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Original Article

Liquid-based cytology in the fine needle aspiration of parathyroid lesions: a comparison study with the conventional smear, ThinPrep, and SurePath

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Abstract: Liquid-based cytology (LBC) has been progressively used for evaluating fine needle aspiration (FNA) specimens. However, limited studies have examined LBC in FNA of parathyroid lesions. We retrospectively reviewed 24 FNA specimens of parathyroid lesions, including 6 specimens prepared by conventional smear, 12 specimens prepared using ThinPrep method, and 6 specimens prepared using SurePath method. The 18 LBC specimens were also used for cell block preparation and immunostaining for parathyroid hormone (PTH). LBC specimens more frequently showed variable cellularity; microfollicular structure; bubbly or vacuolated cytoplasm; and small, round cells with distinct borders compared to specimens prepared by conventional smear. ThinPrep specimens showed a clean background and fewer isolated cells and naked nuclei compared to specimens prepared using the other methods. SurePath specimens showed many white blood cells in the background and more scattered single cells and naked nuclei compared to ThinPrep specimens. Specimens prepared using the 3 methods often showed colloid-like material but did not contain dense globular colloidal structures. White blood cells in the background of LBC specimens serve as useful indicators for estimating cell size. The nuclear size of parathyroid cells was similar to or smaller than that of inflammatory cells in the background. Cell block sections showed definite histological features of the parathyroid tissue and strong positive immunostaining for PTH. Awareness of these cytologic features of parathyroid FNA specimens prepared using ThinPrep and SurePath methods may help in preventing misdiagnosis. Cell block preparation and PTH immunostaining should be performed for the definitive diagnosis of parathyroid lesions.

Keywords: Fine needle aspiration, cytology, ThinPrep, SurePath, parathyroid

Introduction

The number and location of the parathyroid glands can vary [1]. More than 4 parathyroid glands are present in approximately 25% of the normal population, and locations of the inferior glands are more variable than those of the superior glands [1, 2]. Fine needle aspiration (FNA) of parathyroid lesions can produce diagnostically challenging specimens, especially for patients without any clinical evidence of hyperparathyroidism. Therefore, analysis of FNA specimens of parathyroid nodules located within the thyroid gland often results in their misinterpretation as thyroid nodules. Identification of the ectopic locations of the parathyroid glands and awareness of the cytomorphologic features of parathyroid FNA specimens are important to avoid misdiagnosis in such cases. However, FNA specimens of parathyroid lesions are often cellular and their cytomorphologic features are similar to those of thyroid lesions [3, 4]. FNA specimens of parathyroid lesions showing hypercellularity and microfollicular structures are often misinterpreted as follicular neoplasm of the thyroid gland [5]. Although some studies have investigated the diagnosis of parathyroid lesions by performing FNA [3, 6, 7], their diagnosis by using FNA specimens is still challenging [7-9].

Liquid-based cytology (LBC), which was originally developed for diagnosing gynecologic cervical smears, has been progressively used for preparing both non-gynecologic body fluid and FNA specimens in different countries [10]. LBC has been successfully used for evaluating thyroid FNA specimens to reduce the variability in the quality of cell morphology and artifacts encountered with specimens prepared by con-

Table 1. Cytomorphologic features of parathyroid fine needle aspiration specimens prepared by conventional smear and liquid-based cytology

Characteristics	Conventional smear (n = 6)	ThinPrep (n = 12)	SurePath (n = 6)
Cellularity			
Low	0	3	1
Intermediate	0	5	1
High	6	4	4
Pattern			
Papillary	6	6	4
Microfollicular	6	12	6
Loosely cohesive groups	6	9	3
Tight three-dimensional clusters	6	3	3
Honeycomb sheets	0	1	0
Isolated cells	6	10	6
Capillary network	6	6	4
Naked nuclei	6	10	6
Colloid-like material	6	10	6
Nucleus			
Round to oval	6	12	6
Lymphocyte-like chromatin	6	12	6
Hyperchromatic	6	12	6
Granular	6	12	6
Micronucleoli	0	1	2
Anisokaryosis	0	3	1
Cytoplasm			
Pale blue	6	12	6
Oxyphilic	3	4	3
Bubbly vacuolated	0	8	3
Cell border			
Distinct	6	12	6
Frayed	6	7	3

ventional smear [11-16]. However, little is known about the cytologic features and utility of LBC preparations for evaluating parathyroid lesions.

This study aimed to establish the cytomorphologic features of parathyroid FNA specimens prepared using ThinPrep and SurePath methods and to determine the preoperative diagnostic role of LBC for evaluating parathyroid lesions.

