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Diffuse intrathyroidal dissemination of papillary thyroid carcinoma with no stromal fibrosis at presentation: A pattern of aggressive differentiated thyroid carcinoma

Haisheng Fang [a,1], Yan Si [b,1], Cong Wang [a], Qixing Gong [a], Chong Liu [a], Shui Wang [b,*]

[a] Department of Pathology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, 210029, China
[b] Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, 210029, China

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ABSTRACT

Background: Multifocal Papillary thyroid carcinoma (PTC) is a very common condition. In certain cases, it is possible to find tens to hundreds of foci with a diffuse intrathyroidal spread in the whole thyroid with no stromal fibrosis. Herein, PTC with such features was nominated as diffuse disseminate variant (DDV) PTC. The aim of the present study was to investigate the histopathological characteristics, molecular features, and biological behavior of DDV and compare the characteristics of DDV to diffuse sclerosing variant (DSV) PTC.

Materials and methods: Thirty-four DDV and 23 DSV cases were identified from consecutive surgical specimens diagnosed with PTC between 2014 and 2019. Targeted next-generation sequencing (NGS) was applied to investigate the mutation spectrum of DDV and DSV.

Results: DDV was commonly diagnosed in young patients and exhibited high rates of LNM (100 %), ETE (61.8 %), and LVI (44.1 %); however, they did not differ from DSV ($P > 0.05$). Male patients were more frequently diagnosed with DDV than with DSV ($P < 0.001$). The size of the largest tumor was significantly greater in DDV than in DSV patients ($P = 0.008$). In addition, $BRAF^{V600E}$ mutation was significantly higher in the DDV than in the DSV group ($P < 0.001$). The RET/PTC rearrangement was more frequent in DSV than in DDV patients; however, the difference was not statistically significant ($P = 0.106$). Moreover, DDV had a higher rate of recurrence compared to DSV treated with the same protocol (total thyroidectomy followed by radioactive iodine (RAI) treatment) (47.1 % and 8.7 %, $P = 0.002$).

Conclusions: DDV should be regarded as a novel aggressive variant of PTC with distinct clinicopathological characteristics, aggressive biological behaviors, and a high recurrence.

1. Introduction

Thyroid cancer is the most common endocrine cancer, whose incidence has dramatically increased over recent years [1,2]. In China, thyroid cancer has become the most common form of cancer among Chinese women younger than 30 years old [3]. As the most common histological type of thyroid carcinoma, the incidence of papillary thyroid carcinoma (PTC) has rapidly increased over the decades, accounting for 86.4–96.1 % of all thyroid malignancies in Eastern China [4,5]. Typically, it has an indolent clinical course with 5-year overall survival (OS) rate of 97.5 % [6]. Morphologically, 15 variants of PTC have been identified with various clinicopathologic characteristics and biological

Abbreviations: PTC, papillary thyroid carcinoma; DDV, diffuse disseminate variant; DSV, diffuse sclerosing variant; NGS, next-generation sequencing; RAI, radioactive iodine; ETE, extrathyroidal extension; LVI, lympho-vascular invasion; H&E, hematoxylin and eosin; PTMC, papillary thyroid microcarcinoma; TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer; LNM, lymph node metastases; WHO, World Health Organization; FFPE, formalin-fixed paraffin-embedded; FNAB, fine-needle aspiration biopsy; CCLND, central compartment lymph node dissection; MRLND, modified radical uni- or bilateral neck dissection; ATA, American Thyroid Association; Tg, thyroglobulin; CT, computed tomography; PCR, polymerase chain reaction; SNV, single nucleotide variant; SD, standard deviation; IQR, interquartile range; DFS, disease-free survival; FVPTC, follicular variant of PTC.

* Corresponding author at: Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, No.300 Guangzhou Road, Nanjing, Jiangsu, 210029, China.
E-mail address: ws0801@hotmail.com (S. Wang).
[1] These authors contributed equally to this work.

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behaviors. Some of these variants present prognostic significance, while the other specific subtypes of PTC may behave more aggressively than conventional PTC [7]. Tall cell, columnar cell, hobnail, and diffuse sclerosing variant (DSV) are characteristic of an aggressive variant of PTC [8–10]. In addition, specific clinical and pathological features of PTC, such as old age, large tumor size, multifocality, extrathyroidal extension (ETE), and lymphovascular invasion (LVI), or distant metastasis, have been associated with a high risk of tumor recurrence and cancer-related mortality.

