Pathologic Quiz Case
Tumor in Pigmented Thyroid Gland in a Young Man
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An 18-year-old man presented with an asymptomatic, hard nodule of the right thyroid that was discovered during a routine fitness examination for a high school track team. Ultrasound examination revealed a 2-cm nodule involving the isthmus and lower pole of the right thyroid lobe that was suggestive of malignancy. The patient’s medical history was significant for minocycline therapy in the preceding few years for the treatment of acne. Results of thyroid function tests were within normal limits.

A total thyroidectomy was performed. On gross examination, both lobes of the thyroid gland had diffuse, uniformly dark pigmentation (Figure 1). The cut surfaces of the right lower lobe demonstrated a 1.4-cm-diameter, circumscribed, yellow-tan nodule encroaching on the isthmus (Figure 1). In stark contrast to the jet-black discoloration of the surrounding thyroid parenchyma, the nodule was uninvolved by the pigmentation (Figure 1). The right and left inferior parathyroid glands were biopsied during the thyroidectomy to facilitate surgical repositioning. No pigmentation was noted in the parathyroid tissue.

Microscopically, the thyroid parenchyma showed diffuse brown-black pigmentation of the follicular epithelial cells (Figure 2, arrow, and Figure 3). Few of the macrophages entrapped within the interstitium and colloid also had pigment (Figure 3). The pigment did not fluoresce and was not polarizable. Apart from scattered foci of hemosiderin within peritumoral macrophages and rare follicular epithelial cells, the bulk of the pigment was negative for iron (Prussian blue) stain (Figure 4, inset). The nodule showed a neoplasm with focal lymphovascular invasion. No pigmentation was identified within the neoplastic epithelium (Figure 2). A diffuse, mild, lymphocytic thyroiditis was present. The parathyroid parenchyma was unremarkable histologically and showed no pigmentation.

What is your diagnosis?
Pathologic Diagnosis: Papillary Thyroid Carcinoma in a Minocycline-Induced, Diffusely Pigmented Thyroid Gland

Drug-associated pigmentation due to minocycline therapy seems to be the reason for “black thyroid” in our patient, as there was no history of hemochromatosis, ochronosis, or cystic fibrosis to account for the discoloration. Minocycline use has been well documented as a source of thyroid pigmentation.\(^1,4\) To the best of our knowledge, 29 cases of black thyroid have been reported to date,\(^2,3,6\) 10 of which contained tumors. Four of the 5 papillary carcinomas reported were unpigmented, as in our case. The absence of discoloration of the adjoining papillary carcinoma has been explained in 2 ways. One possibility is that minocycline-associated pigmentation occurs only in the relatively normal, metabolically active thyroid epithelium and therefore is absent in the abnormal neoplastic tissue. The alternative explanation is that the reported tumors were unpigmented because they arose after cessation of the drug.\(^6\) The latter explanation does not hold true for our patient, however, since he was on continuous minocycline therapy up until his thyroidectomy.

Black discoloration of human thyroid in association with minocycline therapy was first reported in 1976.\(^7\) The pigment can be located within the thyroid follicular epithelium, macrophages, and even the colloid, as in the current case. The exact nature of the pigment, its mechanism of deposition, and potential clinical implications are controversial. Since the pigment can be bleached with potassium permanganate/oxalic acid and stained with Fontana-Masson,\(^4\) shared properties with melanin and lipofuscin have been suggested. However, many consider the pigment a novel product of minocycline oxidation by thyroid peroxidase that is potentially preventable with antioxidants.\(^6\) Minocycline appears to act as a reversible competitive inhibitor of thyroid peroxidase over thyroglobulin. This mechanism may also explain the absence of pigmentation in the adjacent, metabolically active parathyroid tissue. The pigment is thought to accumulate in lysosomes with associated disruption of lysosomal transport and function.\(^2\) Besides minocycline, psychotropic drugs like doxepin, lithium carbonate, and tricyclic antidepressants have been particularly reported in association with black thyroids, for which the mechanism is thought to be a lysosomal accumulation of the drugs\(^5\) rather than an oxidation effect.

It is unclear whether minocycline-associated pigmentation has any worrisome clinical significance. However, patients with a long history of minocycline use have presented with hypothyroidism, nodular hyperplasia, adenoma, and carcinoma.\(^5\) Both papillary\(^5,6\) and follicular carcinomas of the thyroid have been described in association with minocycline-associated black thyroid, with variable reports of pigment deposits within the tumor cells and nontumorous tissues. As yet, no carcinogenic role has been ascribed to minocycline. Experimental models have implied potential antithyroid effects for the drug, suggesting that patients on prolonged minocycline therapy should be monitored.\(^10\)

This rare case is being presented for its striking gross and microscopic appearances, which are unmistakable if the surgeon and the pathologist are familiar with their occurrence. The pigmentation appears to be unique for the drugs mentioned, and many experts believe that black thyroid is pathognomonic of minocycline use.\(^1,5\) Given the range of associated pathology documented, especially relatively large unpigmented tumors as in the current case, it raises a potential medicolegal issue: Do patients on long-term therapy with minocycline (or psychotropic drugs) need surveillance for thyroid-associated disease?

References