Thyroid disease and the skin

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Cutaneous manifestations of thyroid disease are protean in nature and can be divided into specific lesions such as the thyroglossal duct cyst and cutaneous metastases from thyroid malignancy, nonspecific signs secondary to thyroid hormone imbalance, and associated dermatologic and systemic disorders.

This review constitutes a summary and update of the cutaneous manifestations of thyroid disease, as previously reviewed by Heymann [1,2]. Details regarding the physiology of the thyroid may be found in Werner and Ingbar’s The thyroid: A fundamental and clinical text [3].

Specific thyroid lesions

Thyroglossal duct cysts

The thyroglossal duct cyst is the most common congenital cystic abnormality of the neck, accounting for 70% of such lesions. Though most present in the first decade of life, they may be encountered throughout adulthood. The majority (65%) are located inferior to the hyoid bone and the remaining are found either juxtahyoid or superior to the hyoid bone.

The thyroglossal duct originates from the endodermal thyroid anlage on the pharyngeal floor at the base of the tongue. Ectopic thyroid tissue may be present anywhere along the route of development and may extend from the larynx to the diaphragm [3]. When attachment to the base of the tongue persists, movement of the thyroglossal duct cyst may be seen with protrusion of the tongue. If retrosternal placement of the thyroid occurs in the setting of goiter development, the superior vena cava syndrome may ensue. Signs of caval compromise include vertical, palpable, dilated, and tortuous cutaneous vessels on the trunk, above the lower margin of the rib cage. Subsequent sequelae include development of facial edema, erythema, cyanosis, neck vein distension, proptosis, conjunctival injection, and swelling of the nasal mucosa [4,5]. Sinus tracts are present in 35% of cases and are secondary to the rupture of an infected cyst or a consequence of surgery [6].

Malignancies develop in less than 1% of thyroglossal duct cysts and are most commonly encountered in elderly women. Rapid growth often portends a worse prognosis [7]. The majority of carcinoma is comprised of papillary adenocarcinoma (75% to 85%) and is found during routine excision of thyroglossal duct cysts [8]. Other variants include mixed papillary and follicular carcinoma, squamous cell carcinoma, and anaplastic carcinoma. Squamous cell carcinoma derived from the thyroglossal duct has a better prognosis than the rare squamous cell carcinoma originating in the thyroid gland [9]. Cases of Hürthle cell carcinoma have also been reported [10]. Excision of the thyroglossal duct, cyst, and a portion of the hyoid bone (the Sistrunk procedure) is the treatment of choice for most of these lesions [7].

Before the removal of a thyroglossal duct cyst, ectopic thyroid tissue must be differentiated from cyst tissue because 75% of patients with an ectopic thyroid gland have no other functioning thyroid tissue present. The incidence of ectopic thyroid tissue has been reported to be as frequent as 1:4000 to 1:8000 in
patients with thyroid disease [11]. Radionuclide scans are recommended preoperatively for prevention of iatrogenic hypothyroidism from the removal of the thyroglossal duct cyst. Ultrasonography may be an acceptable alternative for preoperative evaluation, with the exclusion of patients who are either hypothyroid or do not demonstrate a normal thyroid gland on ultrasound.

**Cutaneous metastases from thyroid malignancies**

To date, fewer than 50 cases of cutaneous metastasis from primary thyroid cancer have been reported in the literature [12]. Lesions may present as solitary or multiple, flesh-colored, violaceous, or blue-colored papules or nodules. Cutaneous metastases are accompanied by thyromegaly or internal metastases in the majority of cases [13]. The scalp appears to be a favored site for follicular and papillary thyroid carcinoma metastases [12]. Virtually all histologic types of thyroid carcinoma have been reported with cutaneous metastases, including follicular, papillary, and mixed follicular-papillary. Immunohistochemical staining with markers for thyroglobulin and calcitonin is helpful in confirming thyroid origination.

