REVIEW ARTICLE

Skin disorders and thyroid diseases

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ABSTRACT. Thyroid disorders have a high prevalence in medical practice; they are associated with a wide range of diseases with which they may or may not share etiological factors. One of the organs which best show this wide range of clinical signs is the skin. This review is an attempt to approach most of the dermopathies reflecting several degrees of harmfulness, coming directly or indirectly from thyroid abnormalities, as well as to update current knowledge on the relationship between the thyroid and skin. We have proposed a primary classification of skin disorders, regarding thyroid involvement, into two main groups: 1) dermopathies associated with thyroid abnormalities, mainly with autoimmune thyroid diseases, like melasma, vitiligo, Sjögren's syndrome, alopecia, idiopathic hirsutism, pre-menstrual acne, bullous diseases, connective tissue diseases, hamartoma syndrome, atopy, leprosy and DiGeorge anomaly; and 2) dermopathies depending on the nature of the thyroid disorder, in which the evolution and outcome of the skin disorder depend on the thyroidal treatment in most cases, such as trophism and skin blood flow, myxedema, alopecia, onychodystrophy, hypo- and hyperhidrosis, xanthomas, intraepidermal *bullae*, carotenodermia, pruritus, flushing, pyodermitis, palmoplantar keratoderma, ecchymosis, etc. In some other cases, the skin disease which developed as a consequence of the thyroid abnormality can remain unaltered despite functional treatment of the thyroid problem, such as pretibial myxedema, thyroid acropachy and some cutaneous manifestations of multiple endocrine neoplasia types 2A and 2B.

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INTRODUCTION

Thyroid disorders have a high prevalence in medical practice; they are associated with a wide range of diseases with which they may or may not share etiological factors. Since manifestations are so varied, their knowledge is interesting not only for endocrinologists but also for internists and other specialists. One of the organs which best show this wide range of clinical signs is the skin, *i.e.* the three layers (epidermis, dermis and hypodermis) and the cutaneous phaneras (hair and nails).

In an attempt to classify these cutaneous manifestations, we have divided them into two main groups: those associated with thyroid diseases (temporarily or not) but in which no cause-effect relationship has been demonstrated, and those dependent on the thyroid disease itself (hyper- and hypothyroidism). The evolution and outcome of the dermopathy will depend, in most cases, on the thyroid function (1).

DERMOPATHIES ASSOCIATED WITH THYROID DISORDERS

These cutaneous disorders are seen with greater incidence in patients affected by thyroid dysfunction than in the general population, though many of the symptoms may overlap with the thyroid disease itself (Fig. 1 and 2).

The most common classical association is dyschromia or pigmentation spots, which may be classified into hyper- and hypochromias that generally share an autoimmune etiology.

The most frequent hyperchromia is melasma, a café-au-lait pigmentation, without prurite or scaling, generally with centrofacial location, and which presents

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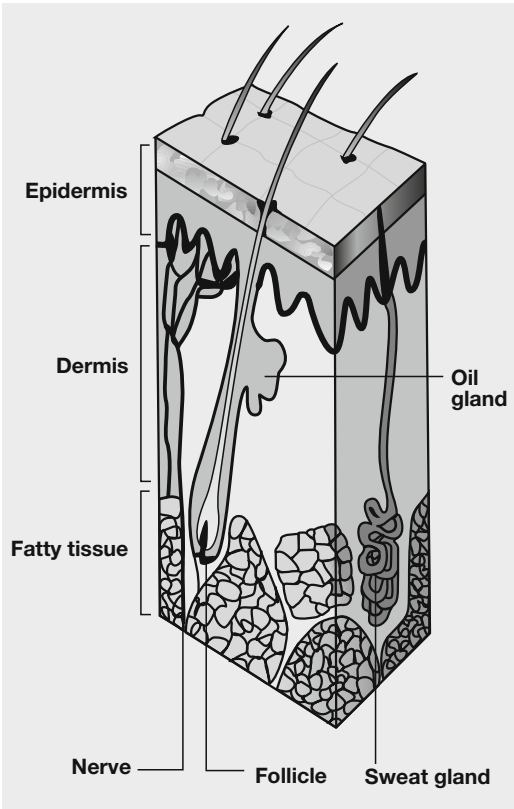


