Infarction of Papillary Thyroid Carcinoma After Fine-Needle Aspiration Case Series and Review of Literature

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IMPORTANCE Although infarction after fine-needle aspiration (FNA) is a rare occurrence, it is a known phenomenon that may lead to difficulties in interpretation for pathologists and in decision-making for head and neck surgeons.

OBJECTIVE To characterize our experience with infarction in papillary thyroid carcinomas (PTCs) after FNA and review existing cases of infarcted PTCs in the literature to better understand this phenomenon.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective case series and review of literature at a tertiary medical center (University of California, Los Angeles [UCLA], Medical Center). All patients who had a surgical pathologic diagnosis of infarcted PTC and who underwent FNA prior to surgery at UCLA from June 2006 to June 2012 were identified. There were 620 cases of PTC and 12 cases of infarcted PTC.

MAIN OUTCOMES AND MEASURE Demographic data, FNA cytologic findings, and surgical pathologic data were gathered for each patient. A comprehensive literature search for infarcted PTC was performed.

RESULTS Twelve cases of infarcted PTC were found in a total of 620 cases of PTC (1.9%). The mean (SD) time interval between the last FNA and surgery was 52 (35) days (range, 13-133 days). All patients received a diagnosis of infarcted PTC after thyroidectomy was performed. Focal infarction was found in 4 patients (33%), and near-total infarction was found in 8 patients (67%). Five patients (47%) had the follicular variant of PTC, making it the most common subtype in our series. A thorough literature search yielded 11 articles reporting a total of 26 cases of infarcted PTC after FNA. To our knowledge, our case series on infarcted PTC is the largest reported series in the literature.

CONCLUSIONS AND RELEVANCE Although infarction of PTC after FNA occurs infrequently, it may lead to difficulties in histologic diagnosis. Awareness of this phenomenon and its histologic associations, along with careful reevaluation of the FNA and surgical specimens, is important for appropriate diagnosis and subsequent treatment. At this point, infarction in PTC should not alarm a head and neck surgeon to change management, but future prospective studies with a large population of patients with infarcted PTCs are needed to establish the impact of infarction on differences in treatment outcomes for therapies that may be used in PTCs.
Fine-needle aspiration (FNA) is well known to be the most reliable method of differentiating between benign and malignant thyroid nodules prior to a patient’s decision to undergo surgical treatment.\(^1\)\(^-\)\(^3\) It has a reported sensitivity of 65% to 99% and specificity of 72% to 100%, making it a more effective tool than other forms of less invasive diagnostic tools, such as ultrasonography and radionuclide scans.\(^4\)\(^-\)\(^5\) Although invasive, the procedure has been shown to be safe and reliable and can be performed rapidly.\(^6\)\(^-\)\(^7\)

Complications of thyroid FNA are rare and consist mainly of minor hematomas.\(^7\)\(^-\)\(^8\) However, the trauma caused by FNA to the thyroid may result in histologic changes that may obscure the correct diagnosis after thyroidectomy.\(^5\)\(^-\)\(^10\) Furthermore, these difficulties may cause misdiagnoses in favor of carcinoma, resulting in possibly unnecessary therapies or more radical surgery.\(^11\)

Infarction of the thyroid nodule is a rare histologic alteration found after FNA.\(^7\)\(^-\)\(^10\) It has been known to occur mainly in Hürthle cell tumors.\(^12\)\(^-\)\(^13\) However, infarction has been shown to occur sporadically in papillary thyroid carcinomas (PTCs) after FNA as well.\(^11\)\(^-\)\(^14\)\(^-\)\(^15\) This has been reported almost solely in cytopathology literature and is underrecognized in otolaryngology. Thus, we sought to characterize our experience with infarcted PTCs after FNA in the hopes of elucidating the phenomenon for head and neck surgeons.

### Methods

A retrospective medical chart review at a tertiary medical center was performed. This study was approved by the University of California, Los Angeles (UCLA), institutional review board (No. 12-000575). From June 2006 and June 2012, 12 patients who had a surgical pathologic diagnosis of infarcted PTC after hemithyroidectomy or total thyroidectomy were identified. All of these patients were verified as having undergone FNA prior to surgery and were thus included in our study. Demographic, FNA cytology, and surgical pathologic information were gathered for each patient. Written informed consent was not obtained because the information was anonymous.