Herein, we observed an index case of PTC, in which the patient experienced recurrence after the initial surgery. Hematoxylin and eosin (H&E) staining showed a papillary thyroid microcarcinoma (PTMC) in the left lobe, where the maximal diameter was 8 mm. Yet, tens and hundreds of small well-differentiated foci diffused in the whole thyroid with follicular or papillae growth pattern; the background thyroid tissue did not show any stromal fibrosis, psammoma bodies, and lymphocytic infiltration. Recent case reports of PTC with diffuse intrathyroidal spread features confirmed the unique patterns of these tumors [11,12]. To collect additional data on this distinctive form of PTC with diffuse follicular/papillae features, we reviewed the PTC medical records in the First Affiliated Hospital of Nanjing Medical University from July 2014 to November 2019, retrieving 33 additional cases. Therefore, the aim of the present study was to establish this unique pattern of PTC as a distinct form of well-differentiated PTC, which was nominated as diffuse disseminate variant (DDV) PTC. Moreover, we wanted to investigate the histopathological characteristics, molecular features, and biological behavior of DDV PTC and compare the characteristics of DDV to DSV PTC.

2. Materials and methods

2.1. Materials

In this retrospective study, we reviewed the electronic medical records of PTC patients admitted to the First Affiliated Hospital of Nanjing Medical University and obtained their clinical data. The surgical pathology specimens were analyzed by two endocrine pathologists, and pathological staging was performed according to the eighth edition of the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) Staging Manual [13]. Each case was evaluated based on the following clinicopathological parameters: age at diagnosis, gender, tumor size, ETE, LVI, lymph node metastases (LNM), psammoma bodies, background lymphocytic infiltration, and radioactive iodine (RAI) treatment. In the event of multiple foci, the diameter of the largest tumor was considered. In the present study, ETE was defined as tumor invasion beyond the thyroid capsule, including invasion to extrathyroidal soft tissues, parathyroid, skeletal neck muscles, peripheral nerve, trachea, and esophagus.

These tumors were classified as DDV PTC according to the following criteria: (a) classic features of PTC, including the typical nuclear features of PTC: optically clear nuclei, nuclear pseudoinclusions, and prominent longitudinal grooves; (b) tens and hundreds of small foci were disseminated throughout the entire lobe or the whole thyroid gland with or without a dominant lesion; (c) the small foci showing a single or several follicular or papillary growth patterns; (d) no stromal fibrosis; (e) rare psammoma bodies or absence of the same; (f) discrete or no lymphocytic infiltration. The exclusion criteria primarily consisted of several tumor foci disseminated in the local part of thyroid, or the small tumor foci found in areas with a maximum of 500 mm apart from the primary tumor.

DSVs were diagnosed according to the fourth edition of the World Health Organization (WHO) classification of Tumors of Endocrine Organs (2017), based on the following inclusion criteria: diffuse tumors involving a single lobe or the entire gland, characterized by dense sclerosis, numerous psammoma bodies, background changes of chronic lymphocytic thyroiditis, and squamous metaplasia [7].

The formalin-fixed paraffin-embedded (FFPE) tissue was collected from the Department of Pathology. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University Ethics Committee (NO. 2,019,053) and conducted in accordance with Helsinki Declaration. All patients provided written informed consent before participation in this study.

2.2. Treatment and follow-up

All patients underwent total thyroidectomy; 32 DDV and 23 DSV patients underwent central compartment lymph node dissection (CCLND), while 29 DDV and 20 DSV received modified radical uni- or bilateral neck dissection (MRLND). In our hospital, all patients accepted levothyroxine suppressive therapy. According to the 2015 American Thyroid Association (ATA) risk stratification [8], high-risk patients were routinely administered RAI therapy after total thyroidectomy, while patients at intermediate-risk, the administration of RAI treatment depended on postoperative serum thyroglobulin (Tg) and/or anti-Tg antibody level. Finally, 28 and 14 patients accepted RAI treatment in DDV and DSV groups, respectively; the cumulative RAI dose was 100–300 mCi. After the initial treatment, the occurrence of lymph node recurrence was established as the indicator of suspicious lymph nodes on imaging tests (ultrasound, computed tomography (CT), or whole-body scan), which was confirmed by fine-needle aspiration biopsy (FNAB) and $BRAF^{V600E}$ mutation by polymerase chain reaction (PCR) or thyroglobulin washout concentration.