Connective tissue diseases:

- ***Systemic lupus erythematosus***
- **Scleroderma**
- **CREST syndrome**
- **Sjögren's syndrome**

Bullous diseases:

- ***Pemphigus***
- ***Dermatitis herpetiformis***

Miscellaneous associations:

- **Pre-menstrual acne**
- **Leprosy**
- **Psoriasis**
- **ANOTHER syndrome**
- **Candida endocrinopathy syndrome**

Hamartoma syndrome:

- **Cowden's disease**
- **Bannayan-Riley-Ruvalcaba**

Dyschromia:

- **Melasma**
- **Vitiligo**
- **Leukomelanoderma**

Atopy:

- **Atopic eczema**
- **Urticaria**
- **Dermographism**

Fig. 1 - *List of dermopathies associated with thyroid diseases independently of thyroid function.*

mainly in dark-skinned women who live in areas of intense sunlight. In previous studies, we established two etiologic groups with positive thyroid autoantibodies: one idiopathic and another related to estrogen - progesterone. In the latter group, about 70% of melasma patients had some thyroidal abnormalities *vs* 40% of patients in the idiopathic group (2). We suggested that sexual steroidal hormones (endogenous as in pregnancy or exogenous, such as oral contraceptives) trigger the development of melasma in women who have a particular genetic predisposition to thyroidal autoimmune diseases.
Among hypochromias, the main expression is vitiligo, which is characterized by achromic areas with hyperpigmented margins. These lesions have an insidious onset, without pruritus or anesthesia, and are not coupled with scaling, atrophy or sclerosis. Generally, they are symmetrically located, mainly in the back of the hands, face, neck, folds and genitals. Its prevalence in the general population is 1-2%, whereas in subjects with Graves' disease it rises to 6-7%. It has been demonstrated that in vitiligo there are antibodies against melanine (3), tyrosinase (4), tyrosinase-related protein-1 (5) and melanocyte-specific protein pmel 17 (6), which enable us to allocate it to the category of autoimmune diseases. In our studies in this field, we also showed that this dyschromia occurs with increased frequency and severity in females. Thus, we saw that 42% of males with vitiligo had an alteration in their thyroidal parameters *vs* 62.5% of females, who had a clearly higher incidence of thyroiditis (7, 8). Hegedus *et al.* found one or more signs of thyroid disease in 43% of patients with vitiligo (9). More recently, Beherens-Williams *et al.* (10) applied an *in vivo* testing of cell-mediated immunity to define the cutaneous delayed-type hypersensitivity (DTH) in the presence or absence of serum thyroid autoantibodies. DTH was evaluated both in normal and depigmented skin of vitiligo patients using the dermal application of seven common recall antigens, together with a negative control. Their *in vivo* studies revealed, however, no clinically significant aberrant cellular immunity in those patients.
The two lesions described above may combine into leukomelanoderma, and may occasionally be associated with Sjögren's syndrome (11, 12).
The Vogt-Koyanagi-Harada's syndrome, which affects the melanocyte-containing tissues, has also

