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Cytologic Features of Diffuse Sclerosing Variant of Papillary Carcinoma
– Cytohistopathologic Analysis of 16 Cases –

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Background : The exact preoperative diagnosis of diffuse sclerosing papillary carcinoma (DSPC) is required for aggressive surgical treatment due to its extended involvement with thyroid and neck lymph nodes. The present study investigated the cytomorphologic characteristics of DSPC and identified cytologic features for preoperative diagnosis of DSPC. **Methods :** A retrospective review of cytologic and histologic features of 16 patients diagnosed with DSPC after thyroidectomy and underwent preoperative fine needle aspiration cytology (FNAC) was performed. **Results :** Prominent psammoma bodies were observed in 16 (100%) and 10 (62.5%) cases of histology and FNAC, respectively. Lymphocytes were observed in nine (56.2%) and four (25.0%) cases, and squamous cells were noted in seven cases (43.7%) and one case (6.2%) on histology and FNAC, respectively. Nuclear grooves and inclusions, which are characteristics of papillary carcinoma, were observed in FNAC and histology slides in all 16 cases. **Conclusions :** DSPC displays prominent psammoma bodies and characteristic nuclear features of papillary carcinoma such as nuclear groove and inclusion in FNAC. However, the preoperative diagnosis of DSPC using only FNAC could be difficult due to the absence of other characteristic features such as lymphocytes and metaplastic squamous cells.

Key Words : Cytology; Diffuse sclerosing; Carcinoma, papillary; Thyroid

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer. It occurs more frequently in women than men. Several histologic variants of PTC have been identified. Among them, diffuse sclerosing papillary carcinoma (DSPC) is a rare variant, comprising 0.3-5.3% of papillary carcinomas.[1-6] DSPC displays characteristic histologic features such as innumerable psammoma bodies, squamous metaplasia, extensive lymphocytic thyroiditis, and dense sclerotic type fibrosis resulting in multinodular tumor nodules.[1,5,6] The disease is known to have a higher incidence of cervical lymph node and lung metastasis, extensive involvement of the thyroid, and larger tumor size.[2,4] In addition, DSPC is reported to demonstrate a higher incidence of tumor recurrence and poor prognosis, which result in aggressive treatment protocols.[2,3] Therefore, an exact preoperative diagnosis of DSPC is required. Fine needle aspiration cytology (FNAC) is a well-established preoperative diagnostic method for PTC.[7-9] However, the cytologic features of DSPC have only been described in a few case reports.[10-12] The purpose of this study was to investigate the cytomorphologic characteristics of DSPC and identify cytologic features, with the aim of improving the preoperative diagnosis of DSPC.

MATERIALS AND METHODS

Patients

A retrospective review of all patients with a diagnosis of papillary carcinoma who underwent surgery at Severance hospital from January 1995 to December 2008 was done. This study was approved by the Institutional Review Board of Severance hospital. Patients who were diagnosed with DSPC and underwent preoperative FNAC were included in the study. Typical diagnostic criteria of DSPC are: (a) diffuse involvement of one or both lobes, (b) numerous micropapillary formations located within cleft-like spaces consistent with lymph vessels, (c) extensive squamous metaplasia, (d) large number of psammoma bodies, (e) marked lymphocytic infiltration, and (f) prominent fibrosis. Among these, numerous psammoma bodies, radiating prominent fibrosis, and diffuse involvement in surrounding thyroid tissue by psammoma bodies through lymphovascular invasion were requirements for the diagnosis of DSPC in this study. Cases showing non-diagnostic and unsatisfactory cytologic features were excluded. Finally, 16 patients with a mean

age of 22.8±13.4 years (range 12-66 years) were included in this study. Fourteen (88%) patients were female. Clinicopathologic parameters such as tumor size, tumor sidedness, lymph node involvement, and distant metastasis were collected from each patients' medical record, as was information concerning ultrasound features of DCPS.

FNAC and histology

FNAC was performed by radiologists using a 23-gauge needle with or without anesthesia. Each aspirate was placed on a glass slide, immediately fixed in 95% alcohol, and stained with Papanicolaou stain. Two cytopathologists interpreted the stain results. The criteria for a satisfactory smear were the presence of six groups of cells with more than 10 cells per group in more than two slides. The presence of a psammoma body, lymphocytes, metaplastic squamous cells, colloid, nuclear groove, nuclear inclusion, papillary structure, and multinucleated giant cells were evaluated in FNAC. The number of psammoma bodies observed in the cytological examinations was determined by counting the number of psammoma bodies in ×100 magnified field in 10 areas and calculating the mean number of psammoma bodies. The numbers were scored on a scale of 1+-3+, with 1+ representing a mean number of psammoma bodies of 1-5, 2+ representing a mean number of 6-15, and 3+ representing a mean number >16. The same two cytopathologists reviewed the corresponding histologic slides, using the aforementioned cytologic features as the basis of the evaluation. Sensitivity, specificity, positive predictive rate, and negative predictive rate of cytologic parameters compared to corresponding histologic features were calculated as:

