

Histological alterations following fine-needle aspiration for parathyroid adenoma: Incidence and diagnostic problems

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Abbreviations:

FNA, fine-needle aspiration; HAFFAP, histological alterations following fine-needle aspiration for parathyroid adenoma; PA, parathyroid adenoma; PFHAT, post fine-needle biopsy histological alterations of the thyroid; WHAFFT, worrisome histological alterations following fine-needle aspiration of the thyroid

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This study aimed to clarify the histological alterations following fine-needle aspiration for parathyroid adenoma and discuss the occurrence of diagnostic problems. Among the 392 patients with parathyroid adenoma who underwent resection, fine-needle aspiration was performed for 21 (5.1%) parathyroid adenoma nodules. Histological findings that were significantly more frequent in cases that underwent fine-needle aspiration were considered histological alterations following fine-needle aspiration for parathyroid adenoma, including the following six findings: thick fibrous capsule (71.4%), multilayered fibrous capsules (14.3%), capsular pseudo-invasion (42.9%), fibrous bands (57.1%), hemosiderin deposition (14.3%), and tumor implantation (14.3%). Eighteen parathyroid adenoma nodules (85.7%) exhibited one or more of the six findings. Tumor cells and adipocytes entrapped within the thick fibrous capsule were occasionally observed. The fibrous bands were frequently connected to the thick fibrous capsule. The number of passes, duration between fine-needle aspiration and resection, tumor size, and purpose of fine-needle aspiration were not related to the incidence of histological findings. Because of the histological alterations following fine-needle aspiration for parathyroid adenoma that can be easily mistaken for signs of atypical adenoma or parathyroid carcinoma, we recommend that the six findings be excluded from pathological findings indicating atypical adenoma or parathyroid carcinoma in patients with preoperative fine-needle aspiration.

KEYWORDS

fine-needle aspiration, needle tract implantation, parathyroid adenoma, thick fibrous capsule

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INTRODUCTION

Fine-needle aspiration (FNA) is a useful preoperative diagnostic tool for tumors. Histological alterations after FNA, including infarction, hemorrhage, tissue granulation, capsular distortion, papillary endothelial hyperplasia and fibrosis, have been reported in some organs.^{1–4} In the thyroid, the findings are well documented,⁵ and referred to as worrisome histological alterations following FNA of the thyroid (WHAFFT)^{6,7} or post-fine-needle biopsy histological alterations of the thyroid (PFHAT).⁵ Some PFHAT can cause problems during histological assessments, making diagnosis difficult, and sometimes leading to misdiagnosis.⁵

Fine-needle aspiration is not recommended for parathyroid adenoma (PA)-suspected nodules owing to the possibility of serious complications, such as massive hematomas, parathyromatosis, and misdiagnoses of malignancies during histological diagnoses.^{8,9} However, when the localization is unusual or the PA is mistaken for a thyroid nodule, FNA may be indicated or performed erroneously.^{10–13} Reports on histological alterations following FNA of the parathyroid are few.^{12,14–17} Therefore, this study aimed to clarify the histological alterations following FNA for parathyroid adenoma (HAFFAP) by comparing the histological findings of PA cases with and without preoperative FNA, and evaluating their incidence.

MATERIALS AND METHODS

We studied 392 patients with 411 PAs who underwent resection at the Kuma Hospital between January 2016 and March 2019. Clinical data were collected from the medical records of Kuma Hospital. FNA was performed on 21 (5.1%) PA nodules and not on the remaining 390 PA nodules. Of the 18 PA nodules with FNA, the number of passes was once in 13, twice in three, three times in one, and five times in one. FNA was performed using a 22-gauge needle under ultrasound guidance, and the aspirated materials were prepared by the press and release method.¹⁸ The needle sizes and number of passes were unknown in the three patients who underwent FNA in previous clinics prior to visiting our hospital. The period between the FNA and the resection ranged from 23 to 43083 (median 111) days. The mean ages of the patients with and without FNA were 58.3 years (range 21–74 years) and 61.0 years (range 9–89 years), respectively. The female-to-male ratios of patients with and without FNA were 4.00:1 and 4.03:1, respectively. To determine the sizes of PA, the largest dimensions were measured on the microscopic preparations. The mean sizes of PAs with and without FNA were 17.2 mm (range 5–43 mm) and 13.9 mm (range 2–45 mm), respectively. The review of histological data was performed by the first author and confirmed by the fourth

author; both of whom are specialists in endocrine pathology. Three patients with direct invasion to adjacent organs, high mitotic count (>1/10 high-power fields), vascular invasion or perineural invasion, which were indicative of parathyroid carcinoma, were excluded. The patients did not present with recurrent hypercalcemia and distant metastasis during follow-up. For PA with capsular pseudo-invasion and tumor implantation, immunohistochemical staining was performed using antibody against Ki-67 (MIB-1, 1:200 dilution; Dako, Glostrup, Denmark). Ki-67 labeling index was estimated by counting at least 500 tumor cells in the hotspot.

