Cytological Characteristics of Papillary Thyroid Carcinoma on LBC Specimens, Compared with Conventional Specimens

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Background: *The cytological findings in conventional specimens (C-S) and liquid-based cytology specimens (LBC-S) are not quite same. The aim of this article is to clarify the cytological findings of papillary thyroid carcinoma (PTC) characteristic of LBC-S.*
Methods: *Out of 5,971 cases diagnosed in a single institution from March to September in 2012, 161 PTC cases with both C-S and LBC-S were reviewed. Additionally, we compared the findings with those in LBC-S of 55 adenomatous or hyperplastic nodule (AN) and 21 follicular neoplasm (FN) cases.*
Results: *Compared to C-S, the incidences of trabecular and hobnail patterns, collagenous stroma, naked capillaries, intercellular spaces, convoluted nuclei, eosinophilic nucleoli, and perinucleolar halo were increased. Pale nuclei were observed in only one of 161 PTC cases. Specificity of convoluted nuclei and perinucleolar halo were 97.4% and 96.1%, respectively.*
Conclusion: *Convoluted nuclei and perinucleolar halo might become a new indicator of PTC in LBC-S. Contrarily, we should be aware that pale nuclei are rarely observed in LBC-S.* Diagn. Cytopathol. 2015;43:108–113.

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Liquid-based cytology (LBC) is a new technique collecting the cytological samples and smearing them thinly, and has been developed in the gynecological field. It is generally known that LBC is useful for reducing unsatisfactory specimens and improving the diagnostic accuracy[1,2]. Recently, LBC is becoming increasingly popular for the non-gynecological cytology[3] including thyroid aspirates.[4]

Although fine needle aspiration cytology (FNAC) of the thyroid is usually performed under ultrasound guidance, adequate samples are not always obtained. The insufficient rates vary 8.93–20.9%.[5,6] Thyroid LBC using needle washout fluid can collect more samples and obtain higher quality.[5–7] Rossi et al.[4] described that the procedure decreases inadequate cases and achieves a diagnostic sensitivity as accurate as conventional method, because of its excellent cell preservation and the decrease in blood components masking follicular cells. However, the cytological findings in conventional specimens (C-S) and LBC specimens (LBC-S) are not quite same.[8–10] Therefore, it is necessary to be familiar with the differences in order to make a diagnosis. So far, there are few reports focusing on cytological findings in thyroid LBC-S.[4–14]

The aim of this report is to clarify the cytological findings of papillary thyroid carcinoma (PTC) characteristic of LBC-S by comparing with those in C-S. Additionally, we verified the diagnostic significances of the findings we found.

Materials and Methods

FNAC were performed by using a 22-gauge needle under ultrasound guidance for 5,971 thyroid nodules in Kuma Hospital from March to September in 2012. In 1,518

Table I. A Procedure of the SurePath Hand Method for Liquid-Based Cytology

1. Centrifuge (1,700 rpm, 10 min)
2. Pour out the supernatant by decantation
3. Add purified water (300 μL) to the sediment and stir
4. Pour the sample (300 μL) into the settling chamber with the pre-coated slide mounted on the slide rack, and allow to stand for 10 min
5. Pour out the supernatant by decantation (turning the slide rack upside down)
6. Add 100% ethyl alcohol (1 mL) along the inner surface of the settling chamber
7. Remove the supernatant on the filter paper by turning the slide rack upside down
8. Repeat 6 and 7
9. Wet-fix after removing the settling chamber

Table II. Background Findings Seen in 161 Papillary Thyroid Carcinoma Cases

	C-S (+)	*LBC-S (+)*
Lymphocytes	79 (49.1%)*	31 (19.3%)*
Foam cells	47 (29.2%)	50 (31.1%)
Multinucleated giant cells	47 (29.2%)	51 (31.7%)
Ropy colloid	23 (14.3%)	15 (9.3%)
Psammoma bodies	4 (2.5%)	11 (6.8%)
Collagenous stroma	55 (34.2%)*	82 (50.9%)*
Naked capillaries	0 (0%)*	15 (9.3%)*

C-S: conventional specimens, LBC-S: liquid-based cytology specimens.
*$P < 0.01$.

nodules of them, both the C-S and LBC-S were prepared. Among them, we examined the preparations of 161 nodules that underwent thyroidectomy in a year after FNAC and were diagnosed as PTC by histological examination. C-S slides were prepared by expressing the aspirated materials from the needle onto slide glasses and compressing by a second slide, and immediately fixed by Cytorop (Alfresa, Japan) which is a cytological fixative. Subsequently, the needles were rinsed gently with 6mL CytoRich RED collection fluid (Becton, Dickinson and Company, U.S.) with hemolytic and proteolytic abilities, and LBC-S were prepared by the SurePath hand method using the fluid (Table I). Both preparations were stained with Papanicolaou method, simultaneously.