2.3. DNA extraction and targeted DNA panel design

Genomic DNA was extracted from each FFPE tissue block. Tissue blocks containing the highest proportion of tumor tissue were selected, and surrounding non-tumorous tissue was manually removed by dissection to increase the proportion of tumor cells. The DNA was isolated from the FFPE tumor tissue using QIAamp DNA FFPE Tissue Kit (QIAGEN, Valencia, CA, USA), according to the manufacturer's instructions. Next-generation sequencing was performed using a hybridization capture-based assay: AmoyDx Thyroid Carcinoma 18genes Panel (ADx TC18, Amoy Diagnostics, Xiamen, China), including selected exons and introns from 18 genes (*ALK*, *BRAF*, *TERT*, *NRAS*, *HRAS*, *KRAS*, *PIK3CA*, *PTEN*, *AKT1*, *TP53*, *CTNNB1*, *PDGFRA*, *TSHR*, *NTRK1*, *RASAL1*, *GNAS*, *PAX8*, and *RET*), which can detect several types of mutation, including single nucleotide variant (SNV), small insertions and deletions, and fusion events of critical genes with any partner. The sequencing depth was $> 9000\times$. All mutations were called by AmoyDx Analyze System.

2.4. Statistical analysis

Summary statistics were used to describe the baseline characteristics. Categorical variables were expressed as numbers and percentages, while continuous variables as means $\pm$ standard deviation (SD) or medians and interquartile range (IQR). The chi-square test and Fisher's exact test were used to analyze the categorical variables, while analysis of variance and Mann–Whitney *U* test was used to analyze continuous variables, respectively. The Kaplan–Meier method with the log-rank test was used for disease-free survival (DFS) analysis. All statistical analyses were performed using the IBM SPSS Statistics 25.0 software package (SPSS, Chicago, IL, USA). $P < 0.05$ indicated statistical significance.

3. Results

3.1. Clinical and pathological futures of DDV

During the study period, 34 (0.7 %) cases with diffuse dissemination features were identified from 4595 PTC patients. The clinicopathological features of DDV are summarized in Table 1. The average age of the

Table 1
Summary of the clinicopathological data and comparison between DDV and DSV PTC.

	DDV (n = 34)	DSV (n = 23)	P-value
Mean age (years)	35.4 ± 10.7 (19–62)	36.0 ± 9.6 (22–55)	0.825
Gender (male)	17 (50.0)	1 (4.3)	< 0.001
Background lymphocytic infiltration	10 (29.4)	23 (100)	< 0.001
ETE	21 (61.8)	9 (39.1)	0.093
LVI	15 (44.1)	14 (60.9)	0.215
Size of the largest tumor, mm	18.0 ± 11.9	10.1 ± 8.3	0.008
Number of involved N1a	6.5 (5, 9)	7 (4, 9.75)	0.677
Number of resected N1a	9 (5.5, 11)	14 (6.5, 15)	0.103
Number of involved N1b	6 (5, 9.5)	6 (2, 12)	0.903
Number of resected N1b	28 (13.5, 44)	28 (10, 39)	0.948
RAI treatment	28 (82.4)	14 (60.9)	0.071
Follow-up time	36.7 ± 17.4	42.4 ± 19.7	0.259
Recurrence	16 (44.1)	2 (8.7)	0.002

Values in parentheses are percentages unless indicated otherwise, values are mean ± SD; number of involved and resected lymph nodes were expressed as medians and interquartile range (IQR). ETE, extrathyroidal extension; LVI, lympho-vascular invasion; RAI, radioactive iodine.

cohort, consisting of an equal number of males and females, was 35.4 ± 10.7 (range: 19–62) years. Most of the patients had a predominant lesion, and the mean size of the largest tumor was 18.0 ± 11.9 mm. The tumors were often described as multiple foci spread around the predominant nodular region through the whole thyroid lobe.

Microscopic examination revealed a predominant lesion characterized by variably sized papillary or follicular structures, accompanied by a marked proliferation of interstitial connective tissue. The tumor cells with classic papillary thyroid carcinoma nuclear features presented as tens to hundreds of small tumor foci radially spread in the entire thyroid (Fig. 1A). These small tumor foci showed a single cancer cell or several follicular or clusters of cancer cells forming papillary structures (Fig. 1B–D). Moreover, no reactive proliferation of connective tissue or a fibrous capsule was detected around these small foci. Also, no background lymphocytic infiltration was observed or was rare and inconspicuous in each case of DDV. Nevertheless, a small number of psammoma bodies were found to be diffused in several cases.

An extrathyroidal extension was present in 21 (61.8 %) cases and LVI in 15 (44.1 %) cases. All patients with lymph node metastasis underwent dissection. Briefly, 32 patients underwent CCLND, and the median number of the lymph nodes involved and removed was 6.5 (range, 1–28) and 9 (range, 2–33), respectively. A total of 29 patients underwent MRLND, and the median number of involved and removed lymph nodes in the lateral compartment was 6 (range, 2–43) and 28 (range, 3–112), respectively.

