Utility of fine-needle aspiration cytology in the identification of parathyroid lesions

ABSTRACT

Objectives: Fine-needle aspiration cytology (FNAC) is a first-line investigation in the evaluation of neck nodules. In an attempt to search for reliable cytomorphological criteria for parathyroid lesions, we systematically evaluated cytomorphology of FNAC of parathyroid lesions.

Study Design: FNAC of 15 parathyroid and 15 hyperplastic thyroid nodules with histological confirmation were reviewed for following features: Cellularity, follicles, bare nuclei, cohesiveness, vascular profiles, cytoplasmic granularity, intracytoplasmic vacuolation, mitosis, macrophages, and colloid.

Results: Vascular proliferation, bare nuclei, intracytoplasmic fat vacuolation, absence of colloid, and high cellularity showed significant association with parathyroid lesions ($P \leq 0.05$). Intracytoplasmic fat vacuolation was 53.3% sensitive and 100% specific for parathyroid. Follicular pattern and papillaroid clusters were also important; however, they achieved nearly significant statistical difference ($P = 0.05$ and $P = 0.06$, respectively). The combination of vascular proliferation and intracytoplasmic fat vacuolation were significantly associated with parathyroid ($P = 0.006$) whereas the absence of bare nuclei and the presence of background colloid were associated with thyroid cytomorphology ($P = 0.03$).

Conclusion: No single cytological feature is helpful in differentiating parathyroid from thyroid lesion. Vascular proliferation, bare nuclei, intracytoplasmic fat vacuolation, high cellularity, and the absence of colloid were significantly associated with the parathyroid origin. The combination of at least two features — vascular proliferation and intracytoplasmic fat vacuoles — were highly suggestive of parathyroid origin.

Key words: Fine-needle aspiration cytology (FNAC); parathyroid; thyroid

Introduction

Neck nodules are easy to access for fine-needle aspiration cytology (FNAC), and thyroid is the commonest organ to present as a neck nodule. FNAC being technically simple and economical becomes the first line of investigation in the workup of these nodules. Thyroid and parathyroid nodules can be clinically indistinguishable; however, advanced imaging and localization modalities can resolve the issue in most of the cases but still there should be a few cases where differentiation of thyroid from parathyroid lesion may not be possible. During the investigation of thyroid nodule, pathologist may come across FNAC of parathyroid lesion and therefore should be aware of the cytomorphological features to differentiate parathyroid from thyroid. Parathyroid lesions

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DOI: 10.4103/0970-9371.175490

Niraj Kumari, Deepthi Mishra, Roma Pradhan, Amit Agarwal, Narendra Krishnani

Departments of Pathology and ‘Surgical Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence: Dr. Niraj Kumari, Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. E-mail: niraj@sgpgi.ac.in
constitute adenoma in 80-85% of the patients followed by hyperplasia in 6-15% of the patients and carcinoma in <1% of the patients.[1,2] Distinguishing thyroid from parathyroid on FNAC is difficult because of the overlapping cytomorphological features, and some studies have also used immunohistochemistry (IHC) for differentiating a parathyroid lesion from thyroid lesion.[3,4] The differentiation of parathyroid hyperplasia, adenoma, and carcinoma is almost impossible on FNAC and it is in fact not required. However some studies have attempted to do so.[5] Our institute being a tertiary care referral center caters to a population from the iodine deficient sub-Himalayan belt because of which we receive many patients with clinically suspected thyroid nodules for FNAC. In the workup of thyroid nodules, we came across patients with clinically suspected as well as incidental parathyroid lesions in the neck and at aberrant locations that underwent FNAC. Absher et al.[4] has reported a comparative evaluation of thyroid and parathyroid morphology but the details of thyroid cases are unclear in their study. We systematically evaluated the features of parathyroid FNAC with age matched and histologically confirmed thyroid FNAC to derive reliable cytomorphologic criteria for their differentiation.