The cytological findings we examined were as follows: (1) background components (lymphocytes, foam cells, multinucleated giant cells, ropy colloid, psammoma bodies, collagenous stroma, and naked capillaries), (2) cellular arrangements (papillary, sheet-like, follicular, trabecular, hobnail-like, tissue fragments, intracellular spaces), and (3) cytoplasm and nuclei (septate intracytoplasmic vacuoles, pale nuclei, nuclear grooves, intranuclear cytoplasmic inclusions, convoluted nuclei, eosinophilic nucleoli, and perinucleolar halo). Septate intracytoplasmic vacuoles were defined as small, uniform, and well-defined vacuoles, with distinct strands of cytoplasm separating them.[15]

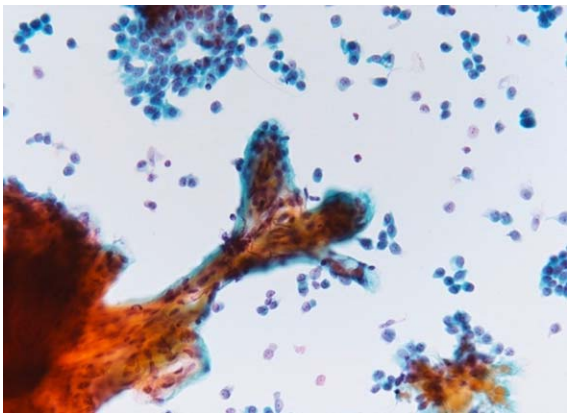

Fig. 1. Collagenous stroma seen in papillary thyroid carcinoma. Note fibroblasts in the connective tissue and no association with carcinoma cells (LBC-S, Papanicolaou stain, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Additionally, in order to assess the diagnostic significance of the cytological findings that were more frequently observed in LBC-S rather than C-S, we examined LBC-S of 55 adenomatous or hyperplastic nodule (AN) and 21 follicular neoplasm (FN) cases confirmed by histological examinations in the same period. The specimens were prepared using needle wash-out fluid, like PTC cases. We observed the following six findings: collagenous stroma, naked capillaries, intercellular spaces, convoluted nuclei, eosinophilic nucleoli, and perinucleolar halo for this purpose. We assessed the statistical significance of their data using Fisher's exact probability test.

Results

Comparison Between LBC-S and C-S on PTC

Background components. Lymphocytes were seen in 19.3% of LBC-S, and 49.1% of C-S ($P < 0.01$). The incidences of the nodules that lymphocytes were observed only in LBC-S or C-S were 3.7% and 33.5%, respectively. On the occurrences of foam cells, multinucleated giant cells, ropy colloid and psammoma bodies, there were not significant differences between LBC-S and C-S (Table II). Collagenous stroma which was composed of collagenous connective tissue with or without fibroblasts and was not associated with PTC cells was observed in 50.9% of LBC-S (Fig. 1). The incidence was significantly higher than that in C-S (34.2%). The incidences of the nodules that collagenous stroma was observed only in LBC-S or C-S were 26.7%and 9.9%, respectively. The LBC-S of 15 nodules (9.3%) revealed the segments of capillaries containing endothelia (naked capillaries), but the finding was not observed in the C-S. The capillaries appeared individually or aggregately (Fig. 2).