sensitivity of 'A' parameter=a/(a+c),
specificity of 'A' parameter=d/(b+d),
positive predictive rate of 'A' parameter=a/(a+b), and
negative predictive rate of 'A' parameter=d/(c+d)

where a=number of cases showing 'A' parameter in cytology and histology, b=number of cases showing 'A' parameter in cytology but not histology, c=number of cases showing 'A' parameter in histology but not cytology, and d=number of cases showing no 'A' parameter in either cytology or histology.

RESULTS

Clinicopathologic and radiologic features of DSPC

Tumors were located in right lobe in 2 (12.5%) cases, left lobe

Table 1. Clinicopathologic and radiologic features of 16 cases of DSPC

Case No.	Age (years)	Sex	Tumor side	Size (cm)	The number of lymph node metastaisis	Distant metastasts	Ultrasound features
1	17	Female	Right	4.0	5		Heterogenous echogenic nodule with posterior shadowing
2	15	Female	Left	3.0	2		Calcified suspicious mass
3	19	Female	Left	1.0	2		Suspicious microcalcified nodule underlying diffuse thyroiditis
4	19	Female	Bilateral	2.0	9		Suspicious nodule with numerous microcalcification
5	12	Female	Bilateral	2.5	24	Lung	Ill-defined calcified mass
6	18	Female	Bilateral	4.0	9	Lung	Suspicious calcified mass occupying near total thyroid
7	19	Female	Bilateral	1.2	1		Ill-defined hypoechoic mass with peripheral microcalcification
8	15	Female	Left	1.5	23		Calcified nodule
9	13	Female	Bilateral	3.0	35		Suspicious microcalcified nodule
10	15	Male	Bilateral	4.0	10		Heterogenous hypoechoic mass with multiple internal microcalcifications occupying nearly the entire thyroid gland
11	39	Female	Bilateral	3.0	11		Suspicious nodule with multiple internal and peripheral microcalcification
12	28	Female	Bilateral	1.3	16		Multiple suspicious nodules
13	66	Female	Bilateral	4.5	14	Lung	Ill-defined calcified mass occupying nearly entire thyroid gland
14	22	Female	Bilateral	1.7	11		Ill-defined hypoechoic mass with multiple internal punctuate microcalcification
15	20	Female	Bilateral	3.5	28		Ill-defined calcified mass
16	29	Female	Right	4.5	1		Hypoechoic calcified mass

DSPC, diffuse sclerosing papillary carcinoma.

in 3 (18.8%) cases, and both lobes in 11 (68.8%) cases (Table 1). The size of the dominant tumor (mean±SD) was 2.8±1.2 cm and all 16 cases demonstrated lymph node metastasis in which the mean number of involved lymph node was 12 (range 1-35). Three (18.8%) cases showed lung metastasis. Ultrasound revealed 14 cases (87.5%) cases of calcified mass and seven cases (43.8%) of microcalcification in internal or/and peripheral areas. Four cases (25.0%) cases showed a hypoechoic nodule.

Cytologic features of DSPC

Table 2 and Fig. 1 show the cytologic characteristics of 16 cases of DSPC. Twelve (75.0%) cases were diagnosed as positive for malignancy and four (25.0%) were diagnosed as suspicious for malignancy due to the low cellularity of follicular cells showing nuclear clearing and grooves. FNAC revealed psammoma bodies, lymphoid cells, squamoid cells, nuclear inclusion, and multinucleated giant cells of varying degrees and proportions. Psammoma bodies were observed in 10 (62.5%) cases. These were independently scattered or intermingled with papillary carcinoma cells (Fig. 1A). Four (25.0%) cases each showed 1+ and 2+ psammoma bodies and two (12.5%) cases displayed 3+ psammoma bodies. Lymphoid cells were identified in four (25.0%) cases; the lymphoid cells were evident as singly scattered forms in the background or intermingled with surrounding benign follicular cells and papillary carcinoma cells (Fig. 1B). Metaplastic squamoid cells were identified in one (6.2%) case as a benign cytologic feature (Fig. 1C). Multinucleated giant cells were noted in four (25.0%) cases. Nuclear grooves and inclusions, which are characteristics of papillary carcinoma, were observed in all 16 cases (Fig. 1D). However, colloid material was not evident in any patient.