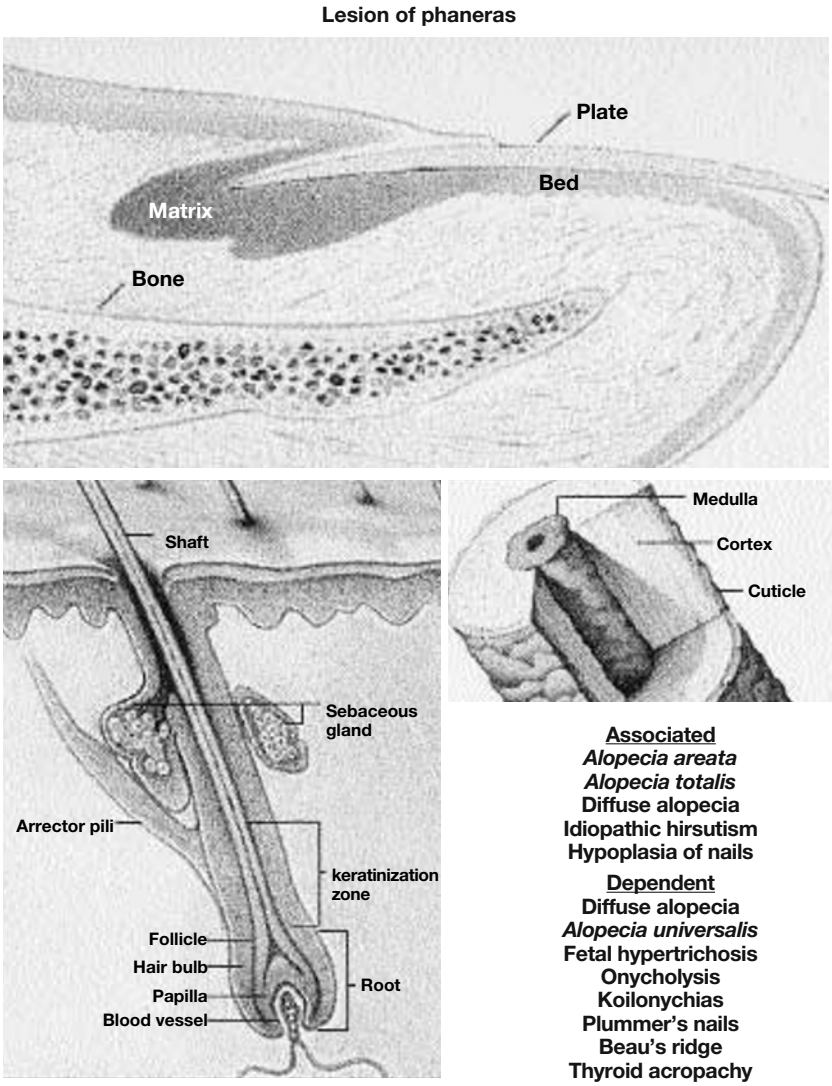


Fig. 2 - *Lesions of phaneras associated with and dependent on thyroid abnormalities.*

been associated with Hashimoto's thyroiditis (13). Like dyschromias, *alopecia areata* (14) is classically associated with thyroid diseases. Its main features are circumscribed bald patches in the scalp or beard. The lesions have a clean appearance and the hair follicles can be observed within them. Genetic factors are undoubtedly important in its etiology, since a direct relation with DQ7, DR4 and DR5 has been demonstrated. As regards *alopecia totalis/universalis* (14), it was HLA-DR11 that showed a more direct relation (30.2 increase in relative risk). Also, polymorphisms were detected in intron 2 of the interleukin 1 receptor antagonist gene, which is associated with severity in other chronic inflammatory autoimmune disorders. Clinical studies revealed that the strongest association is with vitiligo and thyroid diseases. Thyroid disorders (mainly thyroiditis) were reported in 8% of alopecia cases in comparison with 2% of controls. Several studies reported an increased frequency of thyroid autoantibodies in this entity and the presence of antibodies that react with the endothelia of perifollicular capillaries. Furthermore, both pathologies share cellular immunity abnormalities, such as reduced numbers of circulating T suppressor/cytotoxic cells (CD8+ve), with a clear prevalence of CD4+ve cells. Lymphocytic infiltration results in an increased expression of class I and class II HLA antigens. Hair bulb melanocytes are damaged in this process as well, and melanogenesis may cease. There is also a