Cellular arrangements. The incidences of trabecular and hobnail-like pattern were significantly higher

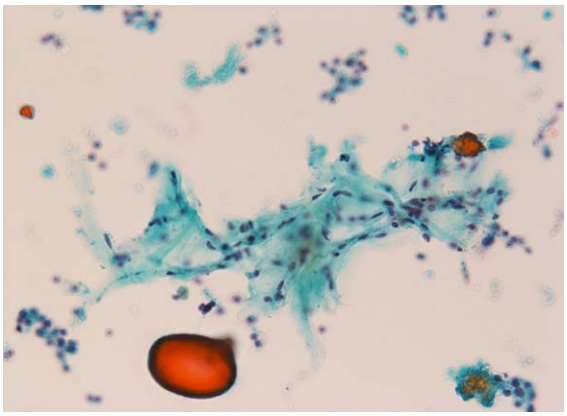

Fig. 2. Naked capillaries seen in papillary thyroid carcinoma. They are not embedded within connective tissue (Papanicolaou stain, LBC-S, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

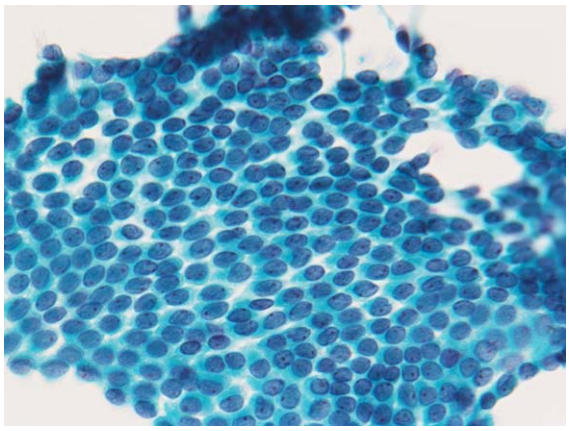

Fig. 3. Papillary thyroid carcinoma. Window-like spaces are present among carcinoma cells forming sheet-like clusters (Papanicolaou stain, LBC-S, ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table III. Cellular Arrangements Seen in 161 Papillary Thyroid Carcinoma Cases

	C-S (+)	*LBC-S (+)*
Papillary	131 (81.4%)*	110 (68.3%)*
Sheet-like	159 (98.8%)	160 (99.4%)
Follicular	59 (36.6%)	75 (46.6%)
Trabecular	31 (19.3%)**	49 (30.4%)**
Hobnail-like	3 (1.9%)*	20 (12.4%)*
Tissue fragments	50 (31.1%)*	16 (9.9%)*
Intercellular spaces	3 (1.9%)*	110 (68.3%)*

C-S: conventional specimens, LBC-S: liquid based cytology specimens.
$^{**}P < 0.01$.
$^{*}P < 0.05$.

Table IV. Cytoplasmic and Nuclear Findings Seen in 161 Papillary Thyroid Carcinoma Cases

	C-S (+)	*LBC-S (+)*
Septate intracytoplasmic vacuoles	2 (1.2%)	7 (4.3%)
Pale nuclei	122 (75.8%)*	1 (0.6%)*
Nuclear grooves	160 (99.4%)	160 (99.4%)
Intranuclear cytoplasmic inclusions	134 (83.2%)	142 (88.2%)
Convoluted nuclei	4 (2.5%)*	66 (41.0%)*
Eosinophilic nucleoli	9 (5.6%)*	144 (89.4%)*
Perinucleolar halo	3 (1.9%)*	102 (63.4%)*

C-S: conventional specimens, LBC-S: liquid-based cytology specimens.
$^{*}P < 0.01$.

($P < 0.05$, $P < 0.01$) in LBC-S (30.4%, 12.4%) than those in C-S (19.3%, 1.9%) (Table III). The incidences of the nodules that trabecular pattern was observed only in LBC-S or C-S were 19.3% and 8.1%, respectively. Conversely, the incidences of papillary pattern and tissue fragments were lower in LBC-S (68.3%, 9.9%) than those in C-S (81.4%, 31.1%). The incidences of the nodules that papillary pattern was observed only in LBC-S or C-S were 8.1% and 21.1%, respectively. Isolated cells seen around the clusters of PTC cells tended to be decreased in LBC-S. The incidences of sheet-like and follicular pattern in LBC-S and C-S were almost same. There were window-like spaces among PTC cells forming sheet-like clusters. The intercellular spaces were seen in 68.3% of LBC-S, but they were rarely seen in C-S ($P < 0.01$) (Fig. 3).