Medullary carcinoma of the thyroid with metastases to the skin has been reported and may be associated with one of the autosomal dominant transmitted multiple endocrine neoplasia (MEN) syndromes. MEN-2a (Sipple syndrome) is comprised of medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma. MEN-2b (multiple mucosal neuroma syndrome) is comprised of medullary thyroid carcinoma, pheochromocytoma, mucosal ganglioneuroma, and a marfanoid habitus. MEN-2a is secondary to a missense mutation of the RET proto-oncogene in chromosome 10, which encodes for the transmembrane receptor tyrosine kinase, while MEN-2b is secondary to a mutation of the intracellular tyrosine kinase domain [1]. Penetrance of medullary carcinoma approaches 100% in these kindreds, and prophylactic thyroidectomy has been suggested [14]. Reports of notalgia paresthetica, macular amyloidosis, or biphasic amyloidosis have been reported in patients with MEN-2a kindreds. Within the families, 50% of patients presented with a pruritic eruption of the interscapular area; of these, all had medullary thyroid cancer [15].

Dermatologists should keep a high index of suspicion for dermal nodules or unusual lesions along the track of a fine needle aspiration of the thyroid gland. Cases have been reported of implantation of both papillary and follicular thyroid cancer along needle tracts [16].

**NonSpecific thyroid-related lesions**

A variety of cutaneous findings may present in the setting of either a hyperthyroid or hypothyroid state. Elucidation of the specific etiology depends on the assistance of history, physical examination, and laboratory confirmation.

**Cutaneous manifestations of hyperthyroidism**

A hyperthyroid state may arise as the result of numerous causes. Excessive thyroxine intake, thyroiditis (including Graves’ disease), a single toxic nodule, a toxic multinodular goiter, or less commonly, a thyrotropin-secreting pituitary adenoma, molar pregnancy, struma ovarii, or metastatic follicular cancer may all result in hyperthyroidism. The specific pathophysiology linking hyperthyroidism to classic cutaneous findings remains to be well explained.

Thyroid hormone appears to play a pivotal role in the growth and formation of hair and sebum production. Thyroid hormone stimulates epidermal oxygen consumption, protein synthesis, mitosis, and determination of epidermal thickness, while effects on the dermis are less well defined [17]. The epidermis is usually found to be thin but not atrophic. The skin in hyperthyroidism is warm, moist, and smooth, bearing a resemblance to infantile skin. Warmth can be attributed to increased cutaneous blood flow and peripheral vasodilatation, which may also lead to the commonly noticed facial flushing and palmar erythema seen in hyperthyroid patients. Generalized hyperhidrosis may be noted with a predilection for the palms and soles. Scalp hair is soft and fine and sometimes accompanied by diffuse, nonscarring alopecia. Approximately 5% of patients may present with nail findings. Characteristic, though not pathognomonic, is the “Plummer’s nail” with a concave contour and distal onycholysis. This finding may also be seen in hypothyroidism, psoriasis, after traumatic injury, or allergic contact dermatitis [17]. Hyperpigmentation may be seen in a distribution resembling that seen in Addison’s disease (creases of the palms and soles, gingiva, and buccal mucosa), and is particularly pronounced in darker skin types.

Scleromyxedema has been reported in the setting of hyperthyroidism. This rare entity is comprised of numerous firm, white, yellow, or pink papules scattered on the face, trunk, axillae, and extremities. It is commonly accompanied by weight loss, monoclonal gammopathy, esophageal dysmotility, vascular disease, Raynaud’s phenomenon, telangiectasia, decreased pulmonary diffusion capacity, neurologic manifestations, joint disease, and myopathy. Cuta-
neous lesions are the result of accumulation of acid mucopolysaccharides, mostly hyaluronic acid, in the dermis, accompanied by large fibrocytes [18]. The palms and soles are typically spared, though swelling of the fingers and calcinosis cutis may occur. Treatment of the hyperthyroid state with radioactive iodine does not improve cutaneous findings [19].

**Graves’ disease**

Graves’ disease is characterized by the aforementioned cutaneous findings of hyperthyroidism in addition to distinctive cutaneous features including pretibial myxedema (dermopathy; 0.5% to 4% of patients) and acropathy (1%). Pretibial myxedema is a misnomer because lesions may appear anywhere, including the preradial aspect of the arms, shoulders, thigh, head, and neck. Clinical presentation may vary from a “peau d’orange” appearance to the extensive infiltration resembling elephantiasis verrucosa nostra. Most often, lesions appear as bilateral, asymmetric, raised, firm plaques or nodules varying in color from pink to purple-brown and sometimes accompanied by woody induration. In rare cases, overlying hyperhidrosis or hypertrichosis may be present [20].

