the latter two indeterminate nodules had suspicious features of malignancy on prior US with FNA-cytology showing an additional focus suspicious for FN of uncertain malignant potential. However, due to extensive fibrosclerotic changes, no malignancy was detected on surgical pathology of this nodule. All three nodules were deemed negative of malignancy on final pathological diagnosis. The remaining nodules with indeterminate cytology displayed nodular hyperplasia on histopathology. *Table 1* displays characteristics of individual cases with variable degrees of FNA cytology and surgical pathological results.

## Discussion

When the final surgical pathology diagnosis shows only degenerative changes in a patient with a previous definitive diagnosis on FNA, clinicians cannot create a complete and thorough management plan. US-guided FNA can result in changes including hemorrhage, fibrosclerosis, siderosis, granulomatous inflammation and squamous metaplasia, which may ultimately alter final pathologic diagnosis. We observed that some of the nodules with indeterminate results on FNA had suspicious features of malignancy on previous neck US, but no malignant cells on surgical pathology. One explanation for the discrepancies between cytopathology and surgical pathology results can be described by inherent sensitivity and specificity of the FNA and subjective findings on the final surgical pathology. Whether this phenomenon is due to a false positive FNA result or a true disappearance of a thyroid tumor is still debatable. Literature reports false positive rates of FNA cytology between 2–10% (4,5). In total, we had four surgical cases that presented with high clinical, imaging or pathological suspicion of malignancy but were ultimately diagnosed as benign by expert pathologists. One of these nodules also underwent Afirma GEC that was reported as "suspicious," carrying

 

**Table 1** Patient and tumor characteristics findings on ultrasound, fine needle aspiration cytology and specimen histopathology

| Case | Age/sex | US findings | FNA findings | Type of surgery | Surgical pathology |
|---|---|---|---|---|---|
| 1 | 41/M | Right nodule: mixed echogenicity, calcification, solid/cystic component, peripheral vascularity | Benign | RL | Cystic nodule with extensive reactive changes with thin rim of compressed parenchyma showing nodular hyperplasia<br>Final diagnosis: Benign; size: 4 cm |
| 2 | 59/F | Right nodule: calcification, suspicious | Benign follicular cells | RL | Fibrous nodule with dense fibrous tissue, calcification and focal ossification in the background of nodular hyperplasia; deeper sections<br>Final diagnosis: benign; size: 0.6 cm |
| 3 | 44/F | Left nodule: microcalcifications | FLUS | TT | Extensive regressive changes secondary to FNA. Small focus of intra-capsular invasion within fibrous tissue—follicular carcinoma. Additional micro-focus of PTC at deeper level arising in atypical follicular neoplasm<br>Final diagnosis: malignant; size: 0.7 cm |
| 4 | 59/F | Right nodule: suspicious | Cystic nodular goiter | LL | Abundant hemorrhage with cystic degeneration, thin rim of fibrous tissue. No discrete lesions identified<br>Final diagnosis: benign; size: 0.9 cm |
| 5 | 46/F | Left nodule: high vascularity | Cystic nodular goiter | LL | Widespread changes with regional squamous metaplasia. xanthomas, granulomatous and inflammatory changes prominent within necrotic tissue<br>Final diagnosis: goiter; size: 3.5 cm |
| 6 | 47/F | Right nodule: microcalcification | Suspicious for malignancy | RL | Residual cells of PTC in follicular tumor showing extensive internal cystic changes. The hemorrhagic cysts measures 4.6 cm<br>Final diagnosis: PTC in follicular tumor; size: 4.6 cm |
| 7 | 53/F | Right nodule: microcalcification | Suspicious for FN | RL | Extensive regressive changes with fibrosis, siderosis, hemorrhage. Focal area of optically clear nuclei but do not interpret PTC, follicular variant<br>Final: benign (negative of malignancy); size: 1.2 cm |
| 8 | 56/F | Left nodule: lower lobe nodule—no suspicious LN. No suspicious features mentioned | FLUS | LL | Nodular hyperplasia with hemorrhagic cysts and focal calcifications. No definite follicular lesions identified<br>Final diagnosis: nodular hyperplasia; size: 3.8 cm |
| 9 | 61/F | Right nodule: predominantly solid, central calcification, high internal vascularity | AUS/FLUS | RL | Nodule with fibrosis and calcification and degenerative changes<br>Final diagnosis: nodular hyperplasia; size: 2 cm |
| 10 | 46/F | Left nodule: increased vascularity. | FLUS | LL | Several nodules with regressive changes including fibrosis, siderosis and macrophage reaction. Rare foci of optically clear nucleoplasm; no PTC detected<br>Final diagnosis: adenomatous hyperplasia (negative of malignancy); size: 2 cm (dominant nodule) |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Case | Age/sex | US findings | FNA findings | Type of surgery | Surgical pathology |
|---|---|---|---|---|---|
| 11 | 59/M | Right nodule: mixed echogenicity, irregular margins and increased central and peripheral vascularity | Cystic nodular goiter | RL | Sx path: adenomatoid nodule with extensive degenerative changes including recent and old hemorrhage, fibrosis and calcification<br>Final diagnosis: goiter; size: 2.1 cm |
| 12 | 51/F | Right nodule: mixed echogenicity, suspicious | Benign colloidal nodule | RL | Sx path: borderline minute fibrosclerosing lesion with atypical microfollicles. Reactive hyperplasia sec to FNA. Occasional nuclear grooving and nuclear irregularity and atypism<br>Final diagnosis: benign (negative of malignancy); size: 1 cm |
| 13 | 53/F | Left nodule: microcalcifications | Cystic nodular goiter | LL | Nodule with regressive changes surrounded by nodular hyperplasia<br>Final diagnosis: nodular hyperplasia; size: 1.2 cm |
| 14 | 39/F | Right nodule: hypoechoic, microcalcification, high internal vascularity, cystic | Follicular neoplasm; suspicious by Afirma | TT | Sx path: multiple cystic hemorrhages replacing thyroid tissue. Deeper sections show intra-capsular extension of follicular tumor<br>Final diagnosis: adenoma with degenerative changes (negative of malignancy); size: 2.7 cm |
| 15 | 56/F | Left nodule: high internal vascularity | Benign | LL | Sx path: dominant nodule entirely replaced by abundant cystic material, heterogeneous features with hyperplastic goiter, gross dystrophic calcification and other degenerative changes<br>Final diagnosis: goiter; size: 4.5 cm |
| 16 | 35/F | Left nodule: large complex nodule with internal vascularity | Benign; nodular goiter | LL | Sx path: grossly, large cystic nodule well circumscribed completely filled with hemorrhage; nodular hyperplasia showing FNA site changes<br>Final: benign; size: 5.5 cm |
| 17 | 85/F | Left nodule: hypoechoic, microcalcification, irregular margins. | Benign; multi-nodular goiter | TT | Sx path: dominant nodule w/focal hemorrhage, Ca/Fib/hürthle cell & degenerative changes (9-fold risk, extensive family h/o PTC)<br>Final: benign; size: 1.6 cm |