Cytoplasm and nuclei. In 75.8% of C-S, pale nuclei characteristic of PTC were seen, but they were very rarely seen in LBC-S (0.6%) (Table IV). Chromatin pattern seen in LBC-S was mostly fine granular (Fig. 4). The incidences of intranuclear cytoplasmic inclusions, nuclear grooves and septate intracytoplasmic vacuoles in LBC-S and C-S were almost same. Convoluted nuclei, in which zigzag irregularity occupy more than half of nuclear membrane, were observed in 41.0% of LBC-S (Fig. 5). The finding was seen in only 4 C-S (2.5%), in which the background was bloody or cystic. The nucleoli were mostly stained dark blue in C-S. In contrast, in LBC-S, they were eosinophilic (89.4%; $P < 0.01$) and were distinctive because of the presence of perinucleolar halo (63.4%; $P < 0.01$) (Fig. 5). The cell shape was well preserved in LBC-S. Especially, in tall cell variant composed of carcinoma cells whose height was more than three times as tall as their width, LBC-S highlighted their cell shape better than C-S (Fig. 6).

Comparison with AN and FN

We compared the incidences of collagenous stroma, naked capillaries, intercellular spaces, convoluted nuclei, eosinophilic nucleoli, and perinucleolar halo that were easily seen in LBC-S of PTC with those of AN and FN (Table V). The incidences of collagenous stroma of PTC, AN and FN were 50.9%, 30.9%, and 42.9%, respectively.

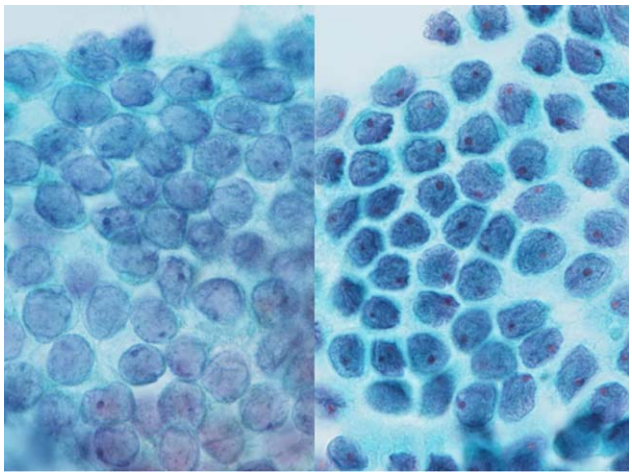

Fig. 4. Papillary thyroid carcinoma (Left: C-S, Right: LBC-S). Chromatin pattern in LBC specimens is not pale but more granular than that in conventional specimens (Papanicolaou stain, LBC-S, ×1,000). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

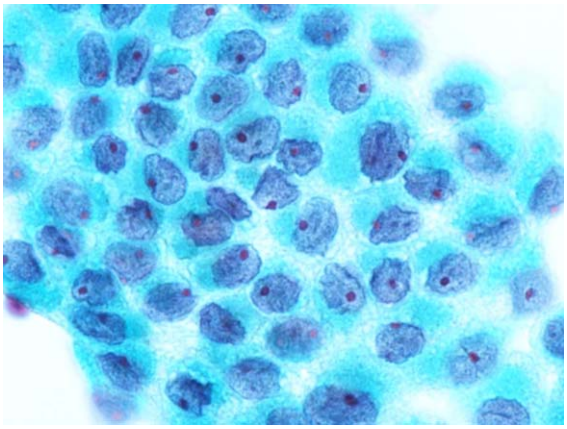

Fig. 5. Convoluted nuclei seen in papillary thyroid carcinoma. More than half of nuclear membrane shows zigzag irregularity. The nucleoli are eosinophilic and associated with perinucleolar halo (Papanicolaou stain, LBC-S, ×1,000). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The incidence of naked capillaries was significantly high in FN (28.6%). Intercellular spaces were seen in 68.3% of PTC, 40.0% of AN, and 9.5% of FN. In AN cases, the spaces tended to be seen in oxyphilic cell clusters. Convoluted nuclei were observed in 40.1% of PTC and 3.6% of AN. No FN cases showed convoluted nuclei. Eosinophilic nucleoli were observed in 89.4% of PTC and 67.3% of AN, but the incidence in FN was low (33.3%). Perinucleolar halo was rarely seen in both of AN (5.5%) and FN (0%). The findings that showed high specificity were convoluted nuclei (97.4%) and perinucleolar halo (96.1%) (Table VI). The sensitivity of the former (40.1%) is lower than the latter (63.4%). Eosinophilic nucleoli revealed the highest sensitivity (89.4%).