At UCLA Medical Center, FNA was generally performed under ultrasonographic guidance, in the presence of a cytopathologist, with a 25-gauge needle attached to a plastic syringe held in a syringe pistol. Four to 5 passes with the needle were typically made to obtain adequate tissue samples. Paraffin-embedded tissue in cell blocks were cut to be 4 to 6 μm in thickness and stained with hematoxylin-eosin. Immunohistochemical assays were used when appropriate. A modified Romanowsky Diff-Quick and/or May-Grünwald-Giemsa staining technique were used concurrently for confirmation. All slides were reviewed by a cytopathologist in the UCLA Department of Pathology. Some FNAs were performed by an outside source, but cytology samples were reexamined by UCLA cytopathologists to confirm diagnoses. Slides of thyroidectomy specimens from the identified patients were pulled from the pathology archives and were reexamined by 1 of us (S.B.), looking for histologic similarities and patterns that could potentially suggest a mechanism for the infarction after FNA.

A literature search was performed using the PubMed electronic database and limited to the English literature. Key terms used in the search included fine-needle aspiration, papillary thyroid carcinoma, and infarction. Older research unavailable electronically was found in the UCLA Biomedical Library medical journal collection. All citations in articles found on PubMed were examined for additional relevant studies. Articles were reviewed for cases of infarction in PTC after FNA and logged in an analytical file.

### Results

#### Demographics

Between June 2006 and June 2012, 12 of 620 cases of PTC found on surgical pathologic examination (1.9%) had a diagnosis of infarcted PTC. Of these 12 patients, 9 (75%) were female and 3 (25%) were male. The mean (SD) age at the time of the last FNA prior to surgery was 53 (13) years (range, 32-76 years). The mean thyroid-stimulating hormone (TSH) level prior to surgery, excluding 1 patient with an unknown TSH level, was 1.7 (0.94) μIU/mL (range, 0.47-3.00 μIU/mL). The mean time interval between the last FNA and surgery was 52 (35) days (range, 13-133 days). No patients reported pain in the thyroid area before surgery. Every patient received radioactive iodine therapy after surgery except for 1 patient, who was determined to be low-risk (with a MACIS [distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size] score of 5.26) and thus would not benefit from radioiodine ablation treatment.\(^16\)

#### Imaging and FNA Cytology

All patients had 1 FNA performed prior to surgery, except for 1 patient who underwent 4 FNAs before surgery. Of the 12 patients, 7 (58%) underwent FNA at UCLA Medical Center, while 5 (42%) underwent FNA at an outside facility. Ten patients (83%) underwent FNA with ultrasonographic guidance, 1 patient with computed tomographic guidance, and another underwent FNA with unknown imaging technique. On ultrasonography, the mean (SD) maximum tumor dimension was 2.2 (1.1) cm (range, 0.9-4.0 cm). Of 8 lesions (67%) found to contain calcifications, 6 had internal calcifications and 2 had peripheral calcifications. Three lesions (25%) were found to contain cystic foci. In 8 patients (67%), the tumor was found on the right side, including 1 in the right thoracic inlet, and in 4 patients (33%), the tumor was found on the left side. All lesions were intrathyroidal.