Next, 33 (97.1 %) cases harbored driver gene mutations. The results showed that $BRAF^{V600E}$ was the most common mutation in DDV, with a mutation frequency of 82.4 % (28/34). The next most frequent mutation in this patient population was fusion rearrangement (14.7 %, 5/34), where 2 (5.9 %) cases exhibited RET−CCDC6 fusion, RET-TRIM33 was observed in 1 (2.9 %) case, and the remaining 2 (5.9 %) cases carried NTRK1-TPM3 fusion rearrangements. Other mutations included TP53,

Table 2
Somatic genetic alterations of 34 DDV and 23 DSV patients.

Genetic variants	DDV (n = 34)	DSV (n = 23)	*P*-value
BRAF V600E	28 (82.4)	4 (17.4)	< 0.001
RET-CCDC6	2 (5.9)	5 (21.7)	0.106
RET-TRIM33	1 (2.9)	1 (4.3)	1
TP53	1 (2.9)	1 (4.3)	1
TPM3-NTRK1	2 (5.9)	0	
TERT	1 (2.9)	0	
TSHR	1 (2.9)	0	
PDGFRA	1 (2.9)	0	
BRAF + TERT + TSHR	1 (2.9)	0	
BRAF + TP53	1 (2.9)	0	
BRAF + TSHR	1 (2.9)	0	
BRAF + PDGFRA	1 (2.9)	0	
ALK	0	1 (4.3)	
GNAS	0	1 (4.3)	
NRAS	0	1 (4.3)	
ALK-STRN	0	1 (4.3)	
BTK-PAX8	0	1 (4.3)	
BRAF + BTK-PAX8	0	1 (4.3)	
TP53 + ALK-STRN	0	1 (4.3)	

Values in parentheses are percentages. DDV, diffuse disseminate variant; DSV, diffuse sclerosing variant.

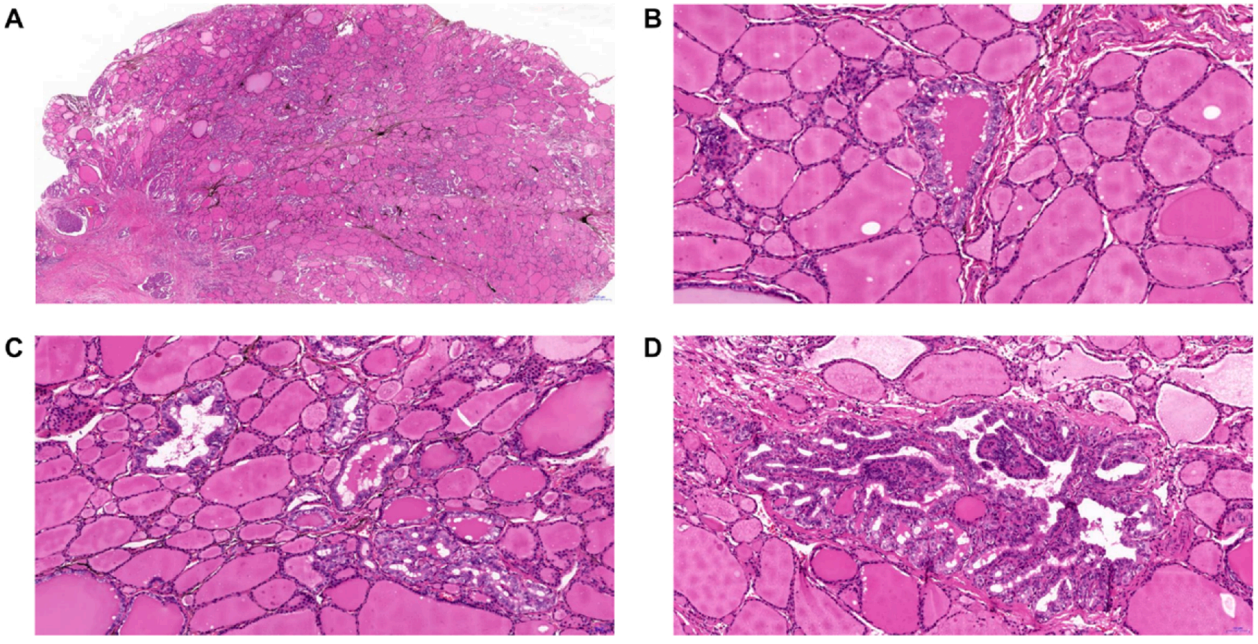

Fig. 1. DDV PTC displayed a predominant lesion and spread in entire thyroid, 20 × (A); small tumor foci showing a single, 400 × (B); or several follicular growth patterns, 200 × (C); or forming papillary structures, 200 × (D).