Materials and methods

We retrospectively reviewed 24 specimens of patients with parathyroid lesions who underwent FNA at the Catholic University of Korea, Seoul St. Mary's Hospital between January 2009 and December 2014. All FNA procedures were performed by radiologists by using 23-gauge needles under real-time ultrasound guidance. Of the 24 FNA specimens, 6 were directly smeared on slides and were immediately fixed using 95% ethanol, 12 were prepared using the ThinPrep method (Hologic Inc, Marlborough, MA), and 6 were prepared using the SurePath method (BD Diagnostics, Franklin Lakes, NJ). The 18 specimens prepared using LBC (ThinPrep and SurePath methods) were also used for preparing cell blocks. All FNA specimens were stained with Papanicolaou stain, and the cell blocks were stained with hematoxylin-eosin. Specimens prepared by conventional smear and LBC were independently reviewed by 2 endocrine pathologists (SHL and CKJ), and all the cytomorphologic features of these specimens were recorded. Discrepancy in the observations of the 2 reviewers was resolved based on consensus.

Presence of parathyroid cells was confirmed by performing histological analysis after surgery (n = 15) and immunocytochemical staining of cell block sections (n = 18) for parathyroid hormone (PTH). Final diagnoses of the lesions were parathyroid hyperplasia (n = 17), parathyroid adenoma (n = 5), and parathyroid carcinoma (n = 2).

Results

Table 1 summarizes the cytologic features of parathyroid FNA specimens prepared by conventional smear and LBC.

Conventional smear

All FNA smears were highly cellular and showed variable architecture, including papillary, microfollicular, loosely cohesive, or tight three-dimen-

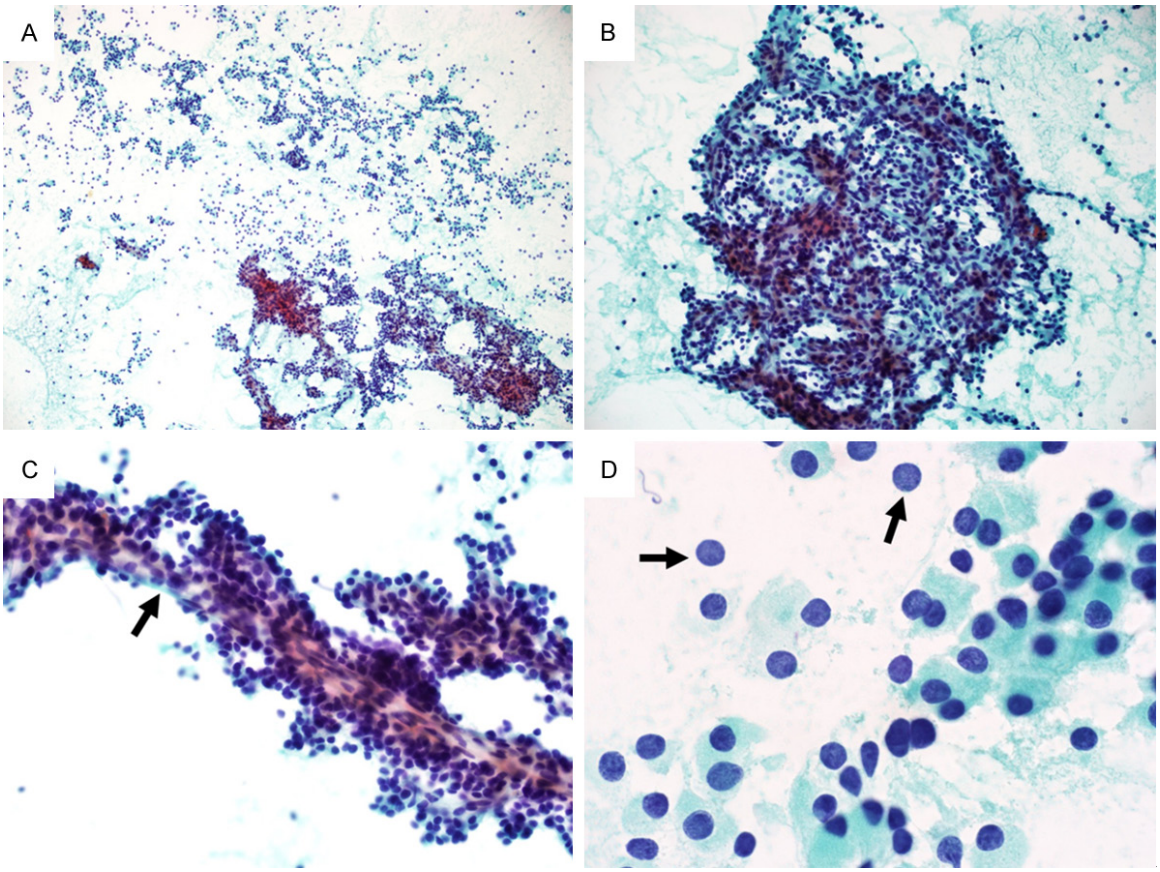

Figure 1. Conventional smears of parathyroid fine needle aspiration specimens. A. The smear is highly cellular and shows dispersed single, small uniform cells; microfollicular clusters; and loosely cohesive tissue fragments (× 100). B. A cluster of cells showing prominent capillary vasculature (× 200). C. Papillary architecture consisting of small, round cells and a fibrovascular core (arrow; × 400). D. Parathyroid cells showing fragile cytoplasm. Naked nuclei (arrows) from ruptured cells; the nuclei are small and round and have finely granular chromatin (× 1000).