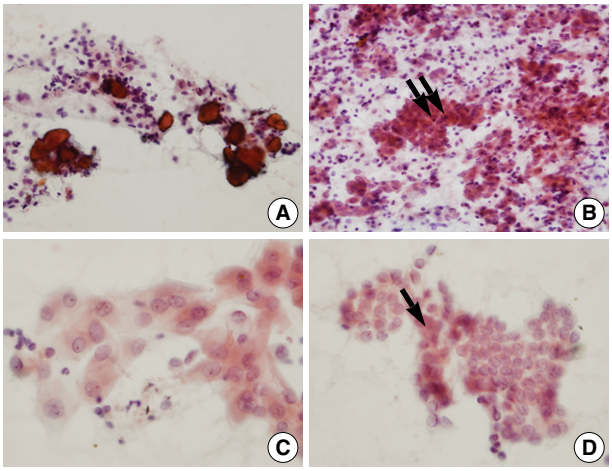

Fig. 1. Cytologic features of DSPC. Cytology reveals multiple scattered psammoma bodies (A, Papanicolaou stain), lymphocytes (arrows) intermingled with tumor cells (B, Papanicolaou stain), metaplastic squamoid cells (C, Papanicolaou stain), and nuclear groove and inclusion (arrow) (D, Papanicolaou stain).

Table 2. Cytologic and histopathologic features of 16 cases of DSPC

Case No.	Cytologic diagnosis	Cytologic features							Histologic features						
		Psammoma body	Lymphoid cells	Squamoid cell	Colloid	Nuclear groove	Nuclear inclusion	Multinucleated giant cells	Psammoma body	Lymphoid cells	Squamoid cell	Colloid	Nuclear groove	Nuclear inclusion	Fibrosis (%)
1	SOM	−	−	−	−	+	+	−	+	−	−	+	+	+	50
2	PFM	3+	+	+	−	+	+	−	+	+	+	−	+	+	90
3	PFM	1+	+	−	−	+	+	+	+	+	−	−	+	+	60
4	SOM	−	+	−	−	+	+	−	+	+	−	−	+	+	30
5	PFM	1+	−	−	−	+	+	+	+	−	+	+	+	+	20
6	PFM	−	−	−	−	+	+	+	+	−	−	−	+	+	30
7	PFM	2+	−	−	−	+	+	+	+	−	−	−	+	+	10
8	PFM	2+	−	−	−	+	+	−	+	−	+	−	+	+	50
9	PFM	−	−	−	−	+	+	−	+	+	−	+	+	+	60
10	PFM	3+	−	−	−	+	+	−	+	−	+	−	+	+	30
11	PFM	2+	−	−	−	+	+	−	+	+	+	−	+	+	20
12	SOM	−	−	−	−	+	+	−	+	+	+	−	+	+	40
13	PFM	2+	−	−	−	+	+	−	+	+	−	+	+	+	40
14	PFM	−	−	−	−	+	+	−	+	−	−	−	+	+	20
15	PFM	1+	+	−	−	+	+	−	+	+	−	+	+	+	20
16	PFM	1+	−	−	−	+	+	−	+	+	+	−	+	+	20

DSPC, diffuse sclerosing papillary carcinoma; SOM, suspicious of malignancy; PFM, positive for malignancy.

Table 3. Sensitivity, specificity, positive predictive rate, and negative predictive rate of cytologic parameters in DSPC

Cytologic parameters	Sensitivity (%)	Specificity (%)	Positive predictive rate (%)	Negative predictive rate (%)
Psammoma body	62.5	n/a	100	0
Lymphoid cells	55.5	100	100	58.3
Squamoid cells	14.3	100	100	60.0
Colloid	0	100	0	68.8
Nuclear groove	100	n/a	100	n/a
Nuclear inclusion	100	n/a	100	n/a

DSPC, diffuse sclerosing papillary carcinoma.

Comparison of cytologic and histologic features of 16 cases of DSPC

Fibrosis was observed to a widely varying degree (10-90%) on histologic slides of DSPC. Psammoma bodies were identified on histologic slide of all 16 cases, but six (37.5%) cases demonstrated no psammoma bodies in FNAC. Lymphoid cells and lymphocytic thyroiditis were observed on histologic slides of nine (56.2%) cases and, among them, four (25.0%) cases showed lymphoid cells on cytology. Squamoid cells were noted on histologic slides of seven (43.7%) cases but, among these, only one (6.2%) case showed squamoid cells on cytology. Five (31.2%) cases demonstrated colloid material in follicles of papillary carcinoma, but none showed colloid material on cytology. Nuclear grooves and inclusions were identified on cytology and histology slides of all 16 cases. Table 3 summarizes results for sensitivity, specificity, positive predictive rate, and negative predictive rate of cytologic parameters compared to the corresponding histologic features in DSPC. Sensitivity and positive predictive rates for psammoma bodies were 62.5% and 100%, respectively. Sensitivity and positive predictive rates for nuclear inclusions were both 100%.

