Case Reports

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Thyroid papillary carcinoma with the 'snowstorm appearance': a clinicopathological analysis of three cases

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Abstract

This current case report presents the detailed clinicopathological analysis of three patients with papillary thyroid carcinoma, each of which presented with the 'snowstorm appearance' on ultrasonography. Ultrasonography of this tumour typically shows a diffusely enlarged thyroid with hypoechoic and heterogeneous internal echoes, and diffusely scattered microcalcifications, which form the 'snowstorm appearance'. Microscopically, case 1 had a large number of psammoma bodies, infiltration of lymphocytes, formation of lymphatic follicles and extensive squamous metaplasia, leading to the diagnosis of a diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC). Case 2 was diagnosed with follicular papillary thyroid carcinoma. Their tumour had numerous calcifications in the stroma and follicles. Case 3 was diagnosed with a multifocal papillary thyroid carcinoma in the background of Hashimoto's thyroiditis. Their tumour showed calcification in the stroma and follicles, together with cervical lymph node metastasis. DSVPTC is a rare variant of thyroid papillary carcinoma. It has the 'snowstorm appearance' on ultrasound, but this can also be found in follicular papillary carcinoma and multifocal thyroid papillary carcinoma. Papillary thyroid carcinoma with the 'snowstorm appearance' has a large number of peripheral lymph nodes metastases, thus requiring radical surgery and postoperative adjuvant therapy.

Keywords

Thyroid papillary carcinoma, diffuse sclerosing thyroid papillary carcinoma, snowstorm appearance, ultrasound, pathology

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Introduction

The characteristic ultrasound appearance of diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is that of a diffusely enlarged thyroid with hypoechoic and heterogeneous internal echoes containing scattered microcalcifications with or without an associated suspicious mass; and the presence of cervical lymph nodes that are suspicious for metastases, thus forming a 'snowstorm appearance'.[1] Can the 'snowstorm appearance' on ultrasound be directly diagnosed as DSVPTC? This case report presents three different variants of thyroid papillary carcinoma, all of which were characterized by the 'snowstorm appearance' on ultrasound. The aim of this detailed analysis of three cases was to gain a better understanding of the characteristic imaging and pathological features of the 'snowstorm appearance' and propose potential treatment guidelines.

Case report

This case report describes the clinical and pathological data of three patients diagnosed with papillary thyroid carcinoma with 'snowstorm appearance' between January 2018 and July 2020 by the Department of Ultrasonography and the Department of Pathology, Anyang Tumour Hospital, Anyang, Henan Province, China. All three cases were confirmed by at least two senior ultrasonologists.

The mean age of the three cases was 41.3 years (range, 16–54 years) (Table 1). None of the three cases had a history of malignancy or tuberculosis. Physical examinations showed that all three patients complained of a neck mass. Case 1 had experienced neck enlargement for 1 month. In case 2, the neck mass has been observed for 2 months. Case 3 became emaciated 4 months previously and found that their neck was increasing in size. Ultrasound examination of case 1 revealed a diffusely enlarged thyroid with hypoechoic and heterogeneous internal echoes containing scattered microcalcifications without an associated suspicious mass, thus forming a 'snowstorm appearance' (Figure 1a). Colour Doppler ultrasound showed profuse blood flow in the lesion with an Adler score of 3. Ultrasound examination of case 2 revealed diffuse enlargement of the bilateral thyroid gland with heterogeneous internal echoes and scattered microcalcifications, forming a similar 'snowstorm appearance' (Figure 1b). Colour Doppler ultrasound showed moderate blood flow in the lesion with an Adler score of 2. Ultrasound examination of case 3 showed diffuse enlargement of the right thyroid gland, uneven internal echo and multiple punctate strong

Table 1. Clinicopathological features of three cases of thyroid papillary carcinoma with a 'snowstorm appearance' on ultrasound imaging.

Case	Age, years	Sex	Lesion site	Nodules or masses	Diagnosis	Lymph node metastasis	Recurrence	Status at follow-up, months
1	16	Female	Bilateral thyroid gland	No	DSVPTC	15/29	–	Alive, 40
2	54	Male	Bilateral thyroid gland	No	Follicular papillary carcinoma	18/55	At 38 months post operation	Alive, 40
3	54	Female	Right thyroid gland	Different sized nodules	Multifocal papillary carcinoma	5/23	–	Alive, 12

DSVPTC, diffuse sclerosing variant of papillary thyroid carcinoma.