sional clusters (**Figure 1A** and **1B**). Numerous isolated cells were scattered throughout the background, and naked nuclei were frequently observed. Capillary networks were frequently observed (**Figure 1C**) while colloid-like material was occasionally observed in all the smears. The nuclei were round to oval, hyperchromatic, and granular, and the cytoplasm was pale blue or oxyphilic. Cell borders were often frayed (**Figure 1D**).

ThinPrep LBC

Specimens prepared using ThinPrep LBC showed variable degree of cellularity. The specimens predominantly showed a microfollicular architectural pattern; however, other patterns were also observed (**Figure 2**). Monolayered, honeycomb-shaped sheets were observed in 1 ThinPrep specimen. Naked nuclei were occasionally observed (**Figure 3**), while colloid-like material and capillary networks were variably observed (**Figure 4**). Nuclear features of these specimens were similar to those observed in specimens prepared by conventional smear. However, the size of the nuclei was smaller and cell borders were better preserved in ThinPrep specimens than in specimens prepared by conventional smear (**Figure 2**). Further, bubbly or vacuolated cytoplasm was more frequently observed and mild anisokaryosis was occasionally observed in ThinPrep specimens (**Figure 3**).

SurePath LBC

Cytomorphologic features of parathyroid cells in specimens prepared using SurePath LBC were not largely different from those of parathyroid cells in specimens prepared using ThinPrep