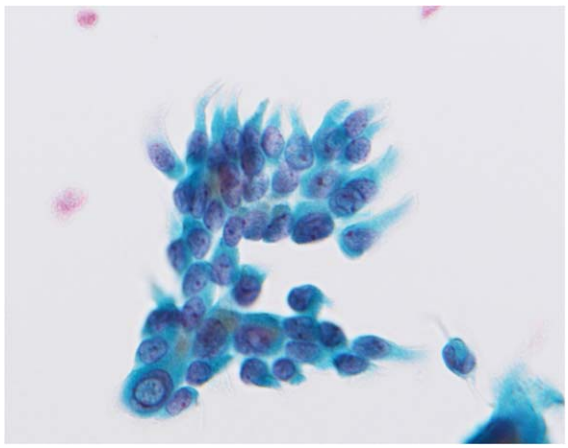

Fig. 6. Tall cell variant of papillary thyroid carcinoma. Tall cell configuration is apparent 0(Papanicolaou stain, LBC-S, ×400). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table V. Incidences of Six Cytological Findings in Papillary Thyroid Carcinomas, Adenomatous or Hyperplastic Nodule, and Follicular Neoplasm

	PTC (161)	*AN (55)*	*FN (21)*
Collagenous stroma	50.9% (82)**	30.9% (17)**	42.9% (9)
Naked capillaries	9.3% (15)**	3.6% (2)	28.6% (6)**
Intercellular spaces	68.3% (110)*	40.0% (22)*	9.5% (2)*
Convoluted nuclei	41.0% (66)*	3.6% (2)*	0% (0)*
Eosinophilic nucleoli	89.4% (144)*	67.3 (37)*	33.3% (7)*
Perinucleolar halo	63.4% (102)*	5.5% (3)*	0% (0)*

C-S: conventional specimens, LBC-S: liquid-based cytology specimens, PTC: papillary thyroid carcinoma, AN: adenomatous or hyperplastic nodule, FN: follicular neoplasm.
*$P < 0.01$.
**$P < 0.05$.

Discussion

Recently, LBC for thyroid aspiration cytology has been used increasingly. So far, approximately 20 reports on the cytological appearance of thyroid LBC have been documented. Most of them were to assert advantages of LBC or to compare the cytological appearance between LBC-S and C-S. Fadda et al.[16] and Kim et al.[5] described that the use of LBC reduced the number of non-diagnostic or indeterminate cases without impairing the ability to detect the distinctive features of carcinoma. However, it is acknowledged that the cytological appearance in LBC-S are not identical to those in C-S.[8–10,17]

According to the report by Fadda et al.[16] the colloid film and the lymphocytic component are more easily

Table VI. Statistical Results of Cytological Findings on Papillary Thyroid Carcinoma

	Sensitivity	*Specificity*	*PPV*	*NPV*
Collagenous stroma	50.9%	65.8%	75.9%	38.8%
Naked capillaries	9.3%	89.5%	65.2%	31.8%
Intercellular spaces	68.3%	68.4%	82.1%	50.5%
Convoluted nuclei	40.1%	97.4%	97.1%	43.8%
Eosinophilic nucleoli	89.4%	42.1%	76.6%	65.3%
Perinucleolar halo	63.4%	96.1%	97.1%	55.3%

PPV: positive predictive value, NPV: negative predictive value.

evaluated on C-S, whereas nuclear detail and colloid globules are better evaluated in LBC-S. The amount of colloid is diminished in LBC. Colloid appears as either dense, dark blue-orange droplets or thin tissue paper-like sheets in benign lesions.[5] Mygdakos et al.[8] and Geers et al.[10] described that a number of morphologic changes were inherent to LBC-S including altered, reduced or lost background material, smaller and more fragmented cell clusters, smaller cell size, well preserved nuclear detail, more prominent nucleoli and more easily visualized cytoplasm. Benign appearing follicular cells are arranged in relatively smaller monolayer sheets, usually with less than 20–25 cells per sheet. The cells have blue cytoplasm and smaller and darker nuclei.[17] Awareness of the cytomorphological features observed with the use of the LBC method is essential to avoiding misinterpretation.[5]

In addition to the above differences, we found the cytological features of PTC cells in LBC-S which were different from those in C-S as follows: (1) an increase in collagenous stroma, naked capillaries and trabecular and hobnail pattern, (2) a decrease in papillary pattern and tissue fragments, (3) the presence of intercellular spaces, (4) a disappearance of pale nuclei, (5) convoluted nuclei, (6) eosinophilic nucleoli and perinucleolar halo, and (7) well-preserved cell shape.