FNA, fine needle aspiration; RL, right lobectomy; FLUS, follicular lesion of undetermined significance; TT, total thyroidectomy; PTC, papillary thyroid carcinoma; LL, left lobectomy; FN, follicular neoplasm; sx path, surgical pathology.

approximately a 40% risk of malignancy. Afirma is an RNA-based molecular test that determines the risk of malignant behavior on an indeterminate cytological sample. This nodule was eventually confirmed as a benign adenoma, due to well-described histologic changes encountered in the nodule (19,20).

FNA is a cost-effective, minimally invasive diagnostic tool that may interrupt and cause traumatic microvascular injury within the nodule, leading to reactive secondary tissue changes. A retrospective case series of 620 patients was performed at UCLA where they reported 12 cases identified with infarction following needle aspiration. Only eight of these nodules had a clear diagnosis of PTC on FNA. Surgical pathology provided a diagnosis of infarcted PTC after surgical excision in all 12 cases (21). There are several other reports on infarcted PTC in the literature that suggest these lesions could be a potential cause of true disappearance of tumors (22-25). The characteristic features of PTC include the presence of nuclear grooves, pseudoinclusions, and papillary fronds, but it can become difficult to differentiate between follicular tumors, PTC and follicular variant of PTC on the basis of cytology. Nevertheless, certain other conditions of the thyroid that mimic histological features of PTC, including Hürthle cell neoplasms, chronic lymphocytic thyroiditis, nodular hyperplasia, hyalinizing trabecular adenoma, and medullary thyroid carcinoma, could lead to a false positive and incorrect cytological diagnosis (26,27).

Because of their infrequent occurrence, data on vanishing tumors involving the thyroid gland is limited in the current literature. Eze *et al*. reported 14 such cases that were prospectively reviewed to identify regressive changes (17). Similar to our results, they observed microscopic development of cystic degeneration, hemorrhage and other reactive changes partially and/or entirely replacing the nodules. Six of the 14 nodules had malignant FNA cytology. Of these nodules, successful diagnosis of malignancy was established in only four nodules, while the rest were rendered benign. They also suggested that FNA cytology may be considered sufficient to support the diagnosis and plan management in such cases. They also supported the requirement of second opinions for surgical pathology, should the need arise (17). Another study at Asan Medical Center reported six cases of disappearing PTC. All of these cases had malignant FNA diagnosis, however, none of the specimens showed malignant cells on resection (18). Another interesting finding reported by this group showed that two of the six cases had lymph nodes positive for PTC with no malignancy in thyroid gland. This is suggestive of true disappearance of papillary tumor.

The vanishing tumor phenomenon has been reported in multiple prostatectomy specimen (15,16). However, unlike thyroid, prostate malignancy is usually initially diagnosed on core needle biopsy, which is usually the sentinel event leading to prostatectomy. One of the major concerns for clinicians is the absence of management guidelines after vanishing tumors are detected. It is not clear whether to continue follow up the patient to detect any signs of recurrence of the disease or deem the patient disease-free. It is also unclear whether modifications are required in current therapeutic strategies after diagnosing vanishing lesions. Another concerning issue is the presence of underlying mutations in thyroid carcinoma. BRAF-mutation has been increasingly associated with PTC that carries an aggressive course (28-30) and poor prognosis with nodal metastasis and distant tumor spread. Therefore, clinicians and surgeons should be aware of these circumstances and involve an expert second opinion when necessary. Additionally, because the specimen final pathology shows only sparse tumor cells and reactive changes, the staging may be altered, adversely affecting patient management. Therefore, efforts must be made to minimize the occurrence of histological alterations following FNA. It may be of importance to utilize the French (capillary) technique in thyroid FNA rather than the more traumatic negative pressure aspiration technique (31,32).

The limitations of this study include (I) known biases of retrospective study, and (II) lack of data on long-term follow-up of these patients which prevents us from commenting on recurrence or further advancement of the disease where vanishing tumors were seen on pathology.

## Conclusions

Vanishing tumors of the thyroid have recently been described as one of the most unusual circumstances in thyroid pathologies. Endocrinologists and thyroid surgeons should be aware of such lesions when providing postoperative counseling.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

 

to declare.

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