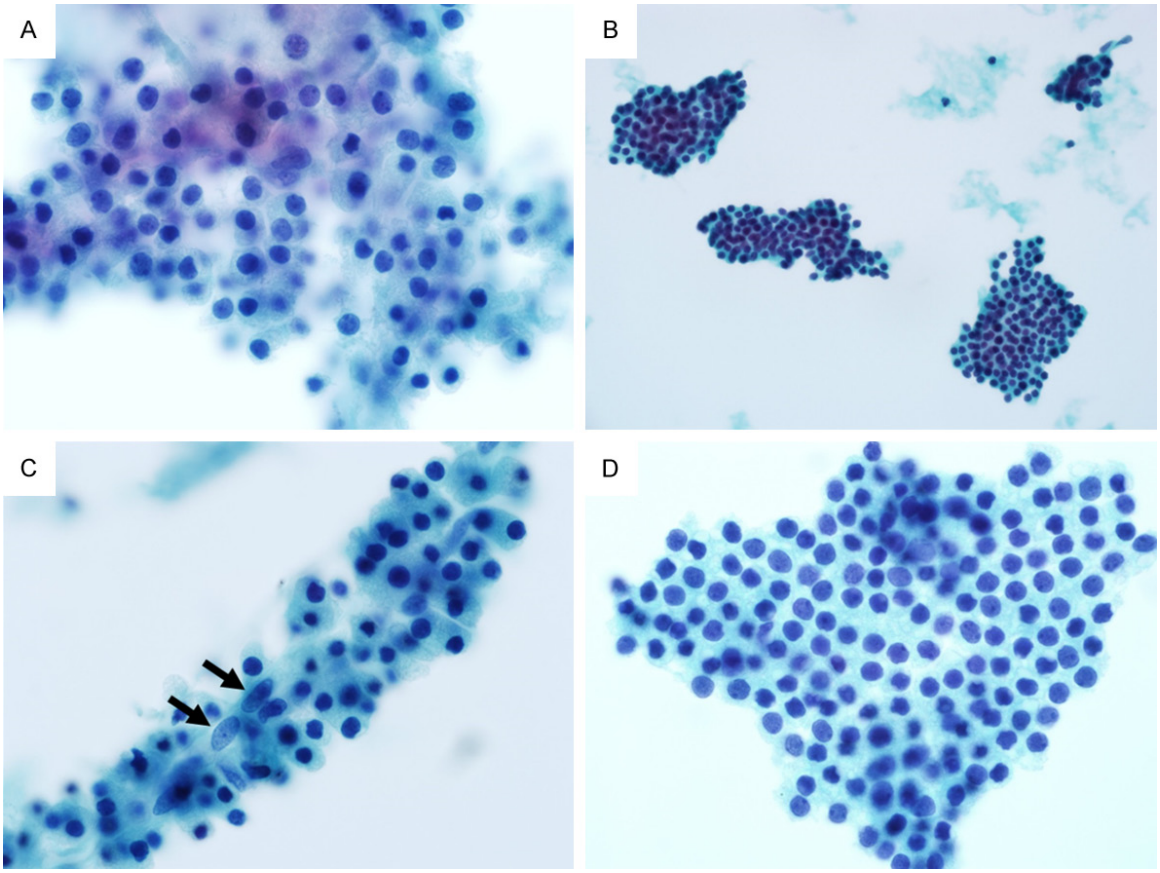

Figure 2. Architectural patterns of parathyroid fine needle aspiration specimens prepared using ThinPrep. A. Loosely cohesive clusters of cells with small, uniform, and round nuclei and well-defined borders (× 1000). B. Tissue fragments showing microfollicular pattern with crowding and overlapping of uniform, small nuclei (× 400). C. Papillary structure consisting of uniform, small cells clinging to the capillary vasculature and endothelial cells (arrows; × 1000). D. A monolayer of parathyroid cells with well-defined borders and centrally located uniform, small nuclei in a honeycomb pattern (× 1000).

LBC. However, SurePath specimens showed thicker three-dimensional clusters, more isolated single cells, and more white blood cells in the background than ThinPrep specimens (**Figure 5**).

Cell blocks

All LBC specimens (n = 18) could be used for preparing cell blocks. Use of cell blocks allowed easy identification of whether cells were of parathyroid or thyroid origin, irrespective of the cell number (**Figure 6**). All the cell blocks, including those with less number of cells, yielded positive results for the immunostaining of PTH (**Figure 6**).

Discussion

Previous studies have indicated that differentiation between parathyroid and thyroid follicular lesions by using FNA specimens is difficult [7, 17-19]. Nevertheless, the cytologic features favoring parathyroid lesion over thyroid follicular lesion are smaller cells having pale scant cytoplasm, round to oval nuclei with stippled nuclear chromatin (so-called salt-and-pepper appearance), prominent vascular network with attached epithelial cells, and the frequent occurrence of single cells and naked nuclei [7]. Cytologic features of parathyroid FNA specimens that lead to their misdiagnosis as thyroid follicular lesions include high cellularity, follicular formation, papillary structure, and presence of colloid-like material [3, 7, 8, 18, 19]. However, these features have been primarily studied using specimens prepared by conventional smear. To our knowledge, only one study has characterized the cytomorphologic features of parathyroid lesions by using ThinPrep speci-