Materials and Methods

Fifteen cases of parathyroid FNAC were analyzed retrospectively by two independent pathologists, and a consensus was achieved on a multi-head microscope after discussion. All the cases had histological confirmation. The cytomorphological features were evaluated and compared with FNAC of 15 age-matched cases of histologically proven hyperplastic thyroid nodules. The cytomorphological features that were evaluated included cellularity, pattern (dispersed, loose aggregates, papillaroid, or tight clusters), presence of bare nuclei, presence of vascular proliferation, degree of anisocytosis and anisonucleosis, cytoplasm granularity, presence of intracytoplasmic fat vacuoles, mitosis, nuclear chromatin, presence of macrophages, and background colloid. Biochemical and imaging parameters were recorded from the hospital information system. Individual or a combination of cytomorphological features were compared between parathyroid and thyroid using Chi-square test and a \( P \) value of <0.05 was taken as significant.

Results

Fifteen cases of ultrasound (US)-guided FNAC of parathyroid lesions were reported over a period of 10 years. There were six males and nine females with age ranging from 35 years to 78 years. Thirteen of 15 cases of parathyroid were located in neck, 1 case was intrathyroidal, and another 1 was located in mediastinum. The number of passes in parathyroid lesions ranged from one to two, whereas the number of passes in thyroid it ranged from one to three. The number of slides prepared for parathyroid FNAC ranged from three to ten (average six slides). The number of slides from thyroid ranged from 2 to 14 (mean seven slides). Eleven cases of parathyroid lesions showed high cellularity (>500 cells), two cases showed moderate cellularity, and two cases showed low cellularity according to the criteria described by Dimashkieh et al.[6] Thirteen cases were parathyroid adenoma, one was hyperplasia, and another one was carcinoma on definitive histopathology. In case of thyroid, all 15 cases were histologically proven hyperplastic nodules. The distribution of cytomorphological features evaluated in both parathyroid and thyroid FNA are detailed in Table 1. Certain features, such as intracytoplasmic fat vacuoles, tight or papillaroid clusters, bare nuclei, and vascular proliferation, were prominent in parathyroid aspirates whereas follicular pattern and the presence of background colloid were prominent in thyroid aspirates [Figure 1a-d]. Dispersed cells were frequently seen in both types of lesions. None of the smears showed mitotic activity either in thyroid or in parathyroid FNAC. At the time of FNAC, serum parathyroid hormone levels were available in nine cases, and it was normal in one case (28 pg/mL) and raised in eight cases ranging from 72.2 pg/mL to 2180 pg/mL (normal level 9-55 pg/mL). In the remaining six cases, the parathyroid hormone (PTH) levels were done after the occurrence of

![Figure 1](image-url)
A parathyroid lesion was suggested on FNAC. Serum calcium was available in 10 cases and was raised in two cases at the time of FNAC (13 mg/dL and 13.7 mg/dL, normal level 8.6-10.8 mg/dL). Vascular proliferation, bare nuclei, intracytoplasmic fat vacuolation, absence of background colloid, and high cellularity were significantly associated with parathyroid lesions ($P$ value <0.05) [Table 2]. Intracytoplasmic fat vacuolation was 53.3% sensitive but 100% specific for parathyroid. Follicular pattern and tight clusters were also important features in differentiating parathyroid and thyroid lesions; however, they could achieve a nearly significant statistical difference ($P$ value = 0.05 and $P$ value = 0.06, respectively). The combination of two or more features, such as vascular proliferation, tight clusters, intracytoplasmic fat vacuoles, bare nuclei and absence of colloid, were also analyzed to see if they are helpful in differentiating the parathyroid cytomorphology from thyroid. The presence of combination of vascular proliferation and intracytoplasmic fat vacuoles were significantly associated with parathyroid cytology ($P$ value = 0.006), whereas the combination of absence of bare nuclei and of presence of background colloid were associated with thyroid cytomorphology ($P$ value = 0.03) [Table 2].