Graves’ dermopathy occurs less frequently than ophthalmopathy, and although it is usually seen with ocular pathology, it may occur alone. The vast majority of patients with dermopathy have Graves’ disease; however it has also been reported in the setting of Hashimoto’s thyroiditis [21]. The status of thyroid function is independent of dermopathy development, and lesions can occur in the setting of a hyperthyroid, hypothyroid, or euthyroid patient. Histologically, the process appears as an accumulation of hyaluronic acid in the dermis more so than in the subcutis. In clinically verrucous lesions, marked hyperkeratosis may also be seen.

The precise pathogenesis of pretibial myxedema remains to be defined. One leading theory is that pretibial fibroblasts are the target for antithyroid antibodies. After stimulation by thyroid autoantibodies, fibroblasts may produce excess glycosaminoglycans. In support of this theory, Chang et al. reported the presence of thyrotropin (TSH) and TSH receptor antibody binding in fibroblasts as well as the presence of RNA encoding the extracellular domain of the TSH receptor [19]. Other theories have implicated T cells as the primary effector of Graves’ dermopathy. T cells may interact with an autoantigen that is either identical or cross-reactive with a thyroid autoantigen in the dermis. In turn, this may induce secretion of cytokines such as glycosaminoglycan-stimulatory lymphokine, interleukin 1, tumor necrosis factor, and gamma interferon, which activate fibroblasts to secrete hyaluronic acid and chondroitin sulfate [22,23]. Anther theory suggests that Graves’ dermopathy is not exclusively caused by site-specific cell properties, but rather by the superimposition of local physical and anatomical factors (trauma and edema) within a subclinical, systemic, connective tissue inflammation. Therefore, the autoimmune state alone may not be enough to elicit the extrathyroidal manifestations of Graves’ disease [24].

Management of dermopathy continues to pose a challenge to physicians. Though there have been reports of successful local excision, overall success remains equivocal and surgery should probably be avoided. A 20-year study of 150 patients with pretibial myxedema demonstrated the value of using topical triamcinolone [25]. It would not be unreasonable to assume that newer ultrapotent steroid or intralesional steroids may show even greater benefit. Other therapies may include octreotide, intravenous immunoglobulin, and intravenous pulse steroids followed by oral steroids [1]. Ultrasonography may be a useful modality in measuring skin thickness and response to therapy or in detecting subclinical dermopathy [26].

Thyroid acropachy is a triad consisting of digital clubbing, soft tissue swelling of the hands and feet, and periosteal new bone formation. The first, second, and fifth metacarpals, the proximal phalanges of the hand, and the first metatarsal and proximal phalanges of the feet are most commonly affected. Pathognomonic radiographic osseous changes are comprised of periosteal reaction of a lamellar type paralleling the diaphyses and has been described as “feathery.” New bone spicules may be arranged perpendicularly to the long axis of the bone. Fewer than 100 cases have been reported, and the cause is unknown. When seen, it is usually accompanied by either exophthalmos and/or pretibial myxedema. Similarly to dermopathy, the majority of patients reported developed acropathy after the diagnosis and treatment of thyrotoxicosis [27]. Patients may be euthyroid or hypothyroid. The vast majority of cases are associated with Graves’ disease. Thyroid acropachy has also been reported to occur in Hashimoto’s thyroiditis and Hürthle cell adenocarcinoma [28,29]. A bone scan may be the most sensitive and objective diagnostic test because it reflects the linear increase in osteoblastic activity in the diaphyseal region of small bones [30].

Most cases of acropathy are asymptomatic and require no therapy. In rare cases, complete remission may occur with time. Therapeutic assessment is difficult because the natural history is variable. Excisional therapy, administration of hyaluronidase, and
local radiotherapy have yielded equivocal results [2]. Successful therapy with topical fluorinated steroids under occlusion has been reported [30].