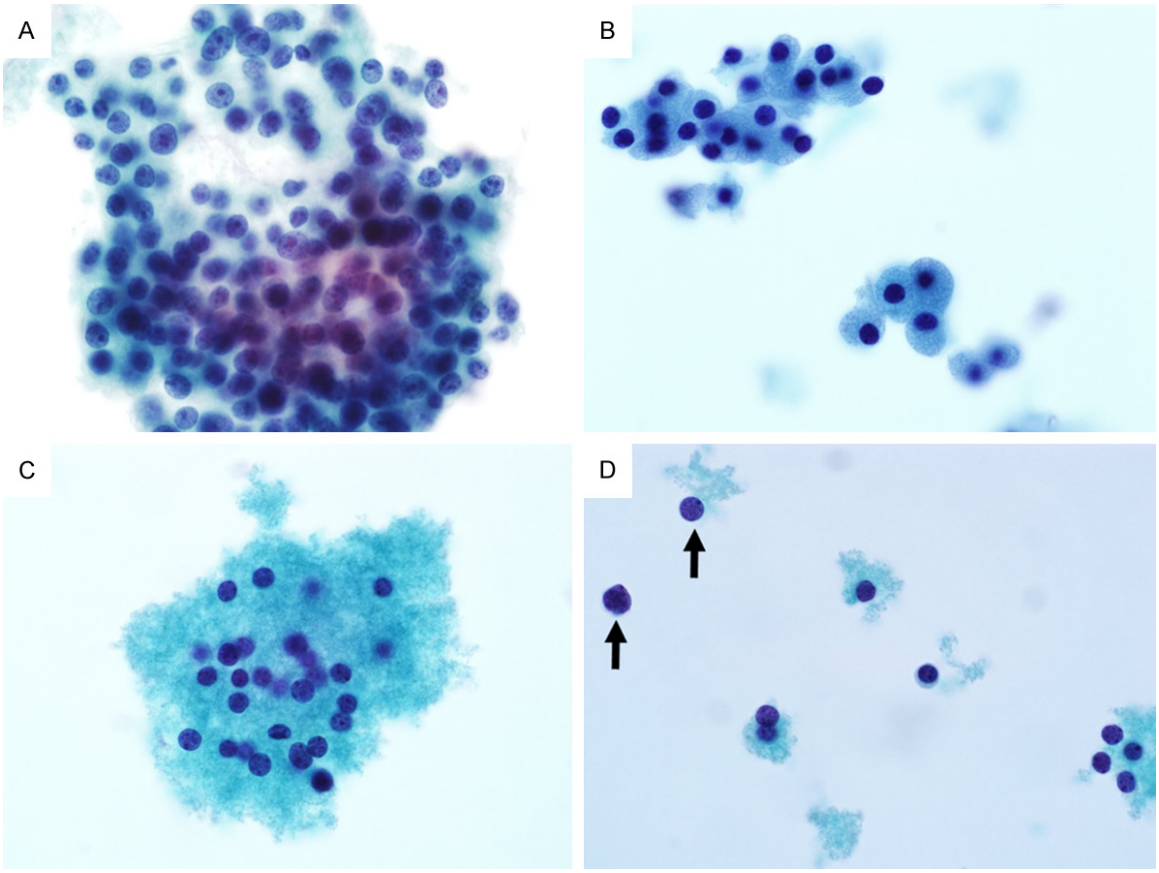

Figure 3. Cytologic features of parathyroid fine needle aspiration specimens prepared using ThinPrep. A. A three-dimensional cluster of parathyroid cells with a microfollicular arrangement. Nuclei showing mild anisokaryosis, granular chromatin, and small nucleoli (× 1000). B. Loose two-dimensional clusters of oxyphilic cells consisting of uniform, round cells with vacuolated cytoplasm and well-define borders. Nuclei are centrally or eccentrically located (× 1000). C. A cluster of parathyroid cells with frayed borders. Their cytoplasmic borders are indistinct (× 1000). D. The cytoplasm is fragile, and naked nuclei (arrows) are observed (× 1000).

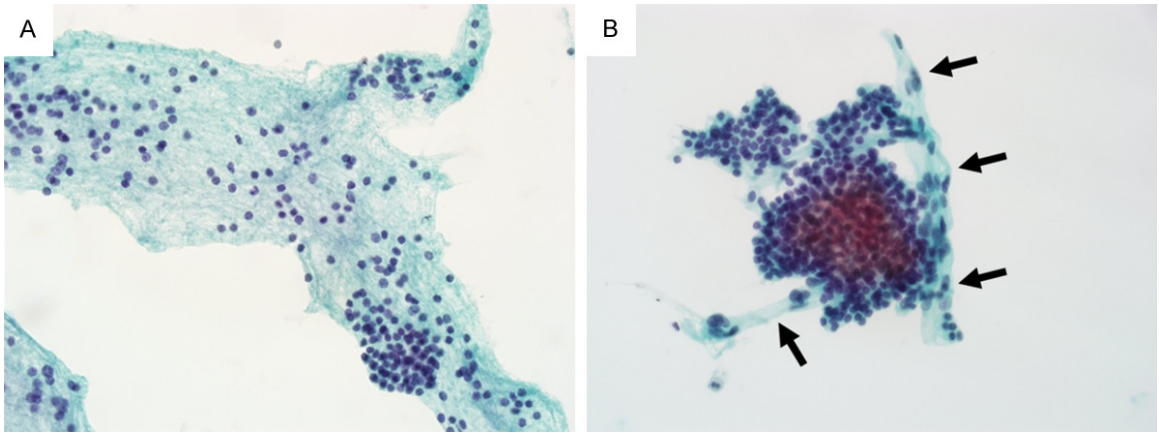

Figure 4. Parathyroid fine needle aspiration specimens prepared using ThinPrep showing stringy colloid-like material mixed with parathyroid cells (A, × 400) and capillary network (B, × 400).

mens. However, characterization of the cytomorphologic features of parathyroid lesions by using SurePath specimens has not been reported to date [20].