rise in the expression of intercellular adhesion molecule 1 (ICAM-1) in both dermal papilla and hair matrix and hair bulb keratinocytes. It was suggested that increased antigen HLA and ICAM-1 expression might result from cytokine release by infiltrating inflammatory cells, though this remains to be confirmed. The investigation of Sterzl *et al*. about the frequency of extrathyroid organ specific and non-specific autoantibodies in patients with autoimmune thyroiditis is interesting. The authors refer 45% of mutual positivity of antibodies against thyroid peroxidase and antibodies against the hair follicles (15). Asanuma *et al.* (16) reported the first documented case of *alopecia universalis* during pregnancy with remission on prednisolone therapy. Autoantibody measurements were positive for the antithyroid and antinuclear antibodies. However, thyroid function and glucose tolerance were normal, and other clinical evidence of collagen vascular disorders were not found.

Researches conducted by our group showed an association between diffuse *alopecia* (17) and thyroid diseases in 60% of the cases, mainly of autoimmune origin, with normal T_3 and T_4 circulating levels but with subclinical abnormalities, such as small goiters and/or hyperresponses of TSH to TRH, as well as the presence of circulating autoantibodies to thyroid peroxidase. In the same study (17), we reported the association of thyroid diseases with idiopathic hirsutism (55.5%) and pre-menstrual acne (50%) in female patients with normal androgenic levels. Only 12.5% of control patients, however, presented thyroid disturbances. In addition to these associations, it is interesting to mention the case report of a 13-year-old girl who presented remission of *acanthosis nigricans*, hypertrichosis, and Hashimoto's thyroiditis with T_4 replacement (18).

Another association described in patients with autoimmune thyroid diseases is *pemphigus* (3), in its *vulgaris* variety as well as in its erythematous and foliaceous manifestations. It may or may not simultaneously appear with the thyroid disease. Among bullous diseases, *dermatitis* herpetiformis (3) also has a strong association with thyroid diseases. It was found that 34% of these patients had clinical or functional thyroidal abnormalities, including hypothyroidism, Graves' disease, toxic multinodular goiter and follicular carcinoma. Antimicrosomal antibodies were significantly present: 38% *vs* 12% in control patients. There was also a preponderance of HLA-B8 and HLA-Dw3 antigens, which are related to Graves' disease and Hashimoto's thyroiditis, respectively. A recent study investigated a cohort of 41 patients, *vs* a control group, demonstrating that *dermatitis herpetiformis* is associated with the atrophic variant of Hashimoto's thyroiditis (19). However, the goitrous variant of Hashimoto's thyroiditis was not seen in any of those patients.

Chronic mucocutaneous candidosis is a complex disorder characterized by chronic and recurrent candida infections of the skin, nails and oropharynx. In over 50% of cases there is an associated endocrine disease to follow an autosomal recessive pattern: Candida endocrinopathy syndrome. Coleman *et al.* reported a new syndrome in which there is vertical transmission of chronic mucocutaneous candidosis within families associated with primary hypothyroidism (20).

Connective tissue diseases, such as *systemic lupus erythematosus* (21) (mainly seronegative types), Scleroderma and the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, scleroderma, telangiectasias) (11, 22) show the strongest association with thyroid diseases. We find a great variety of associated cutaneous manifestations, ranging from xeroderma and sclerosis to purpura and ecchymosis, from butterfly shaped erythema and Raynaud's phenomenon to telangiectasias and calcinosis. A remarkable high prevalence of autoimmune thyroiditis in systemic sclerosis has already been described (23).

Psoriasis (12, 24) is one of the entities most frequently associated with Sjögren's syndrome (11, 12), which is, in turn, related to autoimmune thyroiditis. Few cases of association between these three entities have been described. A gene involved in psoriasis susceptibility was mapped to human chromosome 17q (25) and Torma *et al.* (26) found that the retinoid and thyroid hormone signalling is abnormal in lesional psoriatic skin. The expression of three housekeeping genes (cyclophilin, GAPDH and β-actin) was consistently higher in lesional than in non-lesional skin, and the expression of the nuclear receptor for retinoic acid, vitamin D_3 and thyroid hormone plus the common heterodimer partners, the 9-cis-retinoic acid receptors, were found to be lower in lesional than in non-lesional skin.