TERT, PDGFRA, and TSHR (Table 2). In addition, there were 4 (16.1 %) patients with co-mutation with $BRAF^{V600E}$, including 1 patient with $BRAF^{V600E}$ + TERT + TSHR triple mutations. The included mutations were $BRAF^{V600E}$ + TP53, $BRAF^{V600E}$ + PDGFRA, and $BRAF^{V600E}$ + TSHR, respectively (Table 2). However, the RAS family genes were not detected in this study. Moreover, $BRAF^{V600E}$ mutations and RET/PTC rearrangements were mutually exclusive. There were no statistically significant clinicopathological factors between $BRAF^{V600E}$ positive mutation and $BRAF^{V600E}$ negative mutation cases (Supplementary Table S1).

3.2. Comparison between DDV and DSV PTC clinicopathological characteristics by univariate analyses

Table 1 shows the comparison between DDV and DSV PTC patients. The average age of patients did not significantly differ between the two groups ($P = 0.825$), and male patients were more frequently diagnosed with DDV than DSV ($P < 0.001$). The size of the largest tumor was significantly greater in DDV than in DSV patients ($P = 0.008$). However, many DSV patients showed background lymphocytic infiltration compared with the DDV group ($P < 0.001$, Fig. 2). Other clinicopathological features, such as ETE, LVI, and LNM, did not differ between the two groups. The number of $BRAF^{V600E}$ mutations was significantly higher in the DDV than in the DSV group (Table 2, $P < 0.001$). The RET/PTC rearrangement was the most common driver gene mutation in DSV patients; however, no significant difference was found between the two groups (Table 2, $P = 0.106$). In addition, other somatic genetic alterations showed significant differences between the two groups (Table 2). Moreover, RAI therapy did not differ between the two groups ($P = 0.071$). The mean follow-up was 39.0 months; 16 DDV and 2 DSV patients were detected as lateral LNM after complete remission, and the risk of recurrence was significantly higher in DDV than DSV patients (47.1 % and 8.7 %, $P = 0.002$). The DFS rate was significantly lower in the DDV than in the DSV group ($P = 0.003$, Fig. 3).

3.3. Prognostic factors for recurrence

We examined the prognostic factors associated with lymph node recurrence in patients who did not show distant metastasis at presentation and underwent locally curative surgery. Univariate analysis identified male gender, size of the largest tumor, background lymphocytic infiltration, and $BRAF^{V600E}$ mutation as significant prognostic factors for recurrence, whereas multivariate analysis identified $BRAF^{V600E}$ mutation and the size of the largest tumor as independent prognosis factors for recurrence (Table 3).

4. Discussion

The current retrospective study investigated the clinicopathological features of diffuse disseminate variant PTC in a single center. This variant mainly affects young patients, and in the present study, both genders were equally affected. The current data confirmed that most of the DDV PTC had aggressive behavior and a cervical lymph node recurrence; the median duration to recurrence after surgery was 7.5 (range, 2–20) months. However, due to the short follow-up duration in this study, no distant metastasis and disease-related deaths were noted.

"Diffuse intrathyroidal dissemination" is the term employed to describe tumors characterized by a large number of small foci spread in one or two thyroid lobes. It is the distinct clinicopathological future of DDV. Despite its aggressive behavior with high cervical LNM and recurrence, DDV was not classified as tall cell, columnar cell, hobnail, diffuse sclerosing, or other variant PTC based on the pathological morphology.

PTC usually occurs with unilateral or bilateral multifocal tumors. The frequency of multifocal PTC has been reported to be 18–87 % in several series [14], and the number of malignant foci is usually less than ten; however, several studies reported tens to hundreds of small tumor foci in one lobe or whole thyroid under the microscope [11,12,15]. These authors reported that these small lesions were distributed around the central lesion in a radial form or "fan-out" pattern, and the lesion density decreased with increasing distance from the central lesion. Therefore, these small foci were considered as intrathyroidal metastasis from the central lesion *via* the lymphatic system. In this study, the pathological features of DDVs were similar to those described in previous reports. Whether the multifocal PTC arises from multicentric independent tumors or intrathyroidal metastases spreading from a single tumor remains controversial.

Macroscopically, 2–10 tumor foci were noted in the multifocal PTC; these foci existed as anatomically independent visible nodules, with a diameter ranging from mm to cm. Microscopically, the presence of fibroblastic stromal reaction and lymphocytic infiltration to the surrounding stroma was a crucial morphological feature of each lesion; occasionally, these lesions had a complete capsule. Conversely, most of the DDV patients showed one predominant lesion, and in several DDV cases, many small tumor foci spread in the entire thyroid instead of the dominant lesion. In this case, the reactive proliferation of connective tissue was absent or extremely mild around the small cancer lesions. Immunohistochemistry staining using cyclin D1 and $BRAF^{V600E}$ antibody showed that these small foci were similar to the main lesion [12,16].