Statistical analysis was performed using Fisher's exact test. Results with *P* values less than 0.05 were considered statistically significant. Histological findings that were significantly more frequent in cases that underwent FNA were considered HAFFAP.

RESULTS

Table 1 shows the histological findings of PAs with and without preoperative FNA. Histological findings that were considered as HAFFAP were thick fibrous capsule, multilayered fibrous capsules, capsular pseudo-invasions, fibrous bands, hemosiderin depositions, and tumor implantations. Eighteen PA nodules (85.7%) exhibited one or more of the six lesions.

Thick fibrous capsule

Of the 21 PAs on which FNA was performed, 15 (71.4%) were encapsulated with thick fibrous connective tissue (Fig. 1a). The fibrous capsules tended to encapsulate the PAs entirely, but their thickness varied from place to place. In some of the PA nodules, the capsules were discontinuous. Tumor cells and adipocytes entrapped in the thick fibrous capsule (pseudo-invasive trapping) were observed occasionally (Fig. 1a). The capsules were not associated with any granulation tissue, hemosiderin deposition or inflammatory cell infiltrates. In contrast, the incidence of thick fibrous capsule in the PAs without FNA was lower (6.7%), and there was a significant difference (*P* < 0.001). Out of the 26 PAs with a thick fibrous capsule and without FNA for the PA lesion, seven (26.9%) had histories of FNA for ipsilateral thyroid nodules, three for contralateral thyroid nodules, two for the resection of an ipsilateral PA and one for the spontaneous hemorrhage of the PA.

Multilayered fibrous capsules

Multilayered fibrous capsules were more frequently observed in PAs with FNA (14.3%) than without FNA (0.8%) (*P* < 0.005) (Fig. 1b). One of three cases without FNA

Table 1 Histological findings of parathyroid adenomas with and without preoperative fine-needle aspiration (FNA)

| Histological findings | With FNA (N = 21) | Without FNA (N = 390) | P value |
|-----------------------------------|----------------------|--------------------------|---------|
| Intrathyroidal parathyroid (7) | 19.0% (4) | 0.8% (3) | <0.001 |
| Variant | | | |
| Oxyphilic (64) | 4.8% (1) | 16.2% (63) | |
| Clear (10) | 0% (0) | 2.6% (10) | |
| Endocrine atypia (11) | 0% (0) | 2.8% (11) | |
| Lobulation (89) | 19.0% (4) | 21.8% (85) | |
| Thick fibrous capsule (41) | 71.4% (15) | 6.7% (26) | <0.001 |
| Multilayered fibrous capsules (6) | 14.3% (3) | 0.8% (3) | <0.005 |
| Capsular pseudo-invasion (19) | 42.9% (9) | 2.6% (10) | <0.001 |
| Fibrous bands (38) | 57.1% (12) | 6.7% (26) | <0.001 |
| Cystic formation (56) | 28.6% (6) | 12.8% (50) | |
| Edema (60) | 14.3% (3) | 14.6% (57) | |
| Scar (21) | 4.8% (1) | 5.1% (20) | |
| Granulation tissue (2) | 4.8% (1) | 0.3% (1) | |
| Cholesterol crystal (1) | 4.8% (1) | 0% (0) | |
| Lymphocytic infiltration (11) | 0% (0) | 2.8% (11) | |
| Hemosiderin deposition (8) | 14.3% (3) | 1.3% (5) | <0.01 |
| Tumor implantation (3) | 14.3% (3) | 0% (0) | <0.001 |

previously underwent resection of ipsilateral PA. The findings were focally present and discontinuous. The layers ranged from two to four. Each layer tended to be thinner than the thick fibrous capsule, as mentioned above.

Capsular pseudo-invasion

Capsular pseudo-invasion was defined as tumor cell nests extending outside of the main tumor mass that is constantly associated with haphazardly distributed hyalinized connective tissue. In nine (42.9%) PA with FNA and 10 (2.6%) PA without FNA, a capsular pseudo-invasion was observed ($P < 0.001$) (Fig. 1c). Inflammatory cell infiltration, hemosiderin deposition, or tissue granulation was not observed in the area.