**Hypothyroidism**

Hypothyroidism may result from either inadequate circulating levels of thyroid hormone or target cell resistance to hormonal action. Primary hypothyroidism as a result of glandular failure is the most common cause and most frequently results from autoimmune disease. Other potential causes of primary hypothyroidism include previous therapy with 1^31^, thyroid surgery, antithyroid medication, or infiltrative diseases. Secondary hypothyroidism is the result of pituitary dysfunction with resulting inadequate release of thyrotropin (TSH). Possible causes for secondary hypothyroidism include tumor, infarction, trauma, radiation, or surgical treatment of the pituitary gland. Secondary hypothyroidism is commonly accompanied by other pituitary-related endocrinopathies. Tertiary hypothyroidism caused by hypothalamic failure shares similar etiologies with secondary hypothyroidism; however, primary idiopathic hypothalamic hypothyroidism has been reported. In the rare event of isolated thyroid-releasing hormone (TRH) deficiency, other pituitary functions remain normal and the resulting hypothyroidism may be transient [31].

**Congenital hypothyroidism**

Congenital hypothyroidism (cretinism, congenital athyrosis) occurs when insufficient quantities of thyroid hormone are produced either in utero or during the early perinatal period from primary, secondary, or tertiary hypothyroidism. If unrecognized, a distinctive syndrome of dwarfism, cutaneous and systemic features of hypothyroidism, and mental retardation may occur. Myxedema is classically present with characteristic periorbital puffiness, thick lips, acral swelling, macroGLOSSIA, and/or a smooth, red tongue. Yellowing of the skin may be present secondary to carotenemia (from diminished hepatic conversion of β-carotene to vitamin A), prolonged physiologic jaundice, anemia, and myxedema. A pronounced clavicular fat pad may be present. Hypothermia is common secondary to a decreased metabolic rate with resultant reflexive peripheral vasoconstriction and cool, dry, pale skin. Cutis marmorata may be accentuated in this setting. Hair tends to be coarse, dry, and brittle. Patchy alopecia and/or persistent lanugo hairs may be present. A collodion baby with congenital hypothyroidism has been reported. Other anomalies reported in association with congenital hypothyroidism include cardiovascular abnormalities (ventricular septal defect, patent ductus arteriosus, and pulmonary stenosis), gastrointestinal abnormalities (colic duplication with hypertrophic pyloric stenosis), and musculoskeletal abnormalities (unilateral clubfoot and congenital dislocation of the hip) [32].

The incidence of congenital hypothyroidism is 1 case per 4000 live births. Ninety-five percent of all cases are sporadic and five percent are genetic, most often secondary to dyshormonogenesis [33]. Endemic cretinism, secondary to iodine deficiency in utero, still exists in some regions of the world. Fetal hypothyroidism may also be caused by the transplacental passage of goitrogens [2].

Newborn screening for congenital hypothyroidism is now mandatory in the United States because 33% of infants with the condition present with no abnormal symptoms or signs. The best time to collect blood between 3 and 6 days after birth to avoid the transient physiologic hyperthyroidism noted shortly after delivery.

**Adult hypothyroidism**

Adult-onset hypothyroidism may be insidious in onset and occur over the course of many years. Symptoms commonly associated with onset include fatigue, muscle cramps, weakness, inability to concentrate, and cold intolerance, which patients sometimes falsely attribute to aging [34].

The skin in hypothyroidism is a reflection of the resultant hypometabolic state and subsequent reduced core body temperature and reflex cutaneous vasoconstriction. The skin becomes cool, dry, and pale. Xerosis may present with severity mimicking acquired ichthyosis. Xerosis in hypothyroidism has been reviewed, raising the speculation that topical thyroid hormone could be of potential use in treating xerosis, even in euthyroid patients [35]. Hypohidrosis, possibly accompanied by diminished epidermal steroid biosynthesis, may lead to acquired palmoplantar keratoderma. Skin pallor is the result of cutaneous vasoconstriction and increased deposition of water and mucopolysaccharides in the dermis, which alter the refraction of light. A yellowish hue may be imparted on the skin, particularly on the palms, soles, and nasolabial folds, as the result of carotenemia observed in hypothyroidism [2].