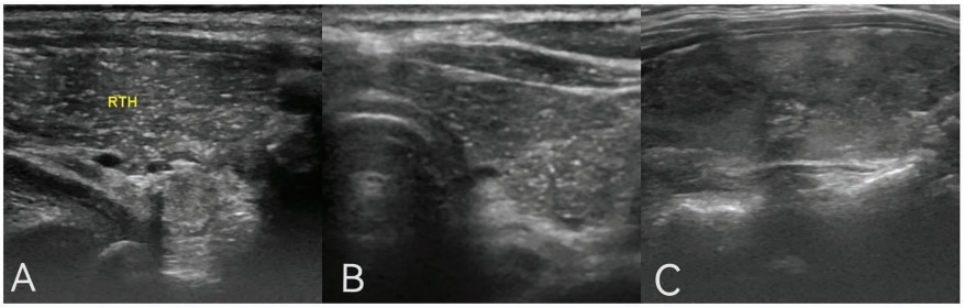

Figure 1. Representative ultrasound images of case 1 (a), case 2 (b) and case 3 (c) showing scattered microcalcifications giving a typical 'snowstorm appearance'.

echoes, which also formed the 'snowstorm appearance' (Figure 1c). Colour Doppler ultrasound showed no obvious blood flow in the lesion with an Adler score of 0.[2] In all three cases, ultrasound examination showed abnormal enlargement of the lymph nodes. All three cases were thought to have thyroid cancer based on the clinical and ultrasound examinations. All three cases underwent radical thyroidectomy and postoperative iodine 131 treatment as described below.

Gross examination of the tumours demonstrated that there were no obvious nodules or masses on multiple sections of the bilateral thyroid in cases 1 and 2. Scattered grey-white nodules were found in case 3. The bilateral cervical lymph nodes were enlarged and the sections were grey-white and red. Tumour specimens were collected during surgery and fixed in 10% buffered formalin for routine processing. Tissue sections (4 μm) were stained with haematoxylin and eosin. Immunohistochemistry was performed according to standard protocols. The following primary antibodies were used: cluster of differentiation (CD) 56 (prediluted; Dako, Glostrup, Denmark) and cytokeratin (CK)19 (prediluted; Dako). All negative and positive controls were included. CK19 was stained in the cytoplasm and CD56 was stained in the cytomembrane. Brown and yellow staining was considered to show positive immunostaining. All three cases were strongly and diffusely positive for CK19, while negative for CD56.

In case 1, tumour cells diffusely infiltrated bilateral thyroid tissues, mostly in dilated lymphatic fissures (Figure 2a). Cancer cells were arranged around psammoma bodies or loose connective tissue (Figure 2b), presenting with a papillary structure and some of them had a hobnail-like appearance. A large number of psammoma bodies, infiltration of lymphocytes, formation of lymphatic follicles and extensive squamous metaplasia were observed (Figure 2c). There was interstitial fibrosis in the region and a small number of tumour nests were seen in the fibrotic background. In more areas, the nuclear chromatin pattern of the carcinoma cells was slightly coarser than that of conventional papillary carcinoma and the nuclei were large and round, while the typical papillary nuclei (grooved nuclei and cytoplasmic inclusions) were not obvious (Figure 2d). Almost no lymph nodes were spared and the metastatic morphology was similar to that of the primary tumour.

In case 2, a large number of scattered calcifications were observed in the background of nodular goitre (Figure 3a). Some tumour cells showed nodular aggregation and follicular growth. Some follicular epithelial cells showed the characteristics

