Solid variant of papillary thyroid carcinoma: an under-recognized entity

Ryuji Ohashi

Abstract. Solid variant of papillary thyroid carcinoma (SVPTC) is a rare morphological variant of papillary thyroid carcinoma (PTC). SVPTC is histologically characterized by predominant solid, trabecular and insular nests of tumor cells while cytological features of PTC such as nuclear grooves and nuclear inclusions are preserved. In fine needle aspiration cytology smears, tumor cells of SVPTC may be presented in cohesive, syncytial or trabecular clusters accompanied by some discohesiveness in the absence of necrosis. Although SVPTC and poorly differentiated thyroid carcinoma (PDTC) share similar histological findings of solid nests, SVPTC can be differentiated from PDTC in the lack of tumor necrosis, severe nuclear atypia, and a higher mitotic index. Immunohistochemical expression of CK19 and HBME-1, common markers of PTC, is decreased in solid nests of SVPTC. In pediatric patients exposed to radiation after the Chernobyl nuclear accident, there was a higher prevalence of SVPTC with RET/PTC3 type rearrangement. BRAF mutations are also reported in a small number of adult patients with SVPTC without any prior radiation exposure. Patients with SVPTC may have a slightly higher incidence of metastasis and recurrence of the tumor compared to conventional PTC, although overall survival rate is comparable. In this article, the current knowledge of SVPTC will be reviewed and discussed with an emphasis on the histopathological feature.

Key words: Thyroid, Papillary carcinoma, Solid variant

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of tumor in the thyroid, accounting for approximately 80% of all thyroid malignant neoplasms. There are several histological variants in PTC without a typical papillary architecture while retaining cytological features of PTC such as nuclear grooves and nuclear inclusions [1]. The most common subtype is follicular variant characterized by predominant follicular architecture. Other variants include solid (insular, trabecular), diffuse seclerosing, encapsulated, oncycic, tall cell, columnar cell and Warthin-like, and cribriform-morular variants [1-3]. Despite its histological differences, these variants have a similar biological behavior although some variants, such as columnar cell variant, may be associated with a less favorable prognosis [4].

Solid variant of PTC (SVPTC) is a rare variant of PTC, accounting for 1–3% of all the subtypes of PTC [2, 5]. SVPTC is characterized by solid, insular or trabecular components, in which tumor cells form hypercellular nests retaining cytological features of PTC. SVPTC was initially introduced by Carcangiu et al. in 1985 who showed that PTC patients with solid components had a higher rate of lung and lymph node metastasis compared to PTC without solid components [6]. Before then, the presence of solid component in PTC was described in the literature from 70s although it was not regarded as a distinct entity [7, 8]. SVPTC gained universal recognition as a PTC variant when Nikiforov et al. in 1985 who showed that PTC patients with solid components had a higher rate of lung and lymph node metastasis compared to PTC without solid components [6]. Before then, the presence of solid component in PTC was described in the literature from 70s although it was not regarded as a distinct entity [7, 8]. SVPTC gained universal recognition as a PTC variant when Nikiforov et al. demonstrated a higher incidence of SVPTC among children and young adult patients exposed to radiation after the Chernobyl nuclear accident, in which up to 34% of all PTC had a predominantly solid growth pattern [5, 9]. After 2005, the occurrence of SVPTC was sporadically reported in adult patients without prior radiation exposure, thus indicating that SVPTC can also affect patients at any age [10, 11]. In this article, the current knowledge of SVPTC will be reviewed and discussed based on recent publications including our own with an emphasis on the histopathological feature.
Histopathology

The tumor of SVPTC is macroscopically described as a well-circumscribed white-tan nodule in the thyroid gland (Fig. 1A, B). There is generally no necrosis or hemorrhage, and no lobe predilection. In order to render the histological diagnosis of SVPTC, identification of a solid, trabecular, or insular component is the first clue in addition to confirmation of preserved nuclear features of PTC (Fig. 1C–E). However, there is controversy over these diagnostic criteria because of the inconsistency in the proportion of solid component within the PTC tumor among previous reports. For instance, Carcangiu et al. initially enrolled PTC cases with solid component >50% of the tumor as SVPTC [6]. In contrast, Nikiforov et al. defined SVPTC as the cases having a solid, trabecular, or insular growth pattern in >70% of the primary tumor nodule [5]. The latest version of WHO classification states that the term “solid variant” should only be used when all or nearly all of a tumor not belonging to any of the other PTC variants has a solid, trabecular, or insular appearance although they do not provide any cut-off value in the proportion (%) of solid components in the tumor [1].

To solve this issue, we conducted a study to assess the clinical significance of solid components in PTC [12]. We retrospectively investigated patients with PTC containing various degree (10 to 85%) of solid components from our archives and divided them into major (solid components >50%) and minor (solid components <49%) groups. The clinicopathological profiles were compared to CPTC without any solid nests. Both major and minor groups exhibited increased incidence of a large-sized tumor, extra-capsular extension, and a high recurrence rate, compared to CPTC. Disease-free survival (DFS) of both groups was significantly shorter than that of CPTC although overall survival was similar among all the groups. Our findings suggest that the presence of solid components in PTC, regardless of the proportion, is related to a shorter DFS.

