

# Estrogen Receptor- and Progesterone Receptor-Positive Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma: A Case Report

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## Key Words

Diffuse sclerosing variant of papillary thyroid carcinoma · Estrogen receptor · Progesterone receptor · E-cadherin · S-100 · Immunohistochemistry

## Abstract

The diffuse sclerosing variant of papillary thyroid carcinoma (DSV-PTC) is a relatively rare tumor. We herein report the case of young woman with DSV-PTC who developed cervical lymph node recurrence 7 years after the initial surgery. A 15-year-old female patient with no medical or family history of thyroid tumors developed a thyroid neoplasm in the right lobe. Right thyroidectomy and regional lymphadenectomy were performed, and the tumor was diagnosed as DSV-PTC. She was followed up as an outpatient. Seven years after the surgery, cervical lymph node recurrence developed. On microscopic examination, the thyroid tumor showed a papillary growth pattern with numerous psammoma bodies and distinct fibrosis. Immunohistochemically, the tumor cells were estrogen receptor and progesterone receptor positive with reduced membranous expression of E-cadherin and were intermingled with S-100-positive dendritic/Langerhans cells. DSV-PTC is characterized by a strong tendency for invasion and metastasis. Thus, accurate diagnosis is clinically important, and a morphological and immunohistochemical understanding of DSV-PTC is necessary.

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## Introduction

The diffuse sclerosing variant of papillary thyroid carcinoma (DSV-PTC), first described by Vickery et al. in 1985 [1], is a histological variant of PTC. It is characterized by diffuse involvement of one or both thyroid lobules with prominent squamous metaplasia, numerous psammoma bodies, and dense sclerosis in intratumoral areas together with a background of lymphocytic infiltration [2]. Extensive lymphovascular invasion indicates frequent metastasis. Because of the early spread of DSV-PTC, a prompt clinical diagnosis and strict follow-up are demanded. DSV-PTC is a major subtype of PTC in young patients [3], with a higher female predominance (male:female ratio, 1:7.5) [2]. However, the frequency of DSV-PTC is 0.3–5.5% among PTC [4–6]. Furthermore, sex hormone receptors have not been examined in DSV-PTC. We herein report a 15-year-old female patient with estrogen receptor (ER)- and progesterone receptor (PgR)-positive DSV-PTC with paratracheal lymph node metastasis in whom recurrence in the right cervical lymph nodes was diagnosed 7 years after the first operation.

## Case Report

### *Clinical Findings*

A 15-year-old female patient with no medical or family history of thyroid tumors consulted an otolaryngological clinic for evaluation of an anterior neck swelling. A thyroid neoplasm was suspected, and she was referred to Kansai Medical University Takii Hospital. Diffuse enlargement of the right thyroid gland with many small calcifications was detected by ultrasonography (fig. 1). Right thyroidectomy and bilateral paratracheal lymph node dissection were subsequently performed. Her postoperative course was uneventful. However, lymph node swelling of the right neck was detected 7 years after the operation and reexcision was performed. During the treatment course, her serum T3, T4, and TSH levels were within the reference ranges and autoantibodies were not detected.

### *Pathological Findings*

On macroscopic examination, the tumor, which had been located in the right lobe, was 22 mm along its major axis without formation of a dominant mass. It was sclerosing and rich in microcalcifications (fig. 2). On microscopic examination, the tumor showed a papillary growth pattern with distinct fibrosis, severe lymphocyte infiltration (fig. 3a), numerous psammoma bodies (fig. 3b), and squamous metaplasia (fig. 3c); all characteristics of DSV-PTC were frequently seen. In high-power fields, many of the tumor cell nuclei exhibited a ground-glass appearance, frequent grooves, and pseudoinclusions (fig. 3d). However, Hürthle (Askanazy) cells were not seen. Tumor invasion extended outside the capsule and reached the mesenchymal tissue, and lymph node metastasis was notable. The tumor cell nuclei were positive for ER and PgR (fig. 4a, b), and the cells were positive for epithelial membrane antigen, cytokeratin 7, thyroglobulin, E-cadherin, and  $\beta$ -catenin. Reduced membranous staining and increased cytoplasmic staining of E-cadherin were notable (fig. 4c). Squamous metaplastic cells were positive for p63 and 34 $\beta$ E12. In addition, dendritic/Langerhans cells were positive for S-100 protein (fig. 4d). However, the tumor cells were negative for cytokeratin 20, bcl-2, c-kit, Wilms' tumor antigen 1, CD56, chromogranin A, synaptophysin, and androgen receptor. The Ki-67 and p53 indices were both <1% (table 1). Right cervical lymph node metastasis was histologically proven.