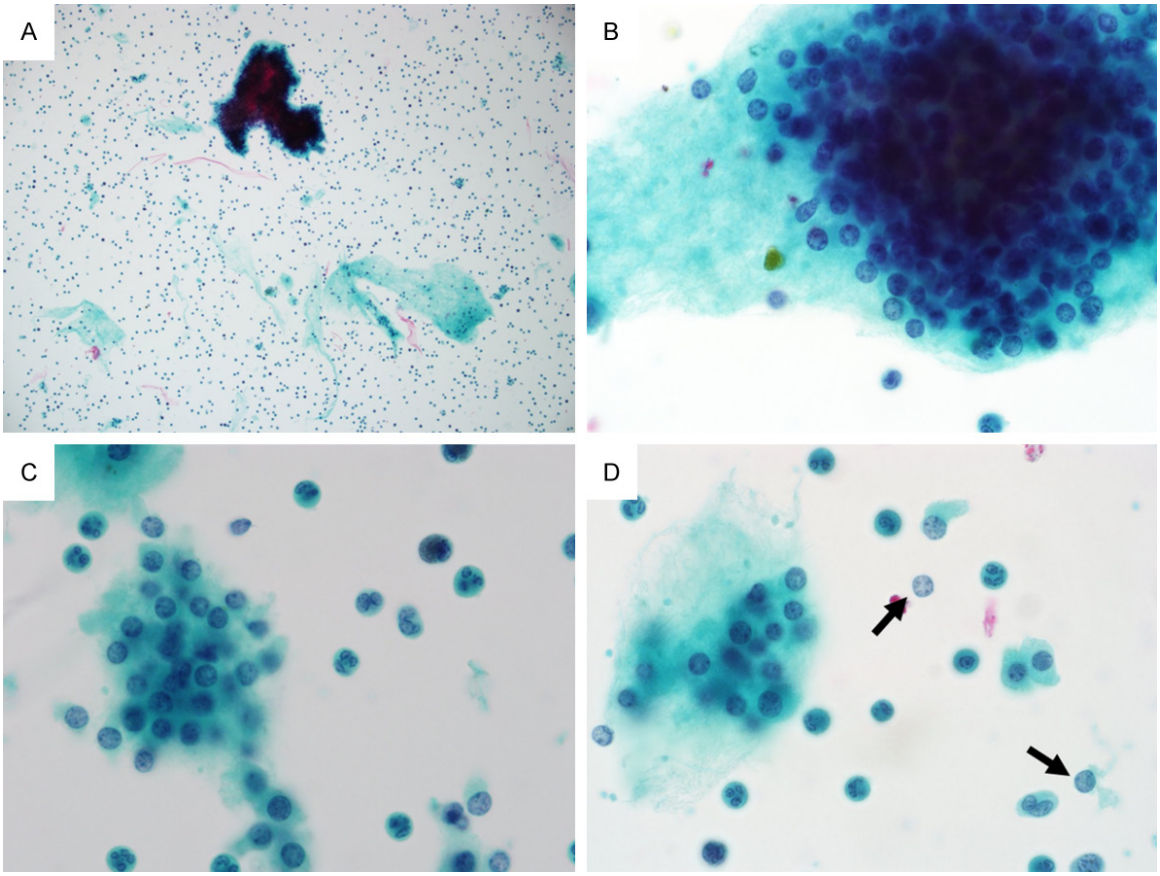

Figure 5. Cytologic features of parathyroid fine needle aspiration specimens prepared using SurePath. A. The aspirate showing three-dimensional clusters, colloid-like material, and many scattered single cells in the background (× 100). B. The central portion of the cell cluster is too thick to accurately evaluate their cytomorphology (× 1000). C. A small fragment with a microfollicular structure is observed. The background has many white blood cells with indistinct cytoplasmic borders (× 1000). D. Naked nuclei are observed (arrows; × 1000).

In our study, the common features of parathyroid lesions observed in the FNA specimens prepare using the 3 methods were microfollicular structure; small, round-to-oval nuclei with lymphocyte-like chromatin; and naked nuclei in the background. These results were consistent with those of previous studies [18-20]. However, comparison of specimens prepared using each method showed that cellularity was lower in specimens prepared using ThinPrep than in those prepared using the other methods. Specimens prepared using ThinPrep showed a clean background and fewer isolated parathyroid cells and naked nuclei than those prepared using the other methods. SurePath specimens showed many white blood cells in the background; therefore, it was difficult to differentiate isolated parathyroid cells and naked nuclei from background white blood cells in these specimens. Specimens prepared using both ThinPrep and SurePath showed higher nuclear detail and better defined cytoplasm than those prepared using conventional smear. Finely granular and stippled salt-and-pepper chromatin pattern was predominantly observed in specimens prepared using SurePath than in specimens prepared using the other methods (**Figure 5**). Bubbly or vacuolated cytoplasm was observed in LBC specimens (**Figures 2A** and **3B**) but not in specimens prepared by conventional smear. Colloid-like material may mimic tissue paper-like colloids present in thyroid LBC specimens (**Figure 4**). However, absence of dense globular colloids serves as an indicator in parathyroid FNA specimens (**Figure 7A**). Oxyphilic parathyroid cells may mimic Hürthle cells of the thyroid gland (**Figure 3**); however, Hürthle cells have larger size and plumper cytoplasm than oxyphilic parathyroid cells (**Figure 7B**). White blood cells present in the back-