Fibrous bands

Fibrous bands were seen in 57.1% of the PAs with FNA and 6.7% of the PAs without FNA ($P < 0.001$) (Figure 1d).

The bands frequently connected to the thick fibrous capsule and frequently contributed to the lobulation of the tumor.

Hemosiderin deposition

Hemosiderin deposition was seen in 14.3% of the PAs with FNA and 1.3% of the PAs without FNA ($P < 0.01$) (Fig. 1e). The deposition appeared in the granulation tissue or hyalinized stroma.

Tumor implantation

Tumor implantation was defined as having the following two findings: (i) presence of tumor cell nests without fat cells outside of the main tumor, and (ii) no continuity with the main tumor (Fig. 1f). Tumor implantation was seen in 14.3% of the PAs with FNA. The lesions appeared as multiple nests in the connective tissue near the PA. Lesion distribution was localized to a single area around the tumors. Each nodule had no stromal reaction and was not surrounded by fibrous connective tissue. The lesions were never associated with mushroom-shaped capsular invasion or capsular invasion with laceration of the capsule, which were characteristic features of capsular invasion of the thyroid follicular carcinoma. The findings were not detected in the PAs without FNA.

Table 2 shows incidences of six HAFFAP lesions in 21 PA nodules from a clinical point of view. In nine patients with primary hyperparathyroidism, the purpose of FNA was a measurement of the parathyroid hormone using needle washout fluid to determine the location of the PA. In nine nodules, FNA was performed for lesions erroneously recognized as thyroid nodules in ultrasound examination. In the remaining three nodules, the reasons were unknown. There was no statistical significance between the two indications. In tumors measuring 15 mm or more, HAFFAP lesions tended to be more frequently seen than the smaller ones, but only fibrous bands showed statistical significance ($P < 0.05$). On the number of passes, the incidences of multilayered fibrous capsules, capsular pseudo-invasion, and fibrous bands were higher in once than twice or more. The duration between FNA and resection was not related to the incidences of HAFFAP. Ki-67 labeling indexes of PAs with capsular pseudo-invasion and tumor implantation were less than 3%.

DISCUSSION

FNA for parathyroid neoplasms increases the risk of massive hemorrhage, tumor seeding, parathyromatosis, or recurrence.^{8,16,19} Therefore, preoperative parathyroid FNA