$BRAF^{V600E}$ was the most common driver mutation in PTC, which has a crucial role in PTC diagnosis, prognosis, and treatment selection. Kimbrell et al. [17] reported that compared to cases with fewer than 4 nodules, those with ≥4 nodules tended to have concordant $BRAF^{V600E}$ mutation status; however, the difference was not statistically significant (50 % *vs.* 89 %, $P = 0.09$). Lu and Xia applied next-generation sequencing and found that most of the separated tumor foci of the multifocal PTC arose as independent tumors [18,19]. These findings indicated that many small tumor foci in the DDV had intraglandular spread rather than occurred as independent multiple tumor lesions.

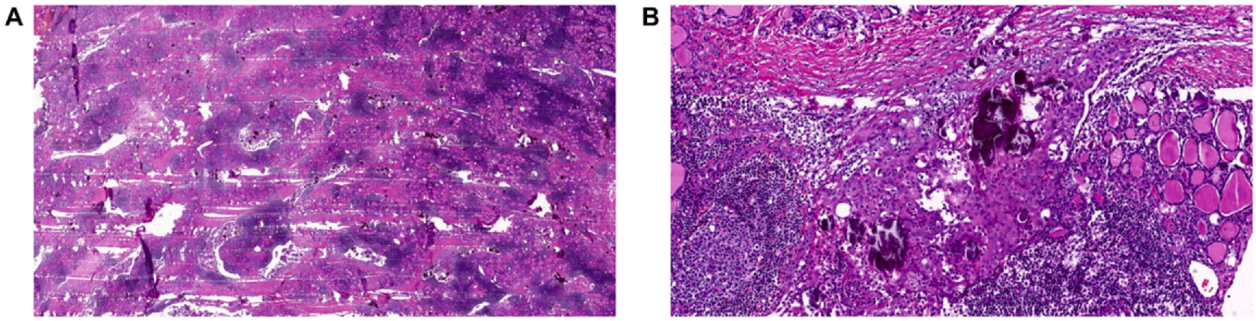

Fig. 2. In DSV PTC, the carcinoma diffused involvement of whole lobes, extensive lymphatic infiltration, numerous psammoma bodies, dense sclerosis, 20 × (A); prominent squamous metaplasia, 200 × (B).

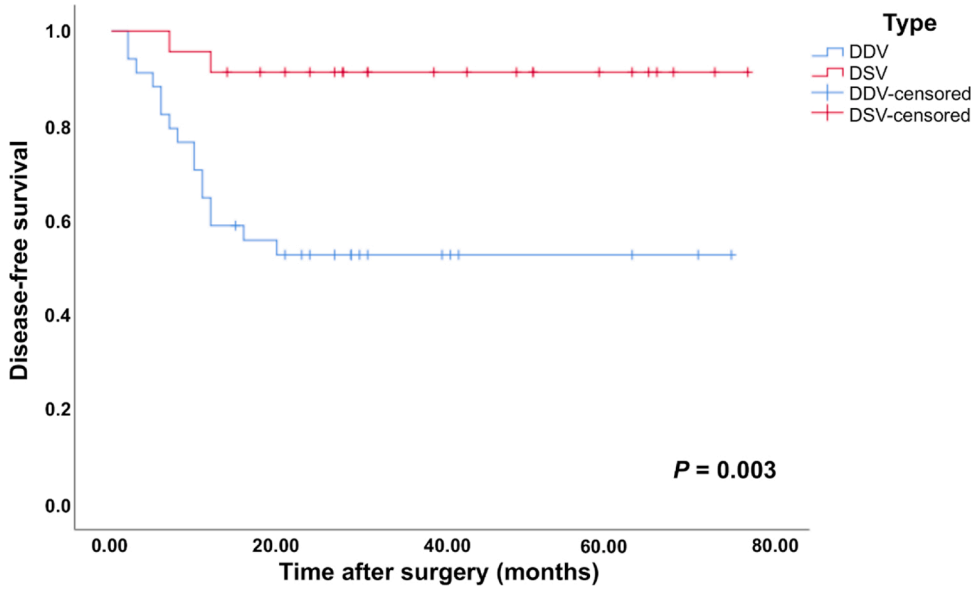

Fig. 3. Comparison of disease-free survival (DFS) rates between the DDV and DSV groups.

Table 3
Multivariate analysis to identify prognosis factors for recurrence related to clinicopathological characteristics.