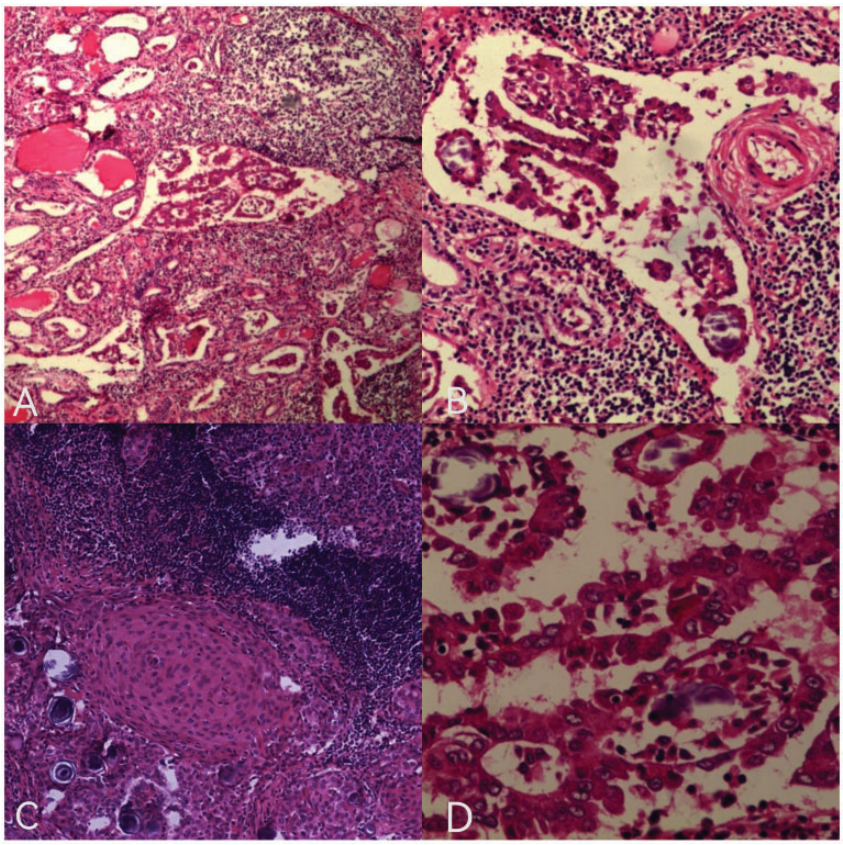

Figure 2. Representative photomicrographs of the tumour specimen from case 1: (a) tumour cells diffusely infiltrated the bilateral thyroid tissues, mostly in dilated lymphatic fissures (haematoxylin and eosin [H&E]; ×40); (b) tumour cells were arranged around psammoma bodies, presenting with a papillary structure (H&E; ×100); (c) a large number of psammoma bodies, infiltration of lymphocytes, formation of lymphatic follicles and extensive squamous metaplasia were observed (H&E; ×100) and (d) the nuclear chromatin pattern of the carcinoma cells was slightly coarser than that of conventional papillary carcinoma and the nuclei were large and round, while the typical papillary nuclei (grooved nuclei and cytoplasmic inclusions) were not obvious (H&E; ×200). The colour version of this figure is available at: http://imr.sagepub.com.

of typical papillary carcinoma nuclei (large nucleus, crowded, irregular karyotype, ground-glass chromatin, cytoplasmic inclusions and grooved nuclei). Most lymph nodes had metastases and the morphology of the metastases still presented a follicular structure, showing blood follicles and typical papillary carcinoma nuclear features (Figures 3b–3d).

In case 3, Hashimoto's thyroiditis was seen in the surrounding area (Figure 4a). Different sized thyroid papillary tumours were distributed in the bilateral thyroid glands, ranging from 0.05 cm to 0.8 cm in size. The tumour showed papillary growth and was multibranched with fibrosis; and the nuclei had the typical nuclear characteristics of papillary carcinoma (large nucleus, crowded, irregular karyotype, ground-glass chromatin, cytoplasmic inclusions and grooved nuclei). After observing multiple sections, calcification was found in the

