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Diffuse sclerosing variant of papillary thyroid carcinoma—an update of its clinicopathological features and molecular biology

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Contents

1. Introduction . . . 65
2. Methods . . . 65
3. Epidemiology . . . 65
4. Clinical features . . . 66
5. Macroscopic features . . . 66
6. Microscopic features . . . 67
7. Pre-operative diagnosis . . . 67
8. Metastases . . . 68
9. Clinical management . . . 68
10. Prognosis . . . 68
11. Expression of common immunohistochemical markers . . . 68
    11.1. Common immunohistochemical markers . . . 68
    11.2. Cell adhesion molecules . . . 69
    11.3. p53 and p63 . . . 69
12. *RET/PTC* rearrangement . . . 69
13. *BRAF* mutation . . . 69
14. Conclusion . . . 70
    Conflict of interest statements . . . 70
    Role of the funding source . . . 70
    Reviewers: . . . 70
    References . . . 70
    Biographies . . . 72

Abstract

Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is an uncommon variant of papillary thyroid carcinoma. The aim of this review is to critically analyse the features of this entity. A search of the literature revealed 25 clinicopathological studies with in-depth analysis of features of DSVPTC. Overall, the prevalence of DSVPTC varies from 0.7–6.6% of all papillary thyroid carcinoma. Higher prevalence of DSVPTC was noted in paediatric patients and in patients affected by irradiation. DSVPTC tends to occur more frequently in women and in patients in the third decade of life. Macroscopically, DSVPTC can involve the thyroid gland extensively without forming a dominant mass. Microscopic examination of DSVPTC revealed extensive fibrosis, squamous metaplasia and numerous psammoma bodies. The latter pathological feature can aid in the pre-operative diagnosis of the entity by fine needle aspiration and ultrasound. Compared to conventional papillary thyroid carcinoma, DSVPTC had a higher incidence of lymph node metastases at presentation. Distant metastases were noted in approximately 5% of the cases. Patients with DSVPTC were recommended to be managed by aggressive

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treatment protocols. It is likely that as a result of this, the prognosis of the patients with DSVPTC was noted to be similar to conventional papillary thyroid carcinoma. Overall, cancer recurrence and cancer related mortality have been reported in 14% and 3%, respectively, of patients with DSVPTC. In immunohistochemical studies, DSVPTC showed different expression patterns of epithelial membrane antigen, galectin 3, cell adhesion molecules, p53 and p63 when compared to conventional papillary thyroid carcinoma. On genetic analysis, the occurrence of *BRAF* and *RAS* mutations are uncommon events in DSVPTC and activation of *RET/PTC* rearrangements are common. To conclude, DSVPTC has different clinical, pathological and molecular profiles when compared to conventional papillary thyroid carcinoma.

Keywords: Diffuse sclerosing variant; Thyroid; Papillary carcinoma; BRAF; Molecular biology; Review

1. Introduction

Papillary thyroid carcinoma accounts for approximately 75% of thyroid cancer [1]. The carcinoma comprises different histological variants of variable clinicopathological features and biological behaviour. Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is an uncommon variant of papillary thyroid carcinoma, characterized by diffuse involvement of one or both lobes of the thyroid gland. This lesion often presents as a diffuse enlargement of the thyroid gland without specific mass [2]. It was first described as a case report by Vickery and colleagues in 1985 [3]. DSVPTC has different clinical and pathological presentation when compared with other thyroid cancers. As DSVPTC is not common, however, detailed study on its clinicopathological features and molecular characteristics have not been undertaken. In this review, we update the currently available data on the clinical, pathological and molecular features of this disease.

2. Methods

All the English language literature that reported features of DSVPTC from PubMed and Google Scholar databases from 1980 to 2013 were analysed. Following this, those series with demographic and clinical data were input into a unified database and analysed using the statistical software, SPSS (statistical package for social science) version 22 (IBM, New York, USA). Only series with three or more cases were included in this analysis. Also, cases that had been presented in more than one study were counted only once to avoid duplication.

Overall, 25 studies with a total of 641 patients with DSVPTC met the criteria for critical analysis of the clinical pathological data (Table 1) [4–32]. Amongst these, the largest series of DSVPTC cases to date was reported in an epidemiological study by Kazaure and colleagues in which 261 cases over a period of 20 years were presented [29].

3. Epidemiology

The prevalence of DSVPTC varies from 0.7–6.6% of all papillary thyroid carcinomas [1,23,33,34]. In regions affected by increased radiation exposure, the prevalence of this entity is different from other regions. For instance, a study on 119 patients diagnosed with papillary thyroid carcinoma in Belarus (the area affected by the Chernobyl accident) showed that the prevalence of DSVPTC in young patients was 13% [35]. The high prevalence of DSVPTC in this study population is attributed to the high levels of radioactive iodine released from the Chernobyl reactor in 1986. In another study, 10% of the paediatric thyroid cancers that occurred following the Chernobyl nuclear accident in 1986 were DSVPTC [36]. Also, aside from the association with radiation, the prevalence of this entity is high in the paediatric population. Koo and colleagues in Korea reported that approximately half of papillary thyroid carcinoma diagnosed in patients less than 20 years old was DSVPTC [26].

DSVPTC tends to occur more frequently in women, similarly to conventional papillary thyroid carcinoma [18,33]. In an early review of literature by Sywak and colleagues, DSVPTC was found to occur more often in patients in their third decade and the male to female ratio was approximately 1–5 [33]. These figures were collected after reviewing 65 cases of DSVPTC reported up until 2001. However, a recent epidemiological study on 261 DSVPTC cases from the USA showed the cancer could occur in older patients with a mean age of presentation at 47 years old [29]. Also, other larger series have shown the mean age of presentation for DSVPTC was 40 years old [19,30]. Some cases of DSVPTC have also been reported in patients older than 60 years [18,22,23,30,37].

After pooling the data from the reported series in the literature, DSVPTC was most often seen in the third decade of life (Fig. 1). The mean age at presentation of patients with DSVPTC was 30 and the median age at presentation was 28. The range of ages at presentation of patients with DSVPTC was from 6 to 78 years. Of the 641 patients, 81% were females ($n = 520$) and 19% were males ($n = 121$). The female to male ratio was 4.3–1. There was no significant gender difference in age at presentation ($p > 0.05$). It is worth noting that the mean age of occurrence of papillary thyroid carcinoma was in the fifth decade of life (mean age = 45 years) [1]. Thus, DSVPTC is more often seen in a younger age group than conventional papillary thyroid carcinoma. However, they can also be seen in patients with advanced age.