The 7 FNAs performed at UCLA all used similar techniques as described in the Methods section, but the techniques used by outside sources on the remaining 5 FNAs was unknown. On FNA cytologic examination, 8 patients (67%) received a diagnosis of PTC, 1 patient was diagnosed as having a Hürthle cell neoplasm (8%), 1 patient was diagnosed as having a follicular lesion of unknown significance (8%), 1 was diagnosed as having atypia of undetermined significance (8%), and 1 was diagnosed as having a benign colloid nodule with cystic degeneration (8%). Surgery was performed on the benign lesion owing to marked tracheal deviation and compressive symptoms.
Surgical Pathologic Findings
A summary of the surgical pathologic findings is presented in Table 1. Of the 12 patients, 11 (92%) underwent total thyroidectomy and 1 (8%) underwent right lobectomy with a subsequent completion thyroidectomy once PTC was diagnosed. The primary surgeon in all cases did not note increased difficulty of surgery, and there were no complications intraoperatively in any cases. The tumor was found within the right lobe of the thyroid in 8 cases (67%) and within the left lobe in 4 cases (33%). The mean maximum tumor dimension was 1.9 (1.3) cm (range, 1.0-6.0 cm). This was not significantly different from measures taken by ultrasonography during FNA before surgery (P = .63). All patients received a diagnosis of infarcted PTC, 5 of which (42%) were of a follicular variant, and 1 of which (8%) was of an oncocytic variant. All patients were diagnosed based on residual viable cells having nuclear features diagnostic of PTC. One patient was found to have concurrent Hashimoto thyroiditis, and another was found to have metastatic PTC as indicated by a positive juxtathyroidal lymph node without extranodal extension.

Focal infarction was found in 4 patients (33%), and near-total infarction (defined as infarction in >90% of the tumor) (Figure, A) was found in 8 patients (67%). Indicators of tissue injury and repair post-FNA included recent hemorrhage, old hemorrhage and hemosiderin deposits, granulation tissue, fibrosis, dystrophic calcification (Figure, B), and osseous metaplasia (Figure, C). The first 4 pathological findings were present in all cases. Dystrophic calcification was found in 5 patients (42%), and osseous metaplasia was found in 2 patients (17%). Fine-needle aspiration may lead to a histologic alteration whereby focal implantation of tumor tissue occurs beyond the capsule, near the needle tract. This is known as pseudoinvasion of the capsule (Figure, D) and was found in 8 patients (67%). Although it would be legitimate to establish a diagnosis of PTC with FNA findings if a specimen is entirely infarcted, we did not have to do this in our cases owing to viable peripheral tissue.

Literature Review
A comprehensive search of the English literature as described in the Methods section, using the keywords fine needle aspiration, papillary thyroid carcinoma, and infarction, yielded 11 articles with a total of 26 cases of infarcted PTC after FNA. The largest series included 8 cases of infarcted PTC. A summary of literature found to contain instances of infarcted PTC is presented in Table 2.

Discussion
To our knowledge, our study represents the largest single case series of infarcted PTCs after FNA, with 12 cases identified over a time period of 6 years at a tertiary medical center. The next largest series included 8 patients and was reported by Kini in 1996. The literature has reported a wide range for the rate in which thyroid nodules undergo infarction after FNA, from 0 to 10%. At the extremes, 1 study reported no instances of infarction, or even tissue damage, in 305 thyroidectomies with preceding FNA, while another reported 8 of 82 cases of thyroid neoplasms (9.8%). In the latter, there was only 1 case of complete infarction in histologic specimens from patients who underwent FNA, but none in specimens from patients with neoplasms with similar pathologic characteristics who did not undergo FNA prior to surgery. Yet in another large review of 1150 thyroidectomies, the overall incidence was 1.4% (22 cases), with 13 cases of Hurthle cell tumor (13 of 110 [11.5%]), and 5 cases of PTC (0.7%). Our findings lie at the lower end of the spectrum, with 12 instances of infarction found in 620 cases of PTC (1.9%). This seems to be consistent with the literature, although data on the rate of infarction in PTCs are sparse. These numbers suggest that even though infarction of PTC after FNA may be rare, it would not be surprising for a head and neck surgeon to encounter such a case.

Changes in the histopathologic characteristics of thyroid lesions after FNA have historically been given the acronym...
WHAFFT, or “worrisome histologic alterations following fine-needle aspiration of the thyroid.” These changes were subdivided into acute and chronic categories, with acute changes occurring within 3 weeks post-FNA and chronic changes occurring after 3 weeks post-FNA. Acute changes consisted of hemorrhage, granulation tissue, giant cells, siderophagia, and so on, and examples of chronic changes consisted of linear fibrosis, metaplasia, pseudoinvasion of capsule, and atypia.8,24 Although infarction is usually considered a late change, it has been placed in both categories. Kini12 reported a case of infarcted thyroid neoplasm as soon as 9 days after FNA. This is consistent with our data, as we found a case of infarction only 13 days after FNA.