**Discussion**

In recent years, several series have reported the cytological features of parathyroid lesions.\(^5,7\) The role of FNAC in parathyroid lesions is limited as a diagnostic modality because of better imaging modalities and localizing scans such as methoxy isobutyl isonitrile (MIBI) and technetium 99. In the presence of clinical evidence of hyperparathyroidism, high-frequency sonography is an accurate and noninvasive means of localizing the enlarged parathyroid glands. However, FNAC is useful for locating

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**Table 1: Distribution of cytological features in parathyroid and thyroid lesions**

| Cytological features | Hyperplasia ($N = 1$) | Adenoma ($N = 13$) | Carcinoma ($N = 1$) | Thyroid lesions |
|----------------------|-----------------------|---------------------|---------------------|-----------------|
|                      | Cellularity           | Cell pattern        |                      |                 |
|                      | High (1)              | Dispersed/ single   | Mild (5)            |                 |
|                      |                       | cells               | Moderate (9)        |                 |
|                      |                       | Moderate (2)        | High (1)            |                 |
|                      |                       | Loose aggregates    | 1                   | 10              |
|                      |                       | Tight and papillaroid clusters | 3 | 1 |
|                      |                       | Follicles           | 5                   | 11              |
|                      |                       | Nuclear pleomorphism | Mild (1)           | Mild (12)       |
|                      |                       | Chromatin           | Stippled            | Stippled        |
|                      |                       | Nucleoli            | Absent              | Absent          |
|                      |                       | Cell borders        | Ill defined         | Ill defined     |
|                      |                       | Cytoplasmic granularity | Present            | Present         |
|                      |                       | Vascular proliferation | Absent            | Absent          |
|                      |                       | Mitosis             | Absent              | Absent          |
|                      |                       | Oxyphil cells       | Absent              | Present (2)     |
|                      |                       | Bare nuclei         | Absent              | Present (13)    |
|                      |                       | Colloid background  | Absent              | Present (2)     |
|                      |                       | Macrophages         | Absent              | Present (1)     |
|                      |                       | Intracytoplasmic vacuoles | Absent            | Absent          |

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**Table 2: Comparison of cytological features between parathyroid and thyroid lesions**