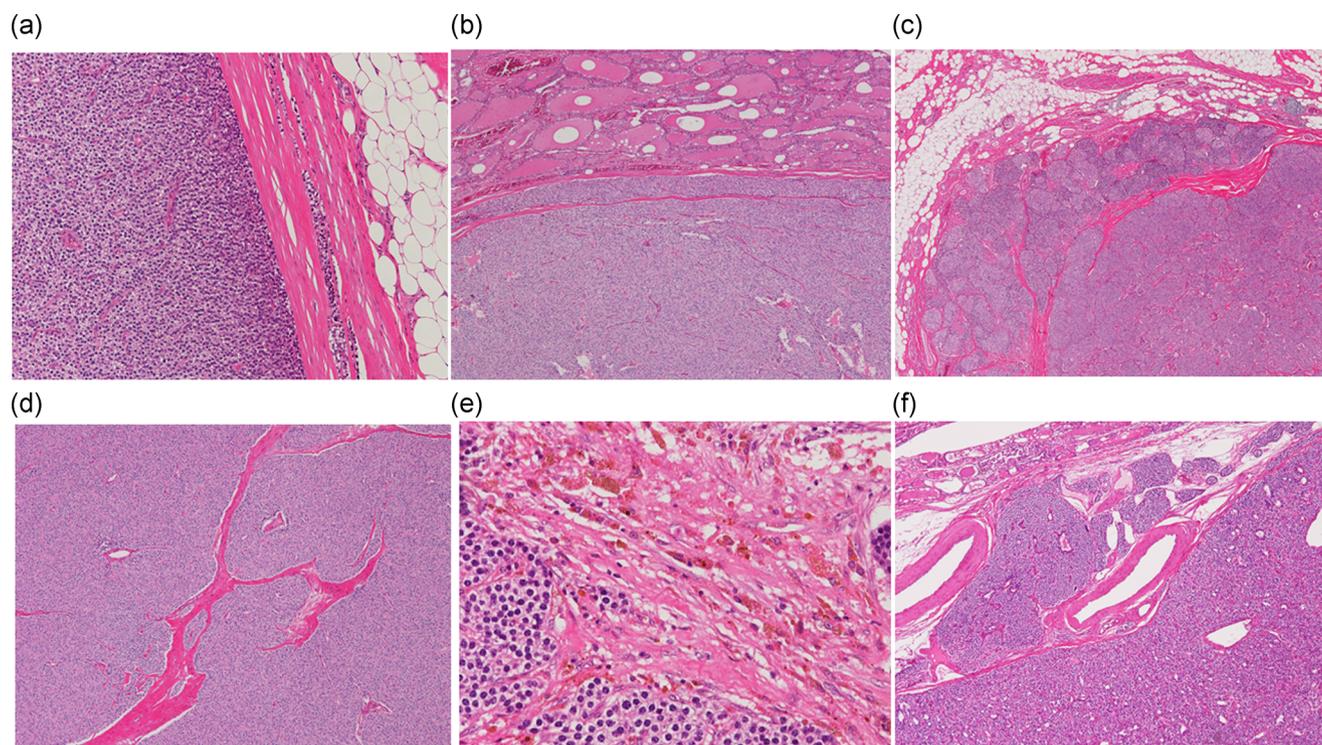


Figure 1 Histological alterations following fine-needle aspiration for parathyroid adenoma. (a) Thick fibrous capsule, (b) multilayered fibrous capsules, (c) capsular pseudo-invasion, (d) fibrous bands, (e) hemosiderin deposition, (f) tumor implantation.

should be avoided when possible, and should not be performed if parathyroid carcinoma is suspected.^{17,20} On histological alterations following FNA of the parathyroid, some findings including fibrotic or inflammatory reactions, cytological atypia, pseudo-invasive trapping, and parathyromatosis have been documented.^{12,14–17}

In the current study, six findings, including thick fibrous capsule, multilayered fibrous capsules, capsular

pseudo-invasion, fibrous bands, hemosiderin deposition, and tumor implantation, were considered as HAFFAP. Among them, multilayered fibrous capsules, capsular pseudo-invasion, and fibrous bands have been described as microscopic findings of atypical adenoma or adenocarcinoma.^{21–23} We recommend that the findings be excluded from pathological findings indicating atypical adenoma or parathyroid carcinoma in patients undergoing

Table 2 Incidences of histological alterations following fine-needle aspiration of 21 parathyroid adenomas

| | | Thick fibrous capsule | Multilayered fibrous capsules | Capsular pseudo-invasion | Fibrous bands | Hemosiderin deposition | Tumor implantation |
|---|-----------------------------|-----------------------|-------------------------------|--------------------------|---------------|------------------------|--------------------|
| Indication | For thyroid nodule (9) | 8 (88.9%) | 2 (22.2%) | 4 (44.4%) | 5 (55.6%) | 0 (0%) | 2 (22.2%) |
| | For parathyroid adenoma (9) | 8 (88.9%) | 0 (0%) | 2 (22.2%) | 4 (44.4%) | 2 (22.2%) | 1 (11.1%) |
| Tumor sizes | <15 mm (10) | 5 (50.0%) | 0 (0%) | 2 (20.0%) | 3* (30.0%) | 1* (10.0%) | 1 (10.0%) |
| | ≥15 mm (11) | 10 (90.9%) | 3 (27.3%) | 5 (45.5%) | 9 (81.8%) | 2 (18.2%) | 2 (18.2%) |
| Number of passes | Once (13) | 10 (76.9%) | 2 (15.4%) | 6 (46.2%) | 8 (61.5%) | 1 (7.7%) | 2 (15.4%) |
| | ≥Twice (5) | 3 (60.0%) | 0 (0%) | 0 (0%) | 1 (20.0%) | 1 (20.0%) | 1 (20.0%) |
| Duration between aspiration and resection | <100 days (10) | 7 (70.0%) | 1 (10.0%) | 4 (40.0%) | 5 (50.0%) | 1 (10.0%) | 1 (10.0%) |
| | >101 days (11) | 8 (72.7%) | 2 (18.2%) | 3 (27.3%) | 8 (72.7%) | 2 (18.2%) | 2 (18.2%) |

* $P < 0.05$.

preoperative FNA. Moreover, cytological atypia does not seem to be included in HAFFAP.

The incidence of thick fibrous capsule was the most frequently observed (71.4%) in the PAs with FNA. In the PAs without FNA, the incidence of thick fibrous capsule was significantly low (6.7%). Similarly, Norman *et al.*¹⁵ reported that the incidence of fibrotic reaction was 77%, which was statistically different from that of cases without FNA (4.3%) for parathyroid ($P < 0.0001$). In addition, in 26.9% of PA cases that revealed thick fibrous capsule but did not undergo FNA for the PA lesion, we noticed histories of FNA for thyroid nodules, resections of ipsilateral PA, or spontaneous hemorrhages of PA. According to Patel *et al.*²⁰ fibroses were caused by hemorrhages. We agreed with their theory. Hemosiderin deposition was not observed, indicating a trace of hemorrhage in or around the thick fibrous capsule. Hemosiderin might have disappeared because of the long duration between FNA and the resection.