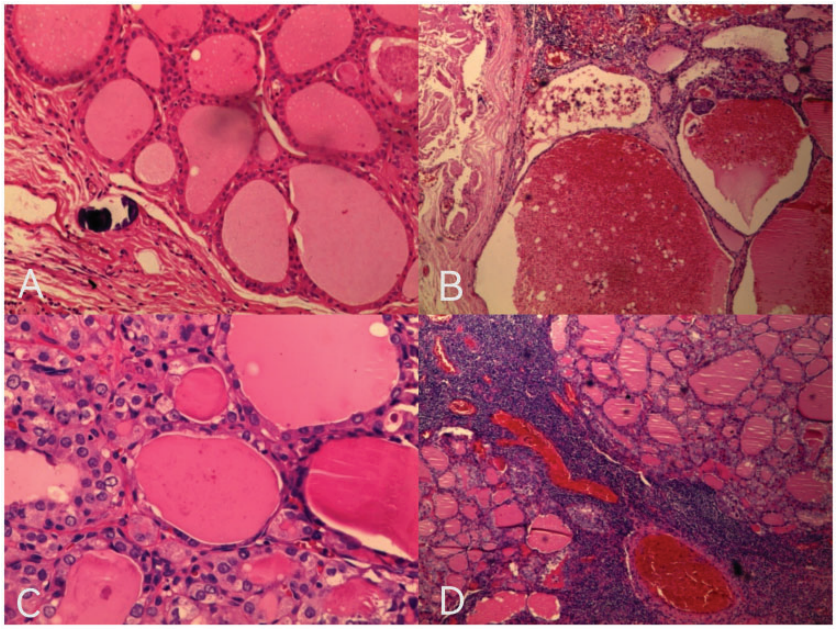

Figure 3. Representative photomicrographs of the tumour specimen from case 2: (a) a large number of scattered calcifications were observed in the background of nodular goitre (haematoxylin and eosin [H&E]; ×100); (b & c) some tumour cells showed nodular aggregation and follicular growth, with blood follicles and typical papillary carcinoma nuclear features (H&E; B ×40; C ×200) and (d) a large number of metastatic foci were found in the lymph nodes, showing a follicular growth pattern (H&E; ×40). The colour version of this figure is available at: http://imr.sagepub.com.

stroma or follicle of each section (Figures 4b–3d). A total of 23 lymph nodes were detected in the bilateral cervical lymph nodes, of which five were found to have metastatic carcinomas. The morphology of the metastatic carcinomas was consistent with that of the primary tumour.

In terms of diagnosis, in case 1, the combination of histological and ultrasound examinations resulted in a diagnosis of DSVPTC. In case 2, based on the histological features and lymph node metastasis, the tumour was diagnosed as a follicular thyroid papillary carcinoma. In case 3, based on the histological and gross examinations, the tumour was diagnosed as a multifocal papillary carcinoma.

All three patients received radical thyroidectomy and postoperative iodine 131 treatment. The patients followed the surgeon's advice and no adverse or unanticipated events occurred during the treatment. Case 1 received iodine 131 treatment twice postoperatively, with dosages of 106.07 mci and 142.86 mci. Case 2 received iodine 131 treatment twice postoperatively, with dosages of 111.04 mci and 144.89 mci. Case 3 received iodine 131 treatment twice postoperatively, with a dosage of 145 mci each time. There was no recurrence after 12–40 months of follow-up in cases 1 and 3. Case 2 had cervical lymph node metastasis at 38 months after surgery.

This case report was approved by the Institutional Research Ethics Committee of the Anyang Tumour Hospital (no. 2022WZ05K01). The Institutional Research Ethics Committee waived the requirement for approval and signed informed consent because this study was not an intervention

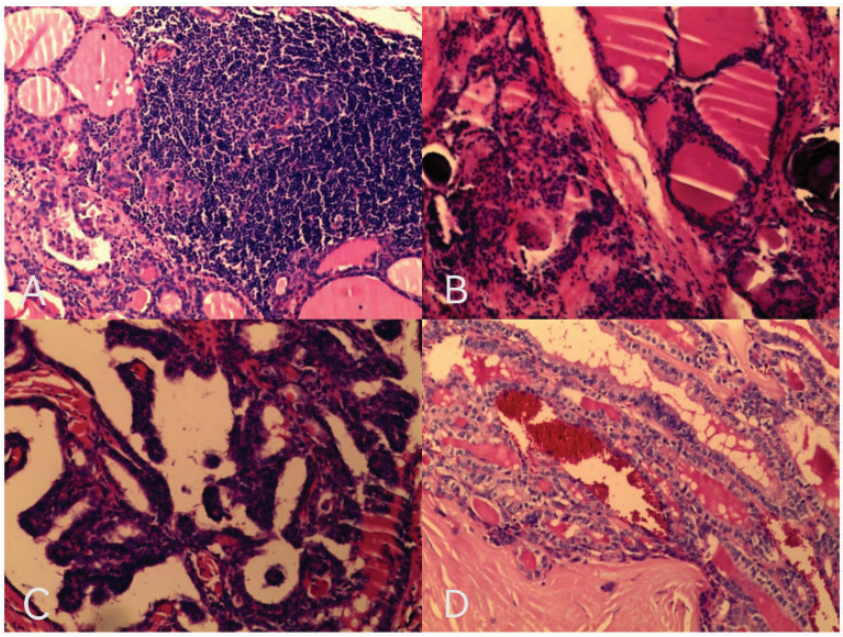

Figure 4. Representative photomicrographs of the tumour specimen from case 3: (a) Hashimoto's thyroiditis was found in the peripheral thyroid (haematoxylin and eosin [H&E]; ×100); (b) scattered calcified foci were observed in the stroma and follicles (H&E; ×100); (c) the tumour showed papillary growth and was multibranched with fibrosis (H&E; ×100) and (d) fibrosis around the tumour (H&E; ×100). The colour version of this figure is available at: http://imr.sagepub.com.