Mechanisms have been postulated as to how FNA may induce infarction of a thyroid nodule. The needle may interrupt the microvasculature during entry or may cause traumatic venous thrombosis. This may be exacerbated by multiple passes with rigorous aspiration, by extraction of large amounts of tissue, and by a large needle size.8,20,21 Although it may be possible to reduce damage with a smaller-gauge needle, we elect to use 25-gauge needles at UCLA as opposed to higher-gauge needles that may be used at other institutions because

<table>
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<tr>
<th>Source</th>
<th>Study Type</th>
<th>Cases of Infarcted PTC</th>
<th>Near-Total Infarction</th>
<th>Focal Infarction</th>
<th>Days Between FNA and Surgery</th>
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<tr>
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<td>Case report</td>
<td>1</td>
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<td>Unknown</td>
<td>20</td>
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<tr>
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<td>Case report</td>
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<td>1</td>
<td>0</td>
<td>24</td>
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</table>
we believe the damage inflicted at this needle diameter is minimal. In addition, most specimens are adequately obtained within 4 to 5 passes. With our technique, we have not encountered infarction caused by FNA in nonthyroid entities, neoplastic or otherwise. Vulnerability to infarction may be affected by the biologic characteristics of the lesion.8,9 For instance, Hürthle cell tumors have been observed to undergo infarctions more frequently than other follicular lesions and papillary carcinomas, which may be due to different blood flow requirements or microvascular architecture among thyroid neoplasms.10 Hürthle cells also have structurally and functionally abnormal mitochondria, which could lead to decreased energy production, making them more vulnerable to oxidative stress.13 The increased number of mitochondria in Hürthle cells may elicit a similar effect.25 Furthermore, infarction occurs more often in, and is almost exclusive to, neoplastic lesions compared with hyperplastic or colloid nodules, likely owing to elevated energy requirements.7,12,22,25 When tumors of the thyroid are encapsulated, such as in certain follicular neoplasms, stretching of the fibrous capsule from hemorrhage following FNA may lead to compression of blood vessels that penetrate the capsule, leading to subsequent vascular compromise.25,26 Introduction of infection from FNA may also contribute to infarction.25,27 These theories suggest that infarction on histologic section should raise high suspicion for neoplasm.20,22

In most cases of infarction after FNA, there is retained viable tissue at the periphery of nodules that can help establish the diagnosis. However, histologic changes may be so extensive that establishing a diagnosis becomes very difficult. In these cases, misdiagnosis of a thyroid malignant neoplasm, such as a false-negative, becomes a distinct possibility.8,12,21,22,26 To avoid misdiagnoses, Polyzos and Anastasilakis7 suggested that if the initial diagnosis is not highly suspicious for malignant disease, a repeated FNA should be performed after 3 months of the initial. Moreover, infarction and necrosis may have an impact on thyroid scans. In one study, there was an 18% decrease in uptake of radioisotope in scans performed after FNA compared with those performed prior to FNA.28 Because some physicians use the thyroid scan to minimize surgical procedures in cases of indeterminate cytologic results by avoiding operating on hot or warm nodules, this artifact could potentially have an impact on clinical decision-making in favor of overtreatment.1,2,7 Therefore, even though post-FNA scans are less used, their results should be carefully evaluated if performed.