Cox *et al.* proposed to replace the acronym TASS syndrome (thyroiditis, Addison's disease, Sjögren's syndrome and sarcoidosis) by another acronym, TOASSUC (thyroiditis, other autoimmunity, Sjögren's syndrome, sarcoidosis and ulcerative colitis), because it includes a wider range of disorders (27).

Cowden's disease (3) or multiple hamartoma syndrome is an autosomal dominant disorder which is characterized by warty skin lesions (trichilemmomas) affecting the face, mucous membranes and distal extremities, in association with benign or malignant tumors of the thyroid and breasts. About

two-thirds of patients present with thyroid disease, early multinodular goiter being the most frequent, though there is also a high frequency of solitary nodules, thyroiditis and carcinoma. Perriard *et al.* describe a family with the unusual association of Cowden's disease and Bannayan-Riley-Ruvalcaba's (BRR) syndrome (28). The later is an hamartoma syndrome characterized by early-onset macrocephaly, lipomatosis, hemangiomas, hamartomatous polyps of the gastrointestinal tract, vascular malformations, pigmented maculas of the glans penis (speckled penis) in males, Hashimoto's thyroiditis, and mild intellectual delay. Germline mutations in PTEN, a tumor suppressor gene mapping to 10q23.3, have been found in 13-81% of Cowden's syndrome patients and 57-60% of BRR cases (29). Two cases of 10q deletion encompassing PTEN have also been reported in BRR (30). Gorlin *et al.* proposed to expand the phenotypic spectrum of BRR to include Hashimoto's thyroiditis (31).

There is also an entity termed either hypohydrotic ectodermal dysplasia or ANOTHER syndrome, which associates *alopecia*, nail dystrophy, ophtalmic complications, thyroid dysfunction, hypohidrosis, ephelides/enteropathy and respiratory tract infection. Only three cases of this syndrome have been described (3).

Another association established in the literature is atopy in its different expressions. We might say that the most studied entity is atopic eczema. High histamine levels (in dermic tissue samples of affected patients) were shown to have a relation, still unexplained, to increased circulating histaminase activity in patients with medullar thyroid carcinoma. These findings led to the proposal that the intradermal histamine test should be used to determine the extent of disease dissemination or metastases (32). It is thought that endocrine disorders act as triggering factors in the development of the eczema. A recent finding showed that IgE responsiveness is linked to a locus on chromosome 11q13, close to a gene encoding the β-subunit of the high-affinity IgE receptor. Such *locus* is also involved in the development of type I MEN. Other manifestations of atopy related to both hyper- and hypothyroidism are urticaria and dermographism, though a direct cause-effect relation has not been established. Recently, the association of chronic urticaria and angioedema (CUA) with autoimmune thyroiditis was observed in both patients with thyroid dysfunction and euthyroid subjects (33), and resolution of chronic urticaria was achieved under T_4 treatment (34).

There are entities, such as leprosy (35, 36), which are less habitually associated with thyroid diseases, though the thyroid is neither the only gland affected nor the most frequently affected one, and there is no strong evidence for this relationship in the literature. Some studies have reported decreased thyroid hormone levels with a statistically significant correlation between the T_3 decrease and lepromatose reaction, and between the T_4 decrease and lepromatose leprosy and borderline states. Lepromatose reactions coupled with Type 2 diabetes mellitus and hypothyroidism have also been described.

Sweet's syndrome (acute febrile neutrophilic dermatosis) can be associated with subacute thyroiditis. The role of cytokines might be the link between these two conditions (37).