Factor	Risk ratio	95 % CI	P-value
Histotype (DDV)	1.84	0.15–23.07	0.638
Background lymphocytic infiltration	0.76	0.13–4.44	0.76
BRAF V600E mutation	9.39	1.20–73.35	0.033
Gander (male)	0.61	0.13–2.81	0.529
pT large diameter	1.08	1.00–1.16	0.039

CI, confidence interval; DDV, diffuse disseminate variant.

DSV is a rare variant of PTC that accounts for 0.4–6.6 % of all PTCs [20,21]. In addition to classic nuclear features of PTC, DSV tends to occur in young female patients and is characterized by diffused involvement of a single lobe or the entire gland, usually without the formation of a dominant mass [7,20,22]. Several studies reported that DSV was associated with aggressive behavior and poor prognosis compared to classical PTC, which could be attributed to a high rate of vascular invasion, ETE, LNM, and distant metastasis in DSV [9,10,22,23]. Typically, 23 DSV cases in the current study showed aggressive clinicopathological behaviors; 100 % had LNM, 60.9 % had LVI, and 39.1 % had ETE.

This study also revealed that DDV differed from DSV in several aspects, including ultrasonography features, histopathology, molecular changes, and disease outcomes. In ultrasonography, DDV's sonographic features similar to conventional PTC included a hypoechoic or isoechoic solid nodule with irregular margins, taller-than-wide shape, microcalcifications within the nodule. In contrast, DSV ultrasonography that mimicked Hashimoto's thyroiditis showed diffuse enlargement of the thyroid, heterogenous echogenicity without mass formation, and diffusely scattered microcalcifications (Fig. 4). Grossly, DDV typically presented as an invasive neoplasm with poorly defined margins, a firm consistency, and an ivory-white cut surface, where the remnant thyroid sectioned surface seemed normal. Yet, the thyroid gland of DSV was enlarged, firm, and fibrotic in consistency, the cut surface of the thyroid was grayish-white with no predominant mass. Morphologically, DDV had a predominant mass without stromal fibrosis and could contain a small number of psammoma bodies; the size of the largest tumor was greater than that of DSV. In contrast, the dominant mass was not always observed in DSV, while extensive interstitial fibrosis was common. In addition, the presence of psammoma bodies, squamous metaplasia, and lymphocytic infiltration surrounding thyroid parenchyma was higher

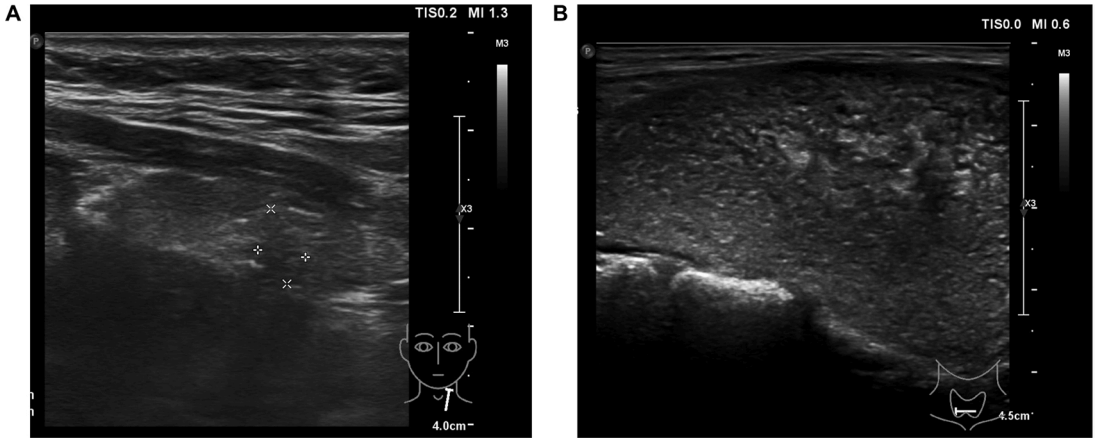

Fig. 4. Sonographic features of DDV and DSV. (A) Longitudinal views of neck ultrasound findings of DDV, the lower left side of the thyroid revealed an irregular hypoechoic nodule with unclear borders, surrounding thyroid tissue was normal. (B) Transverse views of preoperative neck ultrasound findings of DSV, thyroid ultrasonography showed diffusely enlarged, heterogeneous echogenicity without the mass formation and diffusely scattered microcalcifications.

than that in DDV. Although both DSV and DDV were frequently diagnosed in young patients, DSV was more common in female patients and DDV in male patients.