Another confounding factor for the histological diagnosis of SVPTC is assessment of nuclear features characteristic of PTC. The nuclear features may somewhat vary depending on each PTC tumor, and in fact not all the PTC cases have all the typical features including nuclear overlapping, grooves, pseudo-inclusions, and glassy nuclei. To overcome this issue, Nikiforov et al. proposed a new nuclear scoring system (0 to 3) for the diagnosis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features [13]. They defined that the tumor with score >2 should qualify for PTC. We believe that the similar scoring system should be useful to define the histological diagnosis of SVPTC.

One major differential diagnosis of SVPTC is poorly differentiated thyroid carcinoma (PDTC), which is also characterized by solid, trabecular, or insular component in the tumor [14]. PDTC is distinct from SVPTC in that it lacks cytological features of PTC such as nuclear grooves, ground-glass nuclei, and pseudo-nuclear inclusions, but has tumor necrosis and increased mitotic activity, both of which are absent in SVPTC. Distinction of PDTC is important because clinical outcomes of PDTC patients are significantly worse than those of SVPTC (to be discussed later).

Cytological Features

Fine needle aspiration (FNA) is a first line diagnostic tool in the assessment of thyroid nodules to design clinical and surgical management [15]. With regards to FNA cytology of SVPTC, the number of reports in the English literature is still limited [16-18]. These reports along with our observation collectively show that cohesive syncytial fragments, a trabecular pattern, accompanied by some discohesiveness, in a clean background without necrotic debris are characteristic of SVPTC (Fig. 1F) [19]. A study by Guleria et al. found that the presence of solid fragments and lack of true papillae are helpful in differentiating SVPTC from CPTC [20]. We recently compared FNA cytological features of SVPTC to those of CPTC [21]. We found cohesive solid or trabecular nests, overlapping, enlarged nuclei, pleomorphism, and distinct nucleolus in SVPTC more often than in CPTC, while classical cytological features of PTC, such as nuclear grooves and/or pseudo-nuclear inclusions, were preserved. We further exhibited that the presence of either solid nests or trabecular patterns, and cellular overlapping in FNA smears of SVPTC was associated with a higher recurrence rate of the tumor [21].

Although PDTC and SVPTC share histological findings of solid, trabecular or insular patterns, the presence of tumor necrosis, severe nuclear atypia and increased mitotic nuclei is observed only in PDTC [22-24]. In FNA cytology of PDTC, classical nuclear features of PTC such as nuclear grooves and pseudo-inclusions are usually absent in contrast to SVPTC. These findings indicate that when mild to moderate degree of nuclear atypia and classical nuclear features of PTC are both identified in FNA samples, SVPTC should be considered one of the
differential diagnoses. Another differential diagnosis includes a follicular variant of PTC (FVPTC). FNA smears of SVPTC can sometimes show microfollicular patterns [21]. However, the microfollicular pattern in SVPTC can be accompanied by aniso-nucleosis and prominent overlapping, both of which are not typical for FVPTC [25]. Moreover, cell clusters of FVPTC tend to be flat, whereas those of SVPTC are more likely to be 3-dimensional. Taken together, SVPTC should be postulated as a differential diagnosis rather than FVPTC when 3-dimensional microfollicular clusters with aniso-nucleosis and overlapping are found in FNA smears of the thyroid nodule.
Immunohistochemical Profiles

In thyroid neoplasms, histological detection of malignancy can be sometimes challenging because of similar morphological features shared by benign and malignant lesions. Previous studies showed that immunohistochemical analysis using a variety of antibodies is useful in the diagnosis of thyroid tumors (Table 1). The common markers for PTC include thyroid transcription factor (TTF)-1, thyroglobulin and PAX8, which help distinguish CPTC from normal thyroid follicular cells [26-28]. Cytokeratin-19 (CK19), Hector Battifora mesothelial cell-1 (HBME-1) and galectin-3 are also frequently used in the diagnosis of PTC [29-33]. In PDTC and anaplastic thyroid cancer (ATC), expression levels of CK19 and HBME-1 may be altered or weakened whereas cyclin D1 expression is upregulated, compared to CPTC [34-40]. Kakudo et al. reported that Ki67 labeling index >10% can be a predictor of aggressive thyroid tumors including PDTC [41]. We recently demonstrated that expression levels of both CK19 and HBME1 were lower in solid nests than in papillary components within the tumor of SVPTC [42]. We further found that SVPTC cases with lower expression of CK19 and HBME1 was more likely to have a tumor recurrence after surgery. Our results are similar to the findings in previous reports that show the absence of CK19 and HBME1 in PDTC and ATC [38, 40]. Other immunohistochemical profiles of SVPTC tend to be in an intermediate range between CPTC and PDTC according to our observation (Table 1) (unpublished data). For instance, cyclin D1 and Ki67 nuclear positivity of SVPTC are likely to be higher than those of CPTC but below those of PDTC (Fig. 1G, H). As our findings are based on the limited number of patients, a study enrolling a number of SVPTC cases in correlation with clinical outcomes is necessary to determine the immunohistochemical profile of SVPTC.