| Cytomorphological features | Parathyroid lesions ($N = 15$) | Thyroid lesions ($N = 15$) | $P$ value |
|----------------------------|---------------------------------|---------------------------|-----------|
| Single cells               | 9                               | 8                         | 0.7       |
| Papillaroid/tight clusters | 6                               | 1                         | 0.06      |
| Follicles                  | 6                               | 11                        | 0.05      |
| Vascular proliferation     | 11                              | 3                         | 0.008     |
| Bare nuclei                | 11                              | 5                         | 0.02      |
| Intracytoplasmic fat vacuoles| 8                             | 0                         | 0.002     |
| Background colloid         | 0                               | 13                        | 0.001     |
| Cellularity                |                                 |                           | 0.002     |
| Mild                       | 2                               | 5                         | 0.1       |
| Moderate                   | 2                               | 9                         |          |
| Marked                     | 11                              | 1                         |          |
| Vascular proliferation + tight clusters | 5                           | 1                         | 0.1       |
| Vascular proliferation + intracytoplasmic fat vacuoles | 7                         | 0                         | 0.006     |
| Vascular proliferation + intracytoplasmic fat + tight clusters | 4                        | 0                         | 0.06      |
| Bare nuclei + colloid      | 0                               | 4                         | 0.03      |
incidentally detected lesions in asymptomatic patient presenting as cystic masses or when the lesions are present in abnormal locations.\cite{3,6,9} The morphologic features described are much more variable so that distinction between parathyroid and thyroid cannot be based on the presence or absence of a single feature. In an endemic iodine deficient region, it is difficult to differentiate a parathyroid nodule from a coexistent thyroid nodule, the occurrence of the latter is more common, on clinical and radiological grounds. The differentiation of parathyroid lesions from colloid nodule is easy because of the presence of intact thyroid follicles and colloid in the background but the differentiation with a hyperplastic nodule is difficult. In the present study, two of 15 cases had aberrant location with one intra-thyroidal and the other mediastinal. Nine cases had suspicion of coexisting parathyroid and thyroid nodules, whereas six cases were incidental and sampled with a clinical suspicion of thyroid lesion. Before the cytological diagnosis was made, parathyroid hormone levels were available in nine cases where it was raised in eight cases, and normal in 1 case. Serum parathormone was done in the remaining five cases, later on the level was found to be elevated. In one case, the parathormone level was not available. The cytomorphological features were predominant in parathyroid aspirates including vascular proliferation, high cellularity, and bare nuclei that were seen in 73.3% of parathyroid lesions and in only 7% to 28% of thyroid lesions. Vascular proliferation has been shown by Abati \cite{10} in five out of six cases of parathyroid diagnosed on FNAC, whereas Dimashkieh et al.\cite{6} has shown 6 of 20 cases with prominent vascular network. Most of the studies have shown predominantly moderate cellularity in parathyroid FNACs.\cite{3,4,6,9} In the present study, we found high cellularity in nearly two-thirds (73.3%) of cases according to the criteria mentioned by Dimashkieh et al.,\cite{6} which could be a reason for not having any inadequate aspirate in our series. The presence of bare nuclei has been shown by several studies.\cite{4,6,9} One of the features that we exclusively found in parathyroid lesions but not in thyroid lesions was the presence of multiple tiny intracytoplasmic fat vacuolations that was seen in nearly 50% of cases with 53.3% sensitivity and 100% specificity. We could find only one study by Absher et al.,\cite{4} who reported intracytoplasmic vacuoles in 43% of their cases. Shidham et al. have reported single large fat vacuole in normal parathyroid tissue that decreases in hyperplasia and adenoma cases.\cite{10} There were no normal parathyroid tissue in the present study and this was the reason that multiple small vacuolations were seen instead of single large vacuole. Another important feature seen was papillaroid or tight clusters. This architectural pattern has been reported with similar distribution in most of the studies.\cite{3,4,6,9} Most of the studies reported present a descriptive cytomorphological pattern of parathyroid FNAC. Absher et al.\cite{4} compared their parathyroid cytomorphological features with thyroid FNAC similar to our study. Besides evaluating both thyroid and parathyroid cytology we also correlated the association of individual or combinations of cytomorphological features with thyroid or parathyroid origin that has not been reported till date with the best of our knowledge. We found intracytoplasmic fat vacuolations, vascular proliferation, high cellularity, presence of bare nuclei, and the absence of background colloid to be significantly associated with parathyroid origin ($P$ value $<0.05$) [Table 2]. Intracytoplasmic fat vacuolations with vascular proliferation and bare nuclei with absence of colloid were significant combination findings in detecting parathyroid origin ($P < 0.05$) [Table 2]. A subtle feature that we experienced while evaluating parathyroid smears was the presence of small nuclei with irregular nuclear outline as compared to thyroid follicular epithelial cells.

Immunocytochemical analysis for PTH has been used by a few studies\cite{3,6} that could serve as an adjunct to cytological diagnosis in difficult cases specially at aberrant locations and in incidental nodules. We were not able to differentiate parathyroid hyperplasia, adenoma, and carcinoma on FNAC; however, Tseng et al.\cite{5} have tried to do so. One of the disadvantages of doing parathyroid FNAC, especially in cases of clinically suspected carcinoma, is the occurrence of seeding of the needle track by carcinoma cells. A case of needle track seeding has been reported earlier from our institute.\cite{11} Thus, the use of FNAC should not be encouraged in parathyroid lesions that are clinically, radiologically, and serologically suspected as carcinoma.

**Conclusion**

There are overlaps in the cytomorphologic features of parathyroid and thyroid FNAC smears and no single feature is helpful in differentiating parathyroid lesion from thyroid lesion on FNAC. Constellation of at least two morphological features along with better localizing investigations and serum parathormone levels help to provide definitive diagnosis of parathyroid origin and distinguish it from thyroid lesions. The familiarity with parathyroid cytomorphological features may help in identifying or at least suspecting parathyroid origin in cases of incidental and aberrantly located nodules. We found that vascular proliferation, bare nuclei, intracytoplasmic fat vacuolation, high cellularity, and the absence of background colloid to be significantly associated with parathyroid origin. The presence of combination of vascular proliferation and intracytoplasmic fat were highly suggestive of parathyroid origin.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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