## Discussion

DSV-PTC is a subtype of PTC and is characterized by diffuse enlargement of the thyroid gland and numerous scattered microcalcifications (a so-called 'snowstorm appearance') on ultrasonography [6]. Histologically, DSV-PTC is characterized by papillary growth of atypical cells, similar to conventional PTC [7] with prominent fibrosis, numerous psammoma bodies, frequent squamous metaplasia, and dense infiltration of lymphocytes [2, 3, 8, 9]. In addition, DSV-PTC shows a strong tendency for invasion and metastasis, and metastatic lesions have been frequently reported in lymph nodes, lungs, bones, and brain [10, 11]. The present case fits all of the above-mentioned criteria. Although lymph node metastasis was seen, multifocal tumor emboli in lymphatic channels at the primary site were unremarkable.

Immunohistochemical studies have been performed on DSV-PTC [12–19]. Immunohistochemically, p63 expression in foci of squamous metaplasia is the hallmark for distinguishing between DSV-PTC and conventional PTC [3, 12]. PTC cells are positive for thyroid transcription factor-1, thyroglobulin, and  $\beta$ -catenin [12, 18]. In addition, positive localization of E-cadherin is decreased in the cell membrane and relocation to the cytoplasm occurs [18]. E-cadherin plays a role in cell-cell adhesion. Therefore, it is easy to conclude that the decrement in the membrane level of E-cadherin may promote increased potency of invasion and/or metastasis of DSV-PTC. Because DSV-PTC is characterized by aggressive growth, it has been thought to be associated with a poor prognosis [1]. In contrast, although the recurrence-free survival rate of DSV-PTC is lower than that of non-DSV-PTC, there is no difference in the overall survival rate [3, 19–21]. The reason for the dissociation between the clinical course and survival should be further investigated. Dense accumulations of S-100 protein-positive dendritic/Langerhans cells, usually in areas of lymphocytic infiltration [2] and between tumor cells, correlate with a benign clinical course [13]. Thyroid cancer nuclei are sex hormone receptor positive [14–16], and ER and PgR expression is demonstrated mainly in differentiated thyroid cancer nuclei [14]. However, overexpression of ER and PgR in thyroid cancer suggests their role in carcinogenesis [15]. In small T1-differentiated thyroid cancer, ER positivity and androgen receptor expression are associated with a more aggressive phenotype [16]. Because the present case was ER and PgR positive and androgen receptor negative with accumulation of S-100 protein-positive dendritic/Langerhans cells, a prognostic prediction based on these markers was complex. More reliable markers, which are necessary in order to determine prognosis, must be investigated. In the present case, although the MACIS (metastases, age, completeness of resection, invasion, size) score [22] was 7.85 (table 2), the 20-year survival rate after surgery was estimated as 56%. Strict follow-up is desired in such cases.

In the present tumor, strong infiltration of lymphocytes with a germinal center [7] was seen in the nontumorous thyroid gland. Although approximately 30% of patients with DSV-PTC have positive antithyroid antibodies as part of Hashimoto's thyroiditis [2], autoimmune antibodies were not detected in the present case. Interestingly, Hürthle cells are reportedly absent in DSV-PTC, including in the present case [2, 12]. The cause of lymphocyte infiltration requires further investigation. Taken together, diagnosis of DSV-PTC seems to be possible using ultrasonography and histological investigation.

In conclusion, we herein reported a case of ER- and PgR-positive DSV-PTC. DSV-PTC shows a strong tendency for invasion and metastasis. Although survival remains unpredictable, further studies are necessary to identify good markers with which to predict the prognosis of DSV-PTC. This paper is the first to report ER- and PgR-positive DSV-PTC.

## Disclosure Statement

The authors declare no potential conflicts of interests with respect to the authorship and/or publication of this article.

