

NOTE

## A Case of Black Thyroid Associated with Hyalinizing Trabecular Tumor

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**Abstract.** Black thyroid is an uncommon phenomenon of black pigmentation of thyroid parenchyma induced by chronic minocycline therapy. Thyroid tumors associated with black pigmented thyroid are rare. We describe here a 42-year-old woman with a black thyroid associated with hyalinizing trabecular tumor (HTT). The patient presented with a palpable left-sided thyroid nodule. She had taken minocycline for aphthous stomatitis and an oral ulcer for 9 years. The findings of fine needle aspiration biopsy and BRAF mutation analysis suggested a papillary carcinoma. The patient underwent a near-total thyroidectomy with central compartment node dissection. The surgical specimen showed a diffuse black thyroid and a 2-cm non-pigmented, well-circumscribed nodule in the left thyroid. Histopathologically, numerous black pigmented follicular epithelial cells and colloid were seen throughout the thyroid parenchyma, and the nodule was composed of elongated, polygonal cells in trabecular arrangement and dense hyaline stromas. The tumor cells showed a strong positive cytoplasmic reaction to Ki 67. All of these findings suggested a HTT, or a hyalinizing trabecular variant of papillary carcinoma, arising in a black thyroid. To our knowledge, this is the first case of black thyroid associated with HTT.

*Key words:* Black thyroid, Hyalinizing trabecular tumor, Minocycline

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**BLACK** thyroid, or black pigmentation of the thyroid, was first described in humans in 1976 [1]; to date only 64 cases have been reported in the English language literature [3–14]. The black discoloration usually develops after taking minocycline, a tetracycline derivative, for several years. Thyroid tumors associated with black thyroid are extremely rare, but may include adenomatous hyperplasias, adenomas, and papillary and follicular cancers [3–14]. To our knowledge, however, hyalinizing trabecular tumor (HTT) arising in black thyroid has not previously been reported.

### Case

A 47-year-old woman presented with a 5-year history of a solitary thyroid nodule. She had a history of taking minocycline intermittently over 9 years for aphthous stomatitis and oral ulcer of Behcet's disease. On examination, a mild black discoloration of the teeth and gums was identified (Fig. 1), in addition to the palpable nodule. Neck ultrasound disclosed a well-circumscribed hypoechoic nodule, measuring 2.0-cm diameter, in the left thyroid. Fine needle aspiration biopsy (FNAB) revealed a few clusters of follicular cells with nuclear clearing, grooves, and pseudo-inclusions; and a BRAF mutation (V600E) was detected by the dual-priming oligonucleotide (DPO) primer method. These findings were suspicious for papillary thyroid carcinoma. A near-total thyroidectomy with central compartment node dissection was performed, and intraoperative frozen section of the nodule suggested the

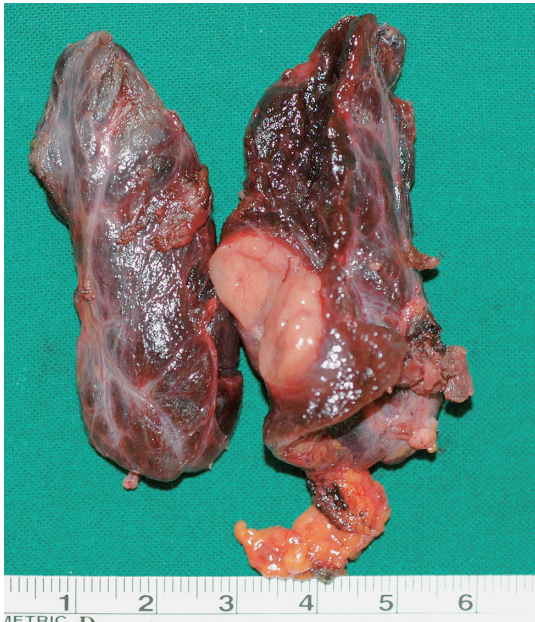
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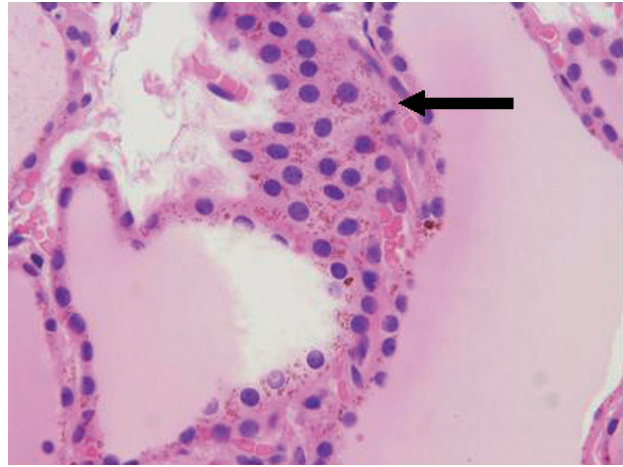


**Fig. 1.** Photograph of the patient showing black pigmented teeth and gingivae.



**Fig. 2.** View of the thyroid. The bilateral thyroids are homogeneous dark black areas. There was a 2 × 1.5-cm, pinkish white, relatively well-defined but not encapsulated solid mass in the left thyroid.

possibility of a hyalinizing trabecular tumor; however, it was unclear whether this tumor was benign or malignant. The surgical specimen was characterized by diffuse black discoloration and a non-pigmented thyroid nodule (Fig. 2). Histologically, numerous dark brown to black pigments were seen in the cytoplasm of the follicular epithelium and the colloid throughout the thyroid parenchyma, except for the nodule (Fig. 3). Microscopic evaluation of the nodule revealed elongated, irregular, polygonal cells arranged in a trabecular pattern, as well as hyaline stromas, intra and