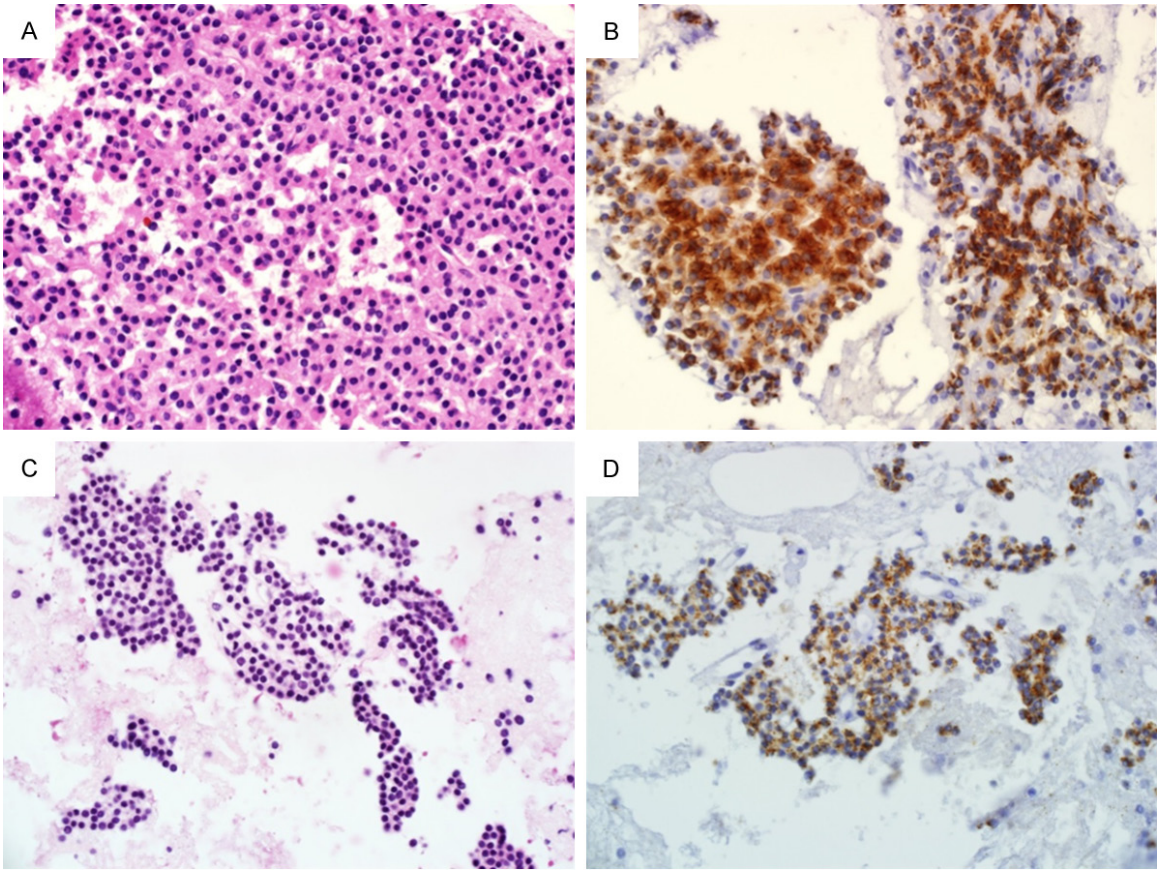

Figure 6. Cell blocks of parathyroid fine needle aspiration specimens. (A) Parathyroid lesions with predominant oxyphilic cells and (B) positive immunostaining for parathyroid hormone. (C) Parathyroid lesions with predominant chief cells and (D) positive immunostaining for parathyroid hormone.

ground can serve as an indicator for estimating cell size (**Figure 7C**). The nuclear size of parathyroid cells is similar to or smaller than that of inflammatory cells in the background while the nuclear size of follicular cells is larger than that of inflammatory cells in the background (**Figure 7C** and **7D**).

Parathyroid FNA specimens often show a papillary architecture, with a fibrovascular core. However, parathyroid lesions can be easily distinguished from papillary thyroid carcinoma based on the absence of the typical nuclear features of papillary thyroid carcinoma [3, 21].

Immunocytochemical staining of PTH or PTH chemical assay of parathyroid FNA rinse is useful for the definitive diagnosis of parathyroid lesions [3-5]. In the present study, all FNA specimens were suitable for preparing cell blocks after LBC. Positive immunocytochemical staining of PTH in cell block sections confirmed the parathyroid origin of cells.

No difference was observed in cytologic features of parathyroid hyperplasia, parathyroid adenoma, and parathyroid carcinoma between conventional smear and LBC specimens in our study, which was consistent with results of previous studies [7, 19, 20].