In this study, the number of $BRAF^{V600E}$ mutations was significantly higher in the DDV than in the DSV group ($P < 0.001$). RET/PTC rearrangement was the most common driver gene mutation in DSV patients, but no significant difference was detected among the two groups ($P = 0.106$). Previous and current studies have demonstrated that $BRAF^{V600E}$ mutations and RET/PTC rearrangements are mutually exclusive [24,25]. In addition, the prevalence of somatic genetic alterations was significantly different between DDV and DSV (Table 2); therefore, we speculated that the molecular pathogenesis of DDV might differ from that of DSV. Multivariate analysis identified $BRAF^{V600E}$ mutation as an independent prognostic factor for recurrence (risk ratio [RR] = 9.9, 95 % confidence interval [CI]: 1.20–73.35, $P = 0.033$), which is consistent with the previous finding that $BRAF^{V600E}$ mutation is associated with aggressive clinical manifestations and poor outcomes [26–28]. During a mean 39.0-month follow-up, cervical lymph node recurrence rate was significantly higher in DDV patients than in DSV patients, although most patients in both groups underwent postoperative RAI therapy. Therefore, we assume that the prognosis of DDV was worse than that of DSV, which suggests that careful ongoing surveillance is critical in DDV patients.

Recent studies reported a diffuse or multinodular follicular variant of PTC (DFV), which was initially described by Sobrinho-Simões et al. in 1990 [29]. The study reported that eight patients developed metastases in the lungs and/or bones with or without concurrent regional lymph node metastases. This phenomenon was predominantly observed in young females with extensive involvement of one or both lobes of the thyroid gland. In addition, DFV endows a prominent follicular growth pattern without papillary structure, either lacking or rarely showing psammoma bodies, fibrosis, and lymphocytic infiltration [29,30]. In most cases, DFV grossly resembles a multinodular goiter instead of a neoplasm with satellite nodules [30]. Moreover, this subtype of PTC shows other features, including aggressive clinical behavior and a high stage at presentation, a notably increased regional lymph node, and vascular invasive distant metastasis [30–33], while about 50 % of the patients (2/4) harbored a $BRAF^{V600E}$ mutation [34].

DFV, similarly to DDV, showed tumor involvement of one lobe or entire thyroid gland, and both subtypes had aggressive clinical behavior. Nevertheless, DFV is a variant of follicular variant of PTC (FVPTC) with nodules displaying a microfollicular or trabecular growth pattern, and infiltration in the thyroid parenchyma is follicular style [30]. On the other hand, DDV is a well-differentiated PTC, whose infiltrative growth pattern is single/several follicular or papillae style. In addition, DFV lacks or has rare psammoma bodies. Nonetheless, a few psammoma bodies were detected in DDV in the current study, while in several cases, diffused psammoma bodies were identified in DDV. Together, these observations led us to hypothesize the presence of different variants between DDV and DFV, and DDV has an extensive scope encompassing DFV.

Nevertheless, the present study has some limitations. First, 34 DDV cases that were presented and analyzed here were collected from a single institution. Thus, additional studies with more cases of DDV from multiple centers are required to validate reported findings further. Second, at a mean follow-up of 36.7 months, the current study showed that DDV patients had a high cervical lymph node recurrence rate. However, as this was a relatively short follow-up, distant metastasis and disease-related deaths were not recorded. Considering that PTC is a slowly progressive disease, an extended follow-up period might be applied in future studies.

5. Conclusion

Diffuse dissemination variant PTC is a well-differentiated thyroid carcinoma with a large number of small tumor foci spread in one lobe or whole thyroid with aggressive biological behavior and no stromal fibrosis at the intrathyroidal region. It is commonly diagnosed in young patients and has high rates of LVI, LNM, ETE, and $BRAF^{V600E}$ mutation. Despite the fact that patients accepted extensive surgical approaches and RAI therapy, the recurrence rate was still high within the first 2 years after the initial surgery. Moreover, although the ideal classification of histological variants of any neoplasm is based on morphology, it also reflects the biological behavior of the tumor and provides guidance for the most effective therapy [35]. Therefore, DDV should be regarded as a novel aggressive variant of PTC and classified as the ATA high-risk group, which requires aggressive treatment and clinical surveillance.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First Affiliated Hospital with Nanjing Medical University (NO. 2019053). The informed consent was waived due to the retrospective nature of the study.

Data statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Shui Wang was involved in the conception and design of the research. Haisheng Fang and Yan Si performed the analysis and interpretation of the data; drafted the manuscript. Haisheng Fang and Cong Wang were involved in reviewed Surgical pathology H&E slides. Qixing Gong was recruited clinical and follow-up data of these patients. Chong Liu was involved in the statistical analysis. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2021.153510.

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