In our study, collagenous stroma that is composed of collagenous connective tissue with or without fibroblasts and is not associated with PTC cells was observed in 50.9% of LBC-S and 34.2% of C-S. The higher incidence of collagenous stroma in LBC-S seems to be caused by a proteolytic behavior of CytoRich RED. Additionally, the preparation process of the SurePath hand method may dissociate stromal and epithelial components. Collagenous stroma has not been described yet. However, it was not characteristic the PTC, because it was also observed in AN and FN. Similarly, naked capillaries tended to be observed in LBC-S rather than in C-S. The pathogenesis probably is also same to collagenous stroma. As the incidence of naked capillaries was considerably higher in FN (28.6%) than PTC (9.3%), the finding seemed to be a feature of FN in LBC-S.

Intercellular spaces were seen in 68.3% of PTC in LBC-S, but were rarely seen in C-S (1.9%). They may be caused by shrinkage of the cytoplasm. The spaces were also seen in 40.0% of AN in LBC-S, but their incidence in FN was only 9.5%. As the cell membrane of FN is usually indistinct except for oxyphilic cell variant, the spaces may be obscure in FN cases. The presence of the intercellular spaces may be useful in distinguishing between PTC and FN in LBC-S.

We have believed that pale nuclei were the most reliable finding indicating PTC. However, the incidence of pale nuclei in LBC-S was 0.6%, and most of nuclei represented granular chromatin pattern. Geers et al. reported that pale nuclei were easily recognized in LBC-S,[10] but according to the figure they showed, the chromatin pattern was not pale, but granular. Nuclear chromatin pattern seems to be affected by fixatives. The formalin included in CytoRich RED may be related to the phenomenon. We should pay attention to the fact that pale nuclei are not a diagnostic clue of PTC in LBC-S.

Convoluted nuclei were characteristic of PTC in LBC-S. They were observed in 41.0% of LBC-S, but in only 2.5% of C-S. They were rarely observed in AN cases, and never in FN cases. The specificity was 97.4%. Geers et al.[10] and Jung et al.[9] reports described that the nuclear irregularity was easily recognized in LBC-S. Kim et al.[5] reported that nuclear membrane of PTC in LBC-S was angulated. We believe their findings are identical to the convoluted nuclei we interpreted. Our data shows convoluted nuclei might be a new clue of PTC. It is not clear why the findings specifically appear in PTC. In LBC fixation, the nucleoplasm of PTC may shrink more highly than those of AN or FN. Perinuclear halo may be another clue indicating PTC, because it was rarely observed in AN (5.5%) and was not detected in 21 FN cases.

The cell shape such as hobnail pattern and tall cell morphology was better preserved in LBC-S. In cases with tall cell variant, LBC-S highlighted their cell shape better than C-S. Lee et al.[18] indicated that LBC improved preoperative diagnostic accuracy of tall cell variant of PTC. However, in our experience, tall cell configuration could be observed even in LBC-S of conventional PTC cases that focally revealed tall cell component in the surgical specimens. LBC-S may mislead us to make a diagnosis of more aggressive variant.

In conclusion, the cytological features characteristic of PTC in LBC-S compared with C-S were as follows: (1) an increase in collagenous stroma, naked capillaries and trabecular and hobnail pattern, (2) a decrease in papillary pattern and tissue fragments, (3) the presence of intercellular spaces, (4) a disappearance of pale nuclei, (5) convoluted nuclei, (6) eosinophilic nucleoli and perinucleolar halo, and (7) well-preserved cell shape. Among them, collagenous stroma, naked capillaries, eosinophilic nucleoli, and well-preserved cell shape are not only observed in PTC, but also in AN or FN in LBC-S. Convoluted nuclei

and perinucleolar halo were specific to PTC, and might become a new indicator of PTC in LBC-S. Additionally, we should be aware that pale nuclei are rarely observed in LBC-S.

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