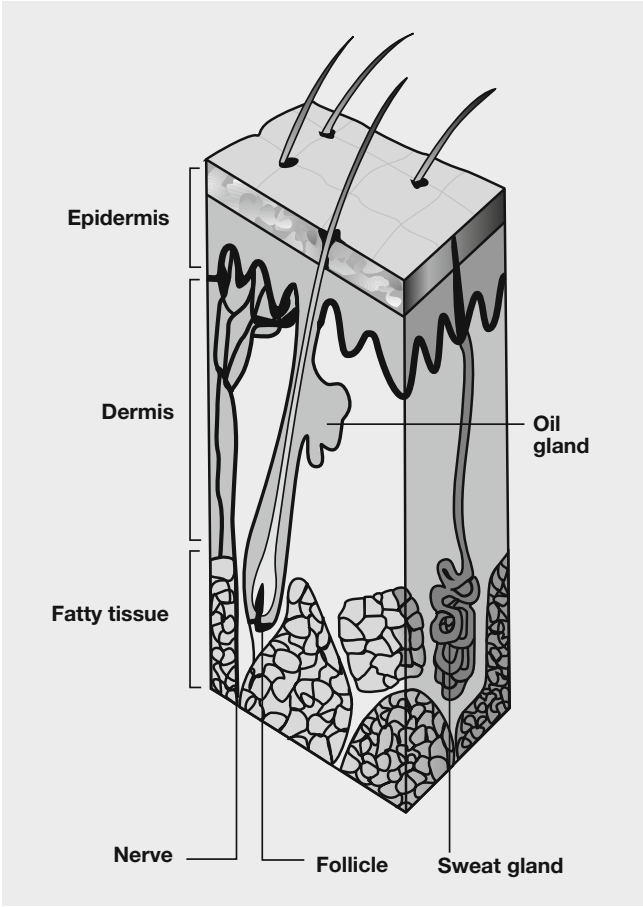
About phaneras, hypoplasia of all nails was described in DiGeorge anomaly, with absent thyroid isthmus, congenital heart defects and multiple malformations in infants (38).

DERMOPATHIES DEPENDING ON THYROID DISORDERS (FIG. 2 AND 3)

Hypothyroid state

In hypothyroidism, the skin is characteristically dry, rough and cool to the touch. This is the result of the direct influence of thyroid hormones on trophism and skin blood flow. Thus, measurements of skin perfusion by Laser-Doppler flowmetry (39) demonstrated that in hypothyroid patients, not undergoing treatment, mean capillary flow velocity, capillary pulse wave amplitude and capillary flow oscillation amplitude were decreased in comparison to euthyroid patients. This decrease was even higher in comparison to hyperthyroid patients. In this case, thyroid opotherapy proved to be effective. Electrodermal abnormalities in the absence of measurable psychiatric symptoms were also observed in hypothyroid subjects. Lower skin conductance levels, lower fluctation rates and prolonged onset latencies, but normal amplitudes, were related to changes of the hypothalamic-pituitary-thyroid axis function (40). Pazos-Moura *et al.* (41) also found that the skin microvascular autoregulatory mechanism is disturbed. They used direct intravital microscopic examination of nailfold capillaries.

Acquired variants of palmoplantar keratoderma (42), seen in hypothyroid patients among others, show an impressive response to specific treatment. The disease may be due to the longer mitotic duration and decrease in epidermal steroidogenesis. Additionally, there is an increased keratin production and a reduction of intercellular lipids, both contributing to changes in transepidermal water loss. The keratoderma can become generalized; in this case it is known as xeroderma or ichthyosiform conditions,



Hyperthyroidism

Hyperhidrosis
Hyperpigmentation
Erythema
Pretibial myxedema
Pruritus
Flushing
Peau d'orange

Hypothyroidism

Xeroderma
Pilose keratosis
Palmoplantar keratoderma
Skin microvascular autoregulatory mechanism disturbed
Hypohidrosis
Generalized myxedema
Intraepidermal *bullae*
Purpura
Ecchymosis
Carotenodermia
Xanthomas
Generalized *pruritus*
Granuloma annulare
Pyodermitis

Fig. 3 - *Skin disorders due to alterations of the thyroid function, both in hyper- and hypothyroidism, and also due to Graves' disease itself.*

more frequently found in severe cases of hypothyroidism. A mild expression of ichthyosis is pilose keratosis, a keratosis in hair follicles with permanent *alopecia*, frequently associated with hypothyroidism, with which it shares an autoimmune etiology. It is more commonly found in teenagers and is mainly located in the back of arms and thighs.