Hair changes may be dramatic and classically manifest as dry, coarse, brittle head and body hair with a tendency to fall out, resulting in diffuse, partial alopecia. Loss of hair from the lateral third of the eyebrow is a common finding. Patients with hypo-
thyroidism have an increased percentage of telogen hairs, which is reversed with normalization of thyroid hormone levels [36].

The most characteristic clinical sign of hypothyroidism is generalized myxedema, which occurs as a result of deposition of dermal acid mucopolysaccharides, particularly hyaluronic acid and chondroitin sulfate. Skin may appear swollen, dry, pale, waxy, and firm to the touch. Despite its edematous appearance, the skin is nonpitting. The face assumes a typical appearance with swollen lips, a broad nose, macroglossia, and puffy eyelids. Drooping of the eyelids may occur and is attributed to decreased sympathetic stimulation of the superior palpebral muscle. Entrapment syndromes such as carpal tunnel syndrome and facial nerve palsy have been reported [37]. Wound healing is impaired, and purpura may be noted as a result of diminished levels of clotting factors and/or loss of vascular support secondary to dermal mucin [2].

Associated cutaneous and systemic diseases

Disorders of the thyroid, particularly autoimmune thyroid disease, have been associated with a number of different cutaneous and/or systemic diseases (Table 1). In some cases, the presence of a particular disease state warrants investigation for thyroid abnormalities (T4 and TSH) or carries an increased risk for development of autoimmune thyroid disease.

Alopecia areata

Thyroid function test abnormalities have been reported to occur in as many as 24% of children with alopecia areata [38]. Despite this seemingly high prevalence, most patients in this same study did not manifest clinically evident thyroid dysfunction. Another study of 143 children demonstrated an incidence of 20% of children with alopecia areata also with clinically evident thyroid disease, antithyroid antibodies, or raised T3 levels [39].

Anemia

Autoimmune thyroid disease has been reported in association with atrophic gastritis (and resultant pernicious anemia). Up to 10% of patients with hypothyroidism may demonstrate pernicious anemia [40]. Pure red blood cell aplasia with severe normochromic normocytic anemia and absent red blood cell precursors in otherwise normal bone marrow has been reported in association with numerous autoimmune disorders (systemic lupus erythematosus, thymoma, and multiple endocrine gland insufficiency). Three patients have been reported to manifest pure red blood cell aplasia with primary autoimmune hypothyroidism. All three patients also demonstrated concordant systemic lupus erythematosus (SLE) [41].

Bullous disorders

Autoimmune thyroid disease (specifically, Graves’ disease) has been reported to occur simultaneously with pemphigus foliaceus and pemphigus vulgaris [42]. One report of a patient with Graves’ disease and pemphigus vulgaris also demonstrated the presence of HLA-DR3 and -DR4, raising the question of genetic susceptibility [43]. Bullous pemphigoid has been observed in patients with Hashimoto’s thyroiditis.
and Graves’ disease [44,45]. Herpes gestationis has been reported to occur with Graves’ disease (with one patient also demonstrating alopecia totalis and ulcerative colitis) [46]. Dermatitis herpetiformis has been reported to have concomitant thyroid disease in as many as 52% of patients [47]. The atrophic variant of Hashimoto’s thyroiditis has been associated specifically with dermatitis herpetiformis and with antigens HLA-B8 and HLA-DRw3 [48].

**Connective tissue diseases**

Autoimmune thyroiditis has been reported in association with dermatomyositis, polymyositis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, and Sjögren’s syndrome [49–54]. Genetic susceptibility and common immunopathogenesis have been explored in a number of cases, and histocompatibility antigens HLA-B8 and DR3 have been noted to appear with increased frequency in autoimmune thyroiditis and adult dermatomyositis, while HLA-DR3 has been noted to be associated with thyroiditis and SLE [55].