Cancer stem cells (CSCs) are tumor cells possessing stem cell features of self-renewal, infinite proliferation, and potential of multi-directional differentiation [43, 44]. Although the CSCs comprise a small population of cancer, they are highly associated with tumor progression, metastasis, drug resistance and recurrence after initial therapy [45]. CSCs recently have attracted great attention in assessment and treatment of cancers in various organs owing to their self-renewal, infinite proliferation, and tumorigenic potential of multi-directional differentiation [43, 44]. Molecular Alterations

Approximately 70% of PTC possess exclusive genetic mutations including RET/PTC rearrangements, and mutations in the BRAF and RAS genes, most of which are capable of activating mitogen-activated protein kinase pathway, leading to distinct gene expression profiles and phenotypes [51, 52]. In pediatric patients who developed PTC following exposure to radiation after the Chernobyl nuclear accident, there was a higher prevalence of RET/PTC rearrangements. Among those patients, the RET/PTC3 type rearrangement was more frequent in SVPTC whereas the RET/PTC1 type occurred predominantly in CPTC [9, 53]. In contrast, a later study found a similar type of RET/PTC rearrangements in both SVPTC and CPTC in patients without any history of radiation exposure [5].

Despite controversy, the presence of BRAF mutations in the thyroid cancer is associated with aggressive behavior, such extra-capsular extension, metastasis, tumor recurrence, and a higher rate of mortality [54-56]. BRAF mutation can be found in the majority of tall cell variant PTC (77%) and CPTC (60%), with the lowest prevalence in follicular variant [57]. In addition to the V600E,
which is the most common type of all BRAF mutations, several rare types have been reported in the thyroid cancer. BRAF triplet deletion of the TGA nucleotides 1799 to 1801 (1799–1801del) was described in a case of SVPTC [10]. Another study found a complex BRAF mutation in a single case of SVPTC [11]. This mutation involves one nucleotide substitution, C1796T, and a CTT triplet insertion, 1798_1799insCTT, located on the same allele, leading to the replacement of a threonine with an isoleucine, T599I, and replacement of a valine with an alanine and a leucine, V600delinsAL. RAS mutations commonly occur in thyroid cancers, namely follicular thyroid carcinoma [58]. With regards to CPTC, RAS mutations also occur in a small population, but its clinical implication remains under debate [59]. To our knowledge, no studies have identified RAS mutations in SVPTC. The further molecular testing is required to reveal the whole genetic background of SVPTC.

Clinical Outcomes

The number of reports on prognosis of patients with SVPTC is small, thus leaving the clinical implication of this histological subtype undetermined. Previous studies exhibited patients with SVPTC had a slightly higher incidence of metastases compared to patients with CPTC [5, 6, 60]. Another study showed that patients with SVPTC were at a significantly higher risk of relapse compared to other subtypes [61]. A recent meta-analysis enrolling 11 previous studies with a total of 205 SVPTC cases revealed that SVPTC has a significantly higher risk for vascular invasion, tumor recurrence, and cancer mortality as compared to CPTC [62]. Despite these reports, it is difficult to strictly determine the prognosis of SVPTC because of the following reasons 1) ambiguous histological diagnostic criteria and 2) the lack of information on the genetic background. A multi-central study involving a great number of cases under the standardized diagnostic criteria is needed to reveal clinicopathological profiles of SVPTC.

Currently, there is no standardized treatment for SVPTC. Because of the higher incidence of recurrence after surgery, a more aggressive approach including a total thyroidectomy accompanied by lymph node dissection may be required when SVPTC is pre-operatively suspected. Radioiodine treatment may also be effective for a subset of SVPTC patients. A prospective study employing a large cohort under the definitive diagnosis of SVPTC is required to design the therapy regimen in the future. Molecular targeted therapy has emerged as one of the therapeutic options to treat a variety of cancers. For locally advanced or metastatic thyroid cancers, the effectiveness of thyrosine kinase inhibitors such as sorafenib and lenvatinib has been reported [63-65]. The efficacy of these new drugs should also be tested for SVPTC patients who are resistant to other conventional therapies.

Summary

Although SVPTC may not be as an aggressive tumor as PDTC or ATC, the accurate diagnosis is important because of a higher risk of metastasis and recurrence, that would affect patients’ life. Although SVPTC is now established as a separate entity in the current WHO classification, the exact disease concept has not been universally accepted due to its ambiguous diagnostic criteria and uncertain clinical outcomes as we addressed in this article. To overcome this, a further analysis of more SVPTC cases is necessary in conjunction with clinical outcomes. Molecular alterations of SVPTC should be fully revealed by using molecular pathology techniques in the advent of personalized medicine, in which molecular target therapy becomes available for each individual.

Disclosure

I declare that there is no conflict of interests.

References