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**Table 1.** Immunohistochemical results

Antibody	Source	Clone	Dilution	Result	
				papillary cell carcinoma	metastatic cells
Epithelial membrane antigen	DakoCytomation, Glostrup, Denmark	E29	1:100	cytoplasm	cytoplasm
Cytokeratin 7	Ventana Medical Systems, Tucson, Ariz., USA	SP52	prediluted	cytoplasm	cytoplasm
Cytokeratin 20	Ventana Medical Systems	SP33	prediluted	–	–
Thyroglobulin	DakoCytomation	polyclonal	prediluted	cytoplasm	cytoplasm
E-cadherin	Takara Bio Inc., Otsu, Japan	HECD-1	1:100	cytoplasm	cytoplasm
β-catenin	Becton Dickinson, N.J., USA	14	1:500	membrane	membrane (partially)
c-kit	Nichirei Biosciences, Tokyo, Japan	polyclonal	prediluted	–	–
p63	Nichirei Biosciences	4A4	prediluted	nucleus (partially)	partially
Bcl-2	SIGNET, Calif., USA	124	prediluted	–	–
Wilms' tumor antigen 1	Novocastra, Newcastle upon Tyne, UK	6F-H2	prediluted	–	–
CD56	Nichirei Biosciences	1B6	prediluted	–	–
Chromogranin A	Diagnostic BioSystems, Calif., USA	LK2H10	prediluted	–	–
Synaptophysin	DakoCytomation	SY38	1:20	–	–
S-100 protein	Nichirei Biosciences	polyclonal	prediluted	–	–
ER	Nichirei Biosciences	SP1	prediluted	nucleus	–
PgR	Nichirei Biosciences	A9621A	prediluted	nucleus	–
Androgen receptor	Novocastra	AR27	1:50	–	–
Ki-67 index	DakoCytomation	MIB1	prediluted	<1%	<1%
p53	Novocastra	Do-7	1:50	<1%	<1%

**Table 2.** MACIS score

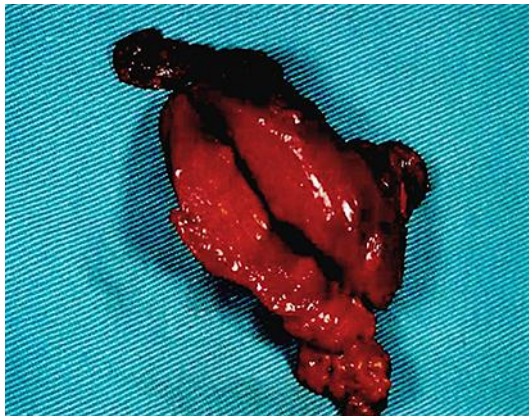
- 1 +3.1 (if age <40 years) or 0.08 × age (if age ≥40 years)
- 2 +0.3 × tumor size (cm, maximum diameter)
- 3 +1 if not completely resected
- 4 +1 if locally invasive
- 5 +3 if spread distantly

Survival score is 1 + 2 + 3 + 4 + 5 (20 years after surgery):

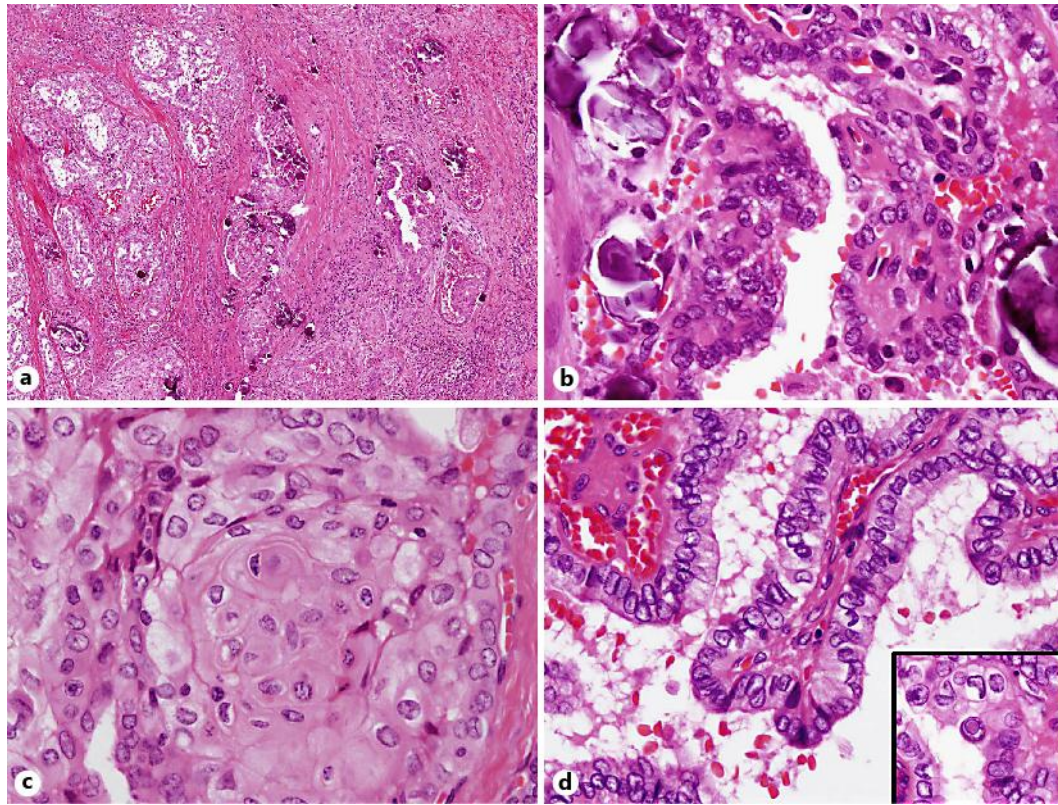
- <6 = 99%
- 6–6.99 = 89%
- 7–7.99 = 56%
- ≥8 = 24%