**Endocrinopathies**

Autoimmune thyroiditis has been noted as part of the Schmidt syndrome, which consists of idiopathic adrenal insufficiency, chronic lymphocytic thyroiditis, insulin-dependent diabetes mellitus, hypoparathyroidism, gonadal failure, pernicious anemia, mucocutaneous candidiasis, and sometimes thyrotoxicosis [56]. Chronic mucocutaneous candidiasis in association with hypothyroidism has been proposed as a distinct entity and possibly transmitted as an autosomal dominant trait. Unlike the polyglandular association with mucocutaneous candidiasis, where patients demonstrate high-titer antimicrosomal or antithyroglobulin thyroid antibodies, those with hypothyroidism alone did not demonstrate detectable autoantibodies, which raises the question regarding the presence of an unidentified, undetectable thyroid autoantigen [57].

Thyroid carcinoma may occur as part of an endocrine-related syndrome. Multiple endocrine neoplasia type 2a (MEN2a), a rare, autosomal dominant genetic syndrome, is comprised of hyperplasia or carcinoma of thyroid C cells (medullary carcinoma), adrenal medullary hyperplasia, pheochromocytoma, and parathyroid hyperplasia. Multiple endocrine neoplasia type 2b (MEN 2b) is comprised of medullary thyroid carcinoma, pheochromocytoma, mucosal and gastrointestinal ganglioneuromatosis, and marfanoid features.

Acanthosis nigricans (AN), a cutaneous manifestation of a number of systemic diseases including endocrine and malignant neoplasms, has been reported in association with hypothyroidism. The relationship has been examined, and it has been suggested that AN is not directly related to thyroid dysfunction, but rather to the resulting effects of hypothyroidism, including obesity and subsequent insulin resistance [58].

**Urticaria**

Since 1983, reports have surfaced regarding the association of thyroid autoimmunity with urticaria. A statistically significant increase in the incidence of urticaria, chronic urticaria, and angioedema when compared to similar control groups has been demonstrated in the literature on several occasions [59]. Urticarial vasculitis has been reported with thyroid autoimmunity [60]. The mechanism by which this association occurs is poorly understood. Thyroid hormone has been used to treat chronic urticaria and/or angioedema in patients with evidence of thyroid autoimmunity with significant success [61,62]. In patients with idiopathic chronic urticaria and/or angioedema, it is warranted to screen for thyroid autoimmunity; if this is demonstrated and the patient is unresponsive to standard therapies, use of levothyroxine in hypothyroid or euthyroid patients should be considered [59].

**Vitiligo**

Vitiligo has been associated with autoimmune thyroid disease presenting as either hyperthyroidism or hypothyroidism, and with Addison’s disease, pernicious anemia, diabetes mellitus, idiopathic heart block, uveitis, melanoma, and ovarian and testicular failure [63]. Kumar et al studied 22 clinically euthyroid patients with vitiligo and demonstrated a lower than normal radioactive iodine uptake (RAIU) in 90% of patients [64].

**Other associations**

Patients with pustulosis palmoplantaris have been demonstrated to have one or more signs of thyroid disease, such as a goiter or abnormal thyroid function tests in up to 53% of patients and the presence of antimicrosomal antibodies, antithyroglobulin antibodies, or both in 40% of patients [65,66].

Sweet’s syndrome (acute febrile neutrophilic dermatosis) has been reported in association with thyroid disease. Nakamura et al reported the case of a patient in whom Graves’ disease was diagnosed three years before the development of Sweet’s syndrome [67].
Another case was described of the simultaneous onset of Sweet’s syndrome and subacute thyroiditis with spontaneous resolution of the thyroiditis [68].

Thyroid disease represents the second most common endocrinopathy in association with McCune-Albright Syndrome (MAS), with reported cases of hyperthyroidism with and without goiter development, TSH-producing pituitary adenomas, and non-autoimmune hyperthyroidism [69]. MAS-associated thyroidopathies have been linked to G-protein mutations with resultant cAMP overproduction, growth of thyrocytes, and/or hormone hypersecretion [70].

Other associated findings/disease states reported in association with thyroid abnormalities include Cowden’s syndrome (thyroid goiter, adenoma, and carcinoma); erythema annulare centrifugum (Graves’ disease); generalized granuloma annulare (autoimmune thyroiditis); AIDS-Kaposi’s sarcoma (thyroid nodules); melasma (increased rate of thyroid dissection of thyrocytes, and/or hormone hypersecretion [70].

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