Multilayered fibrous capsules and fibrous bands were made up of the same components as the thick fibrous capsule and were frequently connected to the thick fibrous capsule. Therefore, it was presumed that the pathogenesis was the same. Fibrous trabeculae are well known as one of the morphological criteria for diagnosing parathyroid carcinoma⁸ but can also be a feature of PA with evidence of hemorrhage or previous surgery.²⁴ In addition, the lobulations formed by fibrous trabeculae that mimic capsular invasion can be observed in PA.²⁴ We observed that tumor tissue was entrapped within the thick fibrous capsule and between the multilayered fibrous capsules. We should not misinterpret them for capsular invasion, even in cases without FNA.

Capsular pseudo-invasion and tumor implantation are the most problematic, and it is challenging to distinguish from true capsular invasions and direct invasions of the adjacent soft tissue, respectively. On thyroid FNA, arguments against the malignant nature are: (i) history of FNA, (ii) presence of other WHAFFT in the vicinity, (iii) linear pattern of invasion, (iv) presence of a single or only a few foci, and (v) absence of vascular invasion.⁵ An association of hyalinized connective tissue in the stroma has also indicated HAFFAP rather than a true capsular invasion, such as a thick fibrous capsule. As parathyroid tissue is readily engraftable, parathyroid auto-transplantations can be performed in conjunction with total thyroidectomies or parathyroidectomies.²⁵ For the same reason, parathyromatosis can appear after neck surgery for hyperparathyroidism.²⁶ Tumor implantation along the needle tract is a well-known complication of FNA for parathyroid carcinoma.¹⁷ In this study, we observed multiple tumor cell nests without encapsulation and stromal fibrosis near the main tumor. Lesion distribution was localized to a single area around the tumors. The lesions were never associated with mushroom-shaped capsular invasion or capsular invasion with laceration of the capsule, which were characteristic

features of capsular invasion of the thyroid follicular carcinoma. Needle tract implantation following thyroid FNA also shows a similar histological appearance.²⁷ Moreover, Ki-67 labeling indexes of PAs with capsular pseudo-invasion and tumor implantation were not high. Therefore, we believe that the multiple tumor cell nests we observed could be due to needle tract implantations; and therefore, they should not be considered as a malignant indicator.

Histological alteration following thyroid FNA has been well documented. According to the review published by Polyzos *et al.*⁵ PFHAT are generally divided into the acute and chronic forms. Acute PFHAT include hemorrhage, granulation tissue formation, poorly formed granulomas, siderophagia, vascular thrombosis, infarction, necrosis and mitoses. Chronic PFHAT include fibrosis, cellular and nuclear atypia, capsular distortion and pseudoinvasion, cystic degeneration, vascular proliferation, papillary endothelial hyperplasia, metaplasia (oncocyte, squamous cell and spindle cell), calcification and cholesterol clefts. The findings were apparently different from those of HAFFAP we described in the present study. We cannot consider WHAFFT and HAFFAP in the same way. It is important to understand that different organs or lesions require different reactions for tissue damage due to FNA. Additionally, it is important to consider the duration between FNA and resection. Acute PFHAT are usually observed in case of surgery within 3 weeks of FNA, whereas chronic PFHAT occur after 3 weeks of FNA.⁵ In our institute, the duration between FNA and operation was usually more than 1 month. Then, all findings observed in this study were suggestive of chronic HAFFAP. We think it is reasonable to say that there was no difference in the frequency of lesions when the cutoff value for the duration of FNA and surgery was set to 100 days.

In conclusion, we demonstrated six histological findings that included thick fibrous capsule, multilayered fibrous capsules, capsular pseudo-invasion, fibrous bands, hemosiderin deposition, and tumor implantation and their incidence. These findings can be easily mistaken for signs of atypical adenoma or parathyroid carcinoma. We recommend that HAFFAP should be excluded from pathological findings indicating atypical adenoma or parathyroid carcinoma in patients undergoing preoperative FNA. In addition, we opined that FNA should be avoided in the preoperative diagnosis of PA.

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DISCLOSURE STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

Conception and design of the study; M Hirokawa, A Miya, A Miyauchi. Acquisition and analysis of data; AS, M Higuchi. Drafting the manuscript; TH, SK.

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