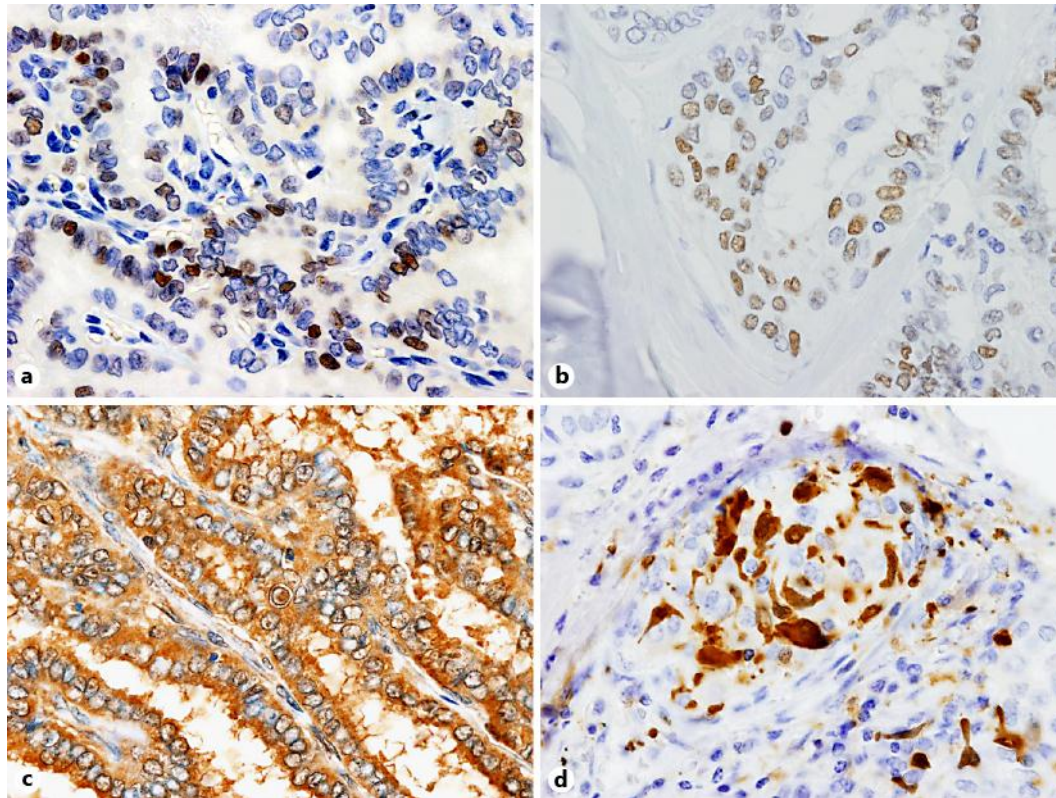
**Fig. 1.** Ultrasonographic findings. Right thyroid lobe enlargement and numerous microcalcifications can be seen.



**Fig. 2.** Cut surface of the right thyroid lobe. An indistinct diffuse lesion with microcalcifications can be seen.



**Fig. 3.** DSV-PTC. **a** Growing papillary tumor with remarkable fibrosis and lymphocytic infiltration can be seen. HE. ×100. **b** Note the numerous psammoma bodies. HE. ×400. **c** Scattered foci of squamous metaplasia can be seen. HE. ×400. **d** Characteristic nuclear features of PTC. Nuclear grooves and intracytoplasmic inclusion body (**inset**) can be seen. HE. ×400.



**Fig. 4.** Tumor cells are positive for ER (a), PgR in the nucleus (b), and E-cadherin in the cytoplasm (c). d Dendritic/Langerhans cells are positive for S-100 protein. Immunohistostaining.  $\times 400$ .