A consequence of thyroid dysfunction that contributes to skin dryness is the decrease in sweating and in sebum secretion, known as hypohidrosis (3).

Generalized myxedema or cutaneous mucinosis is a characteristic sign of the hypothyroid state. Patients present with diffuse edema, without fovea, most prominent in periorbital and acral locations. This disorder is the result of a generalized increase in dermal acid mucopolysaccharides, particularly hyaluronic acid and chondroitin sulfate. Occasionally, generalized myxedema may simulate the musculoskeletal symptoms of polymyositis (43). Transcapillary escape of albumin into the dermis contributes to edema formation. Finally, the dermal concentration of elastic fibers is reduced in the skin from patients with generalized myxedema. Recently, an association between Hashimoto's thyroiditis and mid-dermal elastolysis (loss of elastic fibers in the mid-dermis due to elastophagocytosis, with giant cells and granuloma formation) has also been described (44) as well as reticular erythematous mucinosis and acral papulokeratotic lesions, showing a rapid regression after levothyroxine treatment (45). All these disorders determine the development of friction-induced intraepidermal *bullae* as well as *purpura* and *ecchymosis*. Actually, Le Brun *et al.* (46) recommended thyroid hormone assays in any patient presenting pretibial bullae. They report a case of hypothyroidism and pretibial *epidermolysis bullosa*, which rapidly regressed after hormone therapy. Pathology reported blisters with subepidermal cleavage and a substance which is dense at the electron microscopy.

A reflex cutaneous vasoconstriction as a mechanism to maintain body temperature is induced by hy-

pothermia in hypothyroid patients, resulting in pallor and skin that is cool to the touch (39).
The lack of hepatic metabolization of carotene produces its accumulation in the *stratum corneum*. Carotene then is excreted in sweat and reabsorbed by the skin, with deposition occurring mainly in areas rich in sebaceous glands. This is another factor that may change skin color, giving it a characteristic yellowish tint or carotenodermia. Hypercholesterolemia is also manifested in the skin of hypothyroid patients; both tuberous and eruptive xanthomas (3) are frequently seen. The skin of these patients, as we have seen, is a dermis with delayed cicatrisation and a tendency to develop pyodermitis. Generalized *pruritus* (47) is not rare, though there are discrepancies in the literature as regards this symptom, since in some cases it is reported as associated to and not dependent on thyroid dysfunction.
There were evidences that *granuloma annulare* and autoimmune thyroiditis may be associated (48, 49). Treatment with T_4 resulted in the restoration of a euthyroid state and a progressive decrease in the number of the skin lesions in patients with generalized *granuloma annulare* associated with mild hypothyroidism, which was due to an atrophic autoimmune thyroiditis (50).
Phaneras are also affected by this systemic disorder. The decrease in sebaceous gland output causes hair to be opaque; its growth rate is retarded owing to the delayed initiation of the anagen phase. Hair loss resulting in diffuse *alopecia* is also possible.
The presence of fetal hypertrichosis in hypothyroid newborn babies and the retention or apparition of lanugo hair in children with severe hypothyroidism are well known (3). To investigate the cellular basis of the action of thyroid hormone on hair follicles, Ahsan *et al.* (51) studied the immunohistochemical localization of thyroid hormone receptors in human scalp skin; they were found in the nuclei of the outer root sheath cells, dermal papilla cells, fibrous sheath cells of hair follicles, hair arrector pili muscle cells and sebaceous gland cells. L-T_3 stimulated the *in vitro* proliferation and/or metabolism of all these types of cells significantly, although there were variations on the rate of stimulation. Likewise, there was a correlation between selenium concentration in hair and nails and thyroid morphology, serum concentrations of thyroid hormones and peripheral parameters of hormone actions (Achilles tendon reflex, pulse rate or antrophometric variables) (52). In hypothyroidism, the nails are thin and brittle. They grow slowly and with longitudinal ridging. In addition, onycholysis and koilonychias (flat or concave nails) may develop.