In conclusion, common cytologic features of parathyroid lesions observed in conventional smear specimens are also observed in LBC specimens but at varying degrees. LBC specimens of parathyroid lesions predominantly show a microfollicular structure. ThinPrep specimens show fewer naked cells compared to conventional smear and SurePath specimens. The size of cells in ThinPrep and SurePath specimens is useful for differentiating parathyroid cells from thyroid follicular cells. Cell block

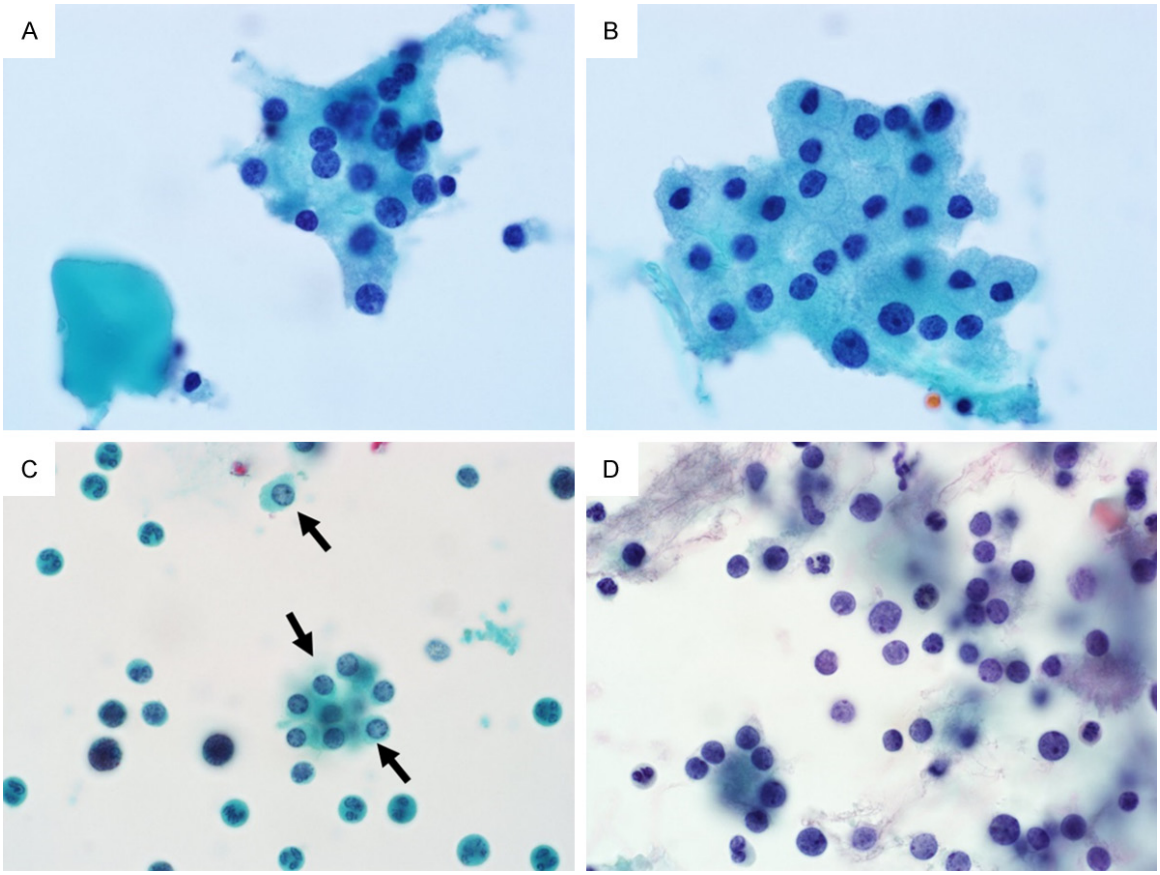

Figure 7. Cytologic features of liquid-based cytology specimens for the differential diagnoses of parathyroid and thyroid lesions. A. A dense globular colloid observed in a thyroid lesion specimen (ThinPrep; × 1000). A parathyroid lesion specimen showing colloid-like material (**Figures 4A** and **5A**) but no dense globular colloidal structure. The size of follicular cells is larger than that of parathyroid cells. B. Hürthle cells of the thyroid gland have larger nuclei and plumper cytoplasm than oxyphilic parathyroid cells observed in **Figure 3** (ThinPrep; × 1000). C. The nuclear size of parathyroid cells (arrows) is similar to or smaller than that of white blood cells in the background (SurePath; × 1000). D. Thyroid follicular cells are larger than white blood cells in the background (SurePath; × 1000).

preparation and PTH immunostaining of FNA specimens is highly effective for the differential diagnosis of parathyroid lesions.

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Disclosure of conflict of interest

None.

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