trial and it was retrospective in nature. Written informed consent was obtained from the three patients for the publication of their case reports and any accompanying images. The reporting of this study conforms to the CARE guidelines.[3]

Discussion

The characteristic 'snowstorm appearance' is often captured by radiology or ultrasound, which is used to describe miliary diffusion of innumerable micronodules in primary or metastatic lesions that can be either inflammatory or neoplastic lesions.[4] The characteristic ultrasound appearance of DSVPTC is that of a diffusely enlarged thyroid with hypoechoic and heterogeneous internal echoes containing scattered microcalcifications with or without an associated suspicious mass; and the presence of cervical lymph nodes that are suspicious for metastases, thus forming a 'snowstorm appearance'.[1] Although the prominent sonographic 'snowstorm appearance' is well known for the diffuse sclerosing variant, cases presenting with localized microcalcifications have also been reported.[5] DSVPTC is a rare variant of papillary thyroid carcinoma; accounting for 0.7–6.6% of papillary thyroid carcinomas.[6,7] Compared with classic papillary thyroid carcinoma (CPTC), DSVPTC is more likely to occur in women.[8,9] DSVPTC has a male–female ratio of approximately 1:4.3.[10] However, it is worth noting that the median age of onset of CPTC is 45 years,[6] while it is 28 years for DSVPTC.[10] The current case 1 was 16 years old. Therefore, DSVPTC is more likely than CPTC to occur in young women.

Fine needle aspiration biopsy is the most popular way to diagnose papillary thyroid carcinoma before surgery.[8] The cytological findings of DSVPTC are as follows: (i) solid cell balls and/or hollow balls containing lymphocytes; (ii) hobnail cells; (iii) septate cytoplasmic vacuoles; (iv) large unilocular vacuoles; (v) squamous differentiation; (vi) abundant psammoma bodies; (vii) lymphocytic background; (viii) the absence or relative lack of characteristic nuclear features of papillary carcinoma.[11] When DSVPTC is suspected, needle aspiration from the non-nodular area is useful to confirm the diagnosis of DSVPTC.[11]

In each of the current three cases, the cut surface of the tumour was grey-white and red, nodular, lobulated or fibre-separated, with a sandy texture. In case 1, the section of thyroid gland was grey and no obvious mass was found in the multiple sections. On microscopic examination, the carcinoma showed marked squamous metaplasia, numerous psammoma bodies, extensive interstitial fibrosis and heavy lymphocytic infiltration with formation of germinal centres. Most of the microscopic findings of case 1 were similar to those reported by previous research.[1] In addition, there were some special findings. A large number of lymphocytes were seen in the thyroid background. Bilateral thyroid tissues were diffusely distributed within cancer nests. Some of the cancer nests showed squamous metaplasia, mostly located in expanded lymphatic fissures. Cancer cells were arranged around psammoma bodies or loose connective tissue, presenting with a papillary structure. Some of the cells had a hobnail-like appearance. Interestingly, careful examination of the nuclei revealed that they lacked the typical features of papillary carcinoma nuclei, such as grooved nuclei and intranuclear inclusions. They were large and round, and their nuclear chromatin was slightly coarser than that of conventional papillary carcinoma, which was consistent with previous cytological findings.[11] In terms of tissue structure, there was a lack of complicated papillary branches seen in classic papillary carcinoma. Instead it was manifested as a single papillary form without branches. The 'snowstorm appearance' in case 1 was also due to many psammoma bodies, which were round, laminated 10–100-mm crystalline calcium deposits present in the epithelium that were associated with papillary carcinoma.[12] A previous study reported on the relationship between the molecular landscape and sonographic imaging of different variants of papillary thyroid carcinoma.[13] Rearrangement of the rearranged in transformation/papillary thyroid carcinomas (*RET*/*PTC*) genes is the most common genetic feature in DSVPTC.[14,15] The ultrasound appearance of DSVPTC harbouring *RET*/*PTC* gene rearrangements is different from *RET*/*PTC1*-positive and *RET*/*PTC3*-positive tumours.[16] Typical diffuse involvement with scattered microcalcifications without any visible nodules is much more frequently observed in *RET*/*PTC3*-driven tumours.[16] The coexistence of DSVPTC and Hashimoto's thyroiditis is characteristic of *RET*/*PTC1* mutations.[16] Microcalcifications are less frequent in *RET*/*PTC1* tumours than in *RET*/*PTC3* tumours.[16]