DISCUSSION

In the present study, we investigated the cytologic and histologic features of 16 cases of DSPC to identify cytologic characteristics for preoperative diagnosis of DSPC in FNAC. In the process of case selection, the number of cases that underwent preoperative FNAC among patients with a diagnosis of DSPC was 17. One case that exhibited an unsatisfactory smear due to cell paucity was excluded. Out of the remaining 16 cases, 13 (81.2%) were judged positive for malignancy in FNAC and three cases (18.7%) demonstrated suspicious cytology due to low cellularity. Therefore, the possibility of diagnosing DSPC as malignant in FNAC was as high as 94%. This high percentage is likely due to the larger size of DSPC.[1,6] Although it has been presumed that DSPC cannot be well-aspirated in FNAC because some cases of DSPC display severe fibrotic and sclerotic areas, presently the three cases of suspicious cytology did not demonstrate severe fibrosis. In the present study, the general characteristics of papillary carcinoma cells such as nuclear groove and inclusion were identified in FNACs of all 16 cases, irrespective of histologic architecture such as papillary, follicular, and solid form. Therefore, these represented the most important cytologic features in diagnosis, which is consistent with previous studies reporting cytologic features of DSPC.[10-12] Psammoma bodies, which are one of the characteristic features of DSPC, were observed in FNACs of 10 (62.5%) cases, similar to previous results showing that 60-100% of DSPC FNACs show psammoma bodies.[10-12] However, out of the six cases lacking psammoma bodies, three were diagnosed as suspicious cytology cases due to low cellularity, indicating that the possibility of identifying psammoma bodies in adequate FNAC could be increased. In this study, five (31.2%) cases showed colloid material in follicles of papillary carcinoma, which presented a follicular pattern on histology slides. However, in these cases colloid material was not demonstrable in FNAC, consistent with a previous report.[10] Presently, metaplastic squamous cells were histologically identified in seven (43.7%) cases, but in only one (6.2%) case in FNAC. Previous reports have described squamous cells in 40-100% of FNACs.[10-12] The discrepancy between the present and previous findings may reflect the fact that the prior investigations were case studies showing typical cytologic features. Metaplastic squamous cells in this study were located mainly in central fibrotic and sclerotic areas showing focal involvement rather than in widespread and diffuse patterns, which was another reason for the low identification rate of squamous cells in FNAC. Presently, nine (56.2%) cases showed lymphocytic thyroiditis on histology but, of these, four cases (25.0%) demonstrated lymphocytes in FNAC; these observations differ from previous studies showing that most cases of DSPC display lymphocytes in FNAC.[10-12] However, only nine (56.2%) cases demonstrated lymphocytic thyroiditis on histology. Therefore, lymphocytic infiltration was not a frequently identified feature in this study. In addition, the degree of lymphocytic thyroiditis varied among cases, and we observed that cases with weak degrees of lymphocytic thyroiditis in histology did not reveal lymphocytes in FNAC.

Cytologic features used to diagnose DSPC typically include numerous psammoma bodies and lymphocytes, squamous cells, absent colloid, and epithelial cells showing classical features of papillary carcinoma such as nuclear grooves and nuclear inclusion.[10-12] In the present study, only one (6.2%) case showed all of these features in FNAC. The previous studies were case reports of typical cases, not a cytohistological analysis like this study, which may well account for the dichotomous findings. In fact, only four (25.0%) cases showed all of the characteristic aforementioned features on histology.

Frequently identified cytologic features in this study were nuclear grooves (100%), nuclear inclusions (100%), and psammoma bodies (62.5%). Therefore, papillary carcinoma could be diagnosed by identifying these features, but a diagnosis of DSPC could not made with confidence. DSPC may represent a subtype that cannot be diagnosed only by FNAC. An imaging study reported that the possibility of DSPC could be raised when the thyroid gland shows diffuse, heterogeneous hypoechogenicity and scattered microcalcifications on ultrasound,[13] and a prominent snowstorm appearance of microcalcifications with enlarged lymph nodes.[11] Therefore, imaging findings combined with cytologic features are important in the diagnosis of DSPC.

In conclusion, DSPC presently showed prominent psammoma bodies and characteristic nuclear features of papillary carcinoma such as nuclear grooves and inclusions in FNAC. However, the preoperative diagnosis of DSPC by only FNAC could be difficult due to the absence of other characteristic features such as lymphocytes and metaplastic squamous cells. Definitive diagnosis of DSPC as an indication for aggressive surgical intervention may require FNAC and diagnostic tools such as radiological imaging.

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