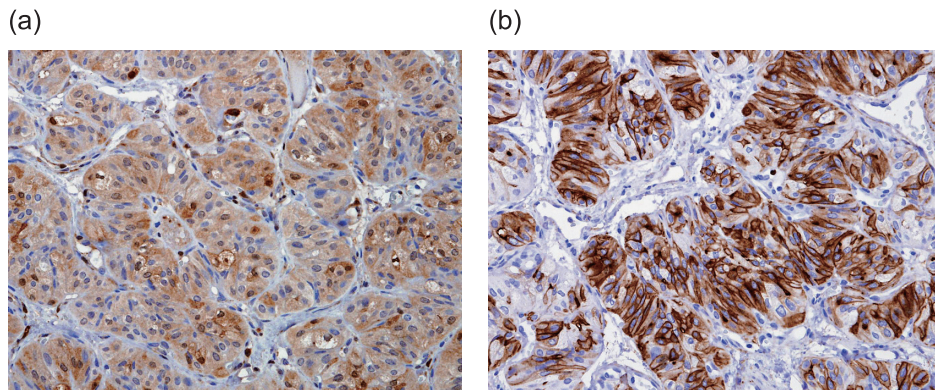


**Fig. 3.** Histopathologic examination of the lesion. The peritumoral thyroid follicular cells contained granular cytoplasmic brown pigmentation (hematoxylin and eosin stain ×400).

peri-trabecular areas, and follicular cells with nuclear clearing, grooves, and pseudoinclusions. The central compartment nodes were negative for metastases. The tumor cells showed cytoplasmic immunoreactivity for galectin-3 and membranous immunoreactivity for Ki67 (Fig. 4a, b). Based on the above findings, the tumor was thought to be HTT, or a hyalinizing trabecular variant of papillary carcinoma, occurring in a black thyroid.

## Discussion

Long-term use of minocycline can cause hyperpigmentation of several organs, including the nails, bones, skin, visceral tissue, oral mucosae, sclerae, and heart valves, as well as the thyroid gland [15]. Minocycline-induced hyperpigmentation of the thyroid gland, or black thyroid, has been considered a rare and harmless phenomenon [3–15], and has been differentiated from other causes of hyperpigmentation, such as hemorrhage, hemochromatosis, ochronosis, cystic fibrosis, and melanin-producing (pigmented)-type medullary thyroid carcinoma [2, 3]. The mechanism of minocycline-induced hyperpigmentation of the thyroid is unclear. Pigmentation may be caused by thyroid peroxidase oxidation of minocycline, and these pigments may accumulate in the lysosome and macrophages that are present in follicular cell cytoplasm [9,16]. Minocycline seems to act as a reversible competitive inhibitor



**Fig. 4.** The tumor cells showed cytoplasmic immunoreactivity for galectin-3 (4a) and membranous immunoreactivity for Ki 67 (4b).

of thyroglobulin for thyroid peroxidase [9]. The pigmentation mainly occurs in metabolically active normal thyroid epithelium and therefore cannot be seen in neoplastic tissue, as in our patient [7]. Psychotropic drugs, such as doxepin, lithium carbonate, and tricyclic antidepressants, can also cause hyperpigmentation of thyroid tissue owing to lysosomal accumulation of the drugs rather than an oxidation effect. Under these conditions, hyperpigmentation is observed in both normal and tumor cells [5].

Since the first report of minocycline-induced black thyroid 1976 [1], 64 additional cases have been reported in the literature [3–14]. Some reports have suggested that the incidence of thyroid cancer in black thyroids is relatively high [4–10], but it is unclear whether minocycline-associated hyperpigmentation of the thyroid is related to development of malignancy [11].

HTT is itself an uncommon thyroid disease and, to our knowledge, HTT arising in a black thyroid has not previously been reported. In 1987, Carney *et al.* described the results of pathologic examinations of a case series of 11 patients with thyroid tumor, which showed polygonal, oval, and spindle cells arranged in a trabecular pattern and separated by a dense, hyalinized stroma [17]. These lesions, termed hyalinizing trabecular adenomas (HTAs), may be misinterpreted as papillary carcinomas, medullary carcinomas, or paragangliomas owing to their unusual histologic features [17]. Initially, HTAs were considered benign, but there have been re-

ports of malignant HTAs showing capsular or vascular invasions, and the more general term of HTT has been proposed to include benign HTA and hyalinizing trabecular carcinomas [18, 19].

HTTs have also been regarded as variants of papillary carcinoma owing to their similar nuclear features, including hypercellularity, nuclear grooves, nuclear inclusions, psammoma bodies, and powdery chromatin, and their similar rates of RET/PTC rearrangement [20–23]. Generally, however, HTTs and papillary carcinomas show different patterns of expression of cytokeratin 19 (CK 19) and high-molecular-weight cytokeratin (HMWCK), and different types of HBME-1, galectin-3, and BRAF mutations [24–29]. HTTs usually show no staining for HMWCK, whereas papillary carcinomas are strongly positive [24, 26]. HTTs also show strong, positive cytoplasmic reaction for MIB-1 (Ki 67), whereas papillary carcinomas are negative [28]. Strongly positive MIB-1 staining is a characteristic finding of HTT [28].

In our patient, the histopathologic features of the tumor and the positive MIB-1 staining were indicative of HTT, whereas the nuclear features and the presence of a BRAF mutation, a finding specific for a papillary thyroid carcinoma, were indicative of the latter [30]. We therefore concluded that this tumor was an HTT, or a hyalinizing trabecular variant of papillary thyroid carcinoma, arising in a black thyroid.

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