Other subtypes of thyroid papillary carcinoma can form a 'snowstorm appearance' similar to DSVPTC. In the current case 2, follicular papillary carcinoma displayed a 'snowstorm appearance' on ultrasound. This 54-year-old male patient had diffuse goitre of the thyroid gland without forming nodules or masses. The lymph nodes around the thyroid gland also showed abnormal enlargement. Some research has suggested that the 'snowstorm appearance' on ultrasound corresponds to pathological sections of lymphocyte infiltration, fibrosis and formation of psammoma bodies.[17] A comparative analysis of the ultrasound

images and pathological sections for case 2 found no areas of massive fibrosis or infiltration of large numbers of lymphocytes other than widely scattered calcifications. The calcifications were formed by psammoma bodies and condensation of follicular colloid. This current case 2 was diagnosed with follicular papillary carcinoma and the metastatic lymph node was also follicular papillary carcinoma. When the 'snowstorm appearance' is observed on ultrasound, physicians need to be highly vigilant and look at the situation in the surrounding lymph nodes so as not to misdiagnose it as Hashimoto's thyroiditis.

The third case in this series was another example of a thyroid cancer with the 'snowstorm appearance' that was not DSVPTC, but a multifocal papillary carcinoma. This 54-year-old female patient presented with Hashimoto's thyroiditis, in which the right thyroid gland was diffusely enlarged with uneven internal echo and scattered hyperechogenicity. The lymph nodes around the thyroid gland also showed abnormal enlargement. Gross examination showed that there were different sizes of grey-white nodules in the bilateral thyroid glands. Microscopic examination showed that different sized thyroid papillary cancers were distributed in the bilateral thyroid glands, ranging from 0.05 cm to 0.8 cm in size. The tumour showed papillary growth and was multi-branched with fibrosis; and the nuclei had the typical nuclear characteristics of papillary carcinoma (large nucleus, crowded, irregular karyotype, ground-glass chromatin, cytoplasmic inclusions and grooved nuclei). Hashimoto's thyroiditis was seen in the surrounding area. After examining multiple sections, calcification was found in the stroma or follicle of each section. Based on these microscopic observations, the 'snowstorm appearance' observed on ultrasound was actually calcification.

Another thing to be aware of is that thyroid cancer, which is characterized by the 'snowstorm appearance' on ultrasound, often has a large number of metastatic foci in the surrounding lymph nodes, even if it is atypical. Ultrasound is still an effective tool for diagnosing thyroid nodules even though it has a relatively low accuracy in differentiating malignant from benign nodules.[17] Elastography, which has emerged as a potential diagnostic method for thyroid nodules, can distinguish malignant from benign nodules based on the elasticity or stiffness of the tissue.[17] The rationale behind elastography is as follows: (i) tissue compression produces strain (displacement) within the tissue; (ii) and this strain is lower in harder tissues than in softer tissues.[17] Therefore, by measuring tissue strain caused by compression, tissue stiffness can be estimated.[17] Since malignant thyroid tissue is generally harder than normal surrounding tissue, tissue hardness observed in elastography provides more precise clinical information than manual palpation does.[18] Ultrasound, X-ray or ultrasonic elastography can be used to avoid misdiagnosis.[1,18] These patients need radical surgical treatment plus postoperative adjuvant treatment and regular examination.

The three cases presented in this current report demonstrate that the 'snowstorm appearance' on ultrasound does not always translate into a diagnosis of DSVPTC under the microscope. The 'snowstorm appearance' is more a result of a diffuse growth pattern of the tumour and microcalcification. However, previous research has shown that microcalcification is an independent risk factor of cervical lymph node metastasis in papillary thyroid carcinoma.[12] Prophylactic central lymph node dissection should be performed in patients with risk factors such as ultrasound features of microcalcification.[19] This indicates that more aggressive treatment should

be considered in patients showing the 'snowstorm appearance' on ultrasound regardless of whether or not the final pathological diagnosis is DSVPTC. Interestingly, a previous study showed that isthmus topography of malignant nodules is a risk factor for metastatic disease regardless of *BRAF* status.[20] This suggests that when thyroid isthmus lesions occur then aggressive treatment should be recommended.

Declaration of conflicting interest

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