Infarction of a thyroid nodule may manifest as ghost shadows of tumor cells or eosinophilic granular material surrounded by granulation tissue and inflammatory infiltrate.25 Ghostly papillary epithelia with psammoma bodies in a necrotic background is a histologic finding that may indicate an infarcted PTC.18 LiVolsi and Merino8 described 3 patterns of infarction, including central necrosis with periphery sparing, triangular necrosis, and complete necrosis of the entire lesion. It may be possible to establish the diagnosis by evaluating the residual tissue from the lesion as in the first 2 patterns, but it is impossible to do so in the third pattern. The fact that two-thirds of our cases exhibited near-total infarction suggests that complete necrosis may be more the norm than the outlier. This seems to be consistent with the literature because in all articles found to have descriptions of the extent of infarction in PTCs, 13 of 14 cases showed near-total infarction. Nevertheless, because staining is preserved for a period of time in some necrotic thyroid neoplasms despite cellular necrosis, immunohistochemical analysis may be used as an adjuvant when the diagnosis becomes difficult. In such cases, staining with thyroid transcription factor-1 and thyroglobulin may be advisable. In one series of 20 necrotic thyroid tumors, 18 cases showed thyroglobulin immunoreactivity, including 4 of 5 PTCs and an insular carcinoma that demonstrated retained staining even in necrotic portions. Only 2 cases of anaplastic thyroid carcinoma failed to stain with thyroglobulin.19 Furthermore, in infarcted PTCs, there may be a positive staining reaction for CD44, which can be used to confirm the diagnosis.21 We did not have to use immunohistochemical analysis in our cases because a diagnosis could be made from morphologic features of residual tissue. However, if we had encountered a totally infarcted specimen, there would definitely have been added cost and time spent in using special stains for diagnosis. An additional obstacle to histologic diagnosis may occur during surgery when perinodular granulation tissue of infarcted nodules induces an adhesion reaction to perithyroidal soft tissue and muscles, which may mimic muscular invasion.8

Given the hurdles that must be overcome in the diagnosis of an infarcted tumor, certain measures may be undertaken to minimize infarction. Fine-needle capillary use in lieu of FNA has been reported to reduce trauma to cells and tissues.29,30 Avoiding aspiration needles has also been shown to decrease the rate of WHAFFT.24 Along the same lines, one study found a decreased rate of WHAFFT when a 22-gauge needle was used compared with a 21-gauge needle (statistical results were not presented), and a tendency toward even fewer WHAFFTs with a 23-gauge or 24-gauge needle, although there were very few cases using these sizes.24 Furthermore, large-needle biopsy has been reported to increase tissue damage, leading to increased hemorrhage, necrosis, and granulation tissue along the needle track. However, the data on histologic alterations following large-needle biopsy or core needle biopsy are limited.32 One useful tool is ultrasonographic guidance, which can help direct the needle tip to the desirable site. However, ultrasonography-guided FNA is usually performed on smaller nodules than palpation-guided FNA, resulting in selection bias, and no study has compared the 2 techniques on the same nodules. Also, no study has compared the rate of WHAFFT after ultrasonography-guided FNA vs after palpation-guided FNA.7,33 Ultimately, diagnostic dilemmas may be overcome simply by taking extensive samples of surgical specimens in infarcted nodules.32

It is unclear whether infarction found in PTC surgical specimens portends certain outcomes for a patient undergoing further therapy. Does a patient still need radioiodine ablation treatment in the presence of infarction? Is there any correlation between infarction and the aggressiveness of a malignant neoplasm or the rate of future recurrence? These questions would best be answered by future prospective studies that
include a larger patient populations and longer follow-up times to determine the true impact of infarction in PTCs on outcomes.

In conclusion, although infarction of PTCs is a rare phenomenon that occurs after FNA, its rate is variable and may occasionally be seen by head and neck surgeons. In such circumstances, diagnosis may be clouded by changes on histologic results. The surgeon should be aware of the possibility that FNA may be the cause. Since infarction after FNA occurs most often in neoplasms, the prior FNA results should be reevaluated and the surgical specimens reexamined with immunohistochemical analysis to confirm diagnosis. There is no conclusive evidence for changes in treatment or prognosis, and such conclusions may be exceedingly difficult to prove given the rarity of infarcted PTCs and the already greatly favorable prognosis of PTCs. At this time, otolaryngologists should maintain the mainstream treatments for PTCs once diagnosis is established, pending future prospective studies in the subject.

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Analysis and interpretation of data: Liu, Ahmed, Bhuta.
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Critical revision of the manuscript for important intellectual content: All authors.
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Study supervision: Ahmed, Bhuta, Sercarz.
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REFERENCES

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