Hyperthyroid state

Hyperthyroid patients present an hypermetabolic and hyperdynamic state in cutaneous perfusion (49). Their skin is often warm and moist to the touch, resulting in hyperhidrosis. They also present with erythema, particularly facial and palmar. Flushing occurs as a mechanism for body temperature regulation by dermal vasodilatation. The sebum excretion rate was found to be normal and uninfluenced by therapy. Hyperpigmentation in a localized and/or diffuse distribution (not caused by associated melasma) may occur in hyperthyroid states due to an increased release of pituitary adrenocorticotropic hormone compensating for accelerated cortisol degradation.
Unlike hypothyroid patients, in hyperthyroid cases myxedema appears mainly in pretibial locations and is characterized by sharply circumscribed plaques, though diffuse or elephantiasic presentations may also occur, the latter consisting of edema and superimposed plaques. Pretibial myxedema is most commonly associated with Graves' disease (53). Three to five percent of patients with this disease develop myxedema, and 70-90% of cases are associated with exophthalmous. When the pretibial myxedema is combined with bilateral exophtalmous and acropachyderma of fingers and toes, it is called Diamond syndrome (54). The plaques may have a *peau d'orange* appearance and overlying hypertrichosis is sometimes noted (3). Histologically, pretibial myxedema is caused by accumulation of mucin in the lower two thirds of the dermis that produces wide separation of collagen fibers. Fibroblasts in tissue culture from patients with Graves' disease demonstrated increased hyaluronic acid production as compared with sera from euthyroid patients (55). A heat-stable, protease sensitive, and dialyzable stimulating substance, which differs from thyroid-stimulating immunoglobulins, has been identified. This substance is thought to be involved in the development of myxedema in Graves' disease. It has been suggested that fibroblasts have an intrinsic defect in local degradation of cutaneous proteoglycans, and we have observed, by means of *in vitro* studies, that radiolabeled human serum albumin is selectively accumulated in the skin of pretibial myxedema (56).
An acral ichthyosiform mucinosis in association with Sjögren's syndrome, in the absence of Graves' disease, has been described as a peculiar form of pretibial myxedema (57).
As regards phaneras, hyperthyroid patients may also present with diffuse *alopecia* due to reduction of the anagen phase of the hair cycle, which alters

the anagen/telogen ratio. Exceptionally, we have seen *alopecia universalis* after radioiodide treatment of thyrotoxicosis in psychiatric patients with Graves' disease. Nails are usually shiny and grow more rapidly, though they may also be friable, and the lifting of the distal nail plate gives the hyponychium a ragged and dirty appearance (Plummer's nails). Beau's ridge, a thick transversal ridge, is commonly found (3).

An effect that is rarely seen is thyroid acropachy, which is characterized by a triad of findings: 1) clubbing of the fingers/toes; 2) thickening and fibrosis of the subcutaneous tissue; 3) diaphyseal periosteal proliferation with occasional new bone formation in the distal extremities.

Pruritus is usually part of the constellation of symptoms in hyperthyroidism (41). Thus, assessment of thyroid status is a common practice in laboratory evaluation for this symptom, which is undoubtedly associated with hyperthyroidism.

Thyroid neoplasia

Multiple endocrine neoplasia (MEN), especially type 2B, which is associated with medullary thyroid carcinoma, is characterized by café-au-lait spots, diffuse lentigos, neuromas and neurofibromas (3). In the Carney complex, which combines multiple neoplasia and lentiginosis syndrome, thyroid abnormalities ranging from follicular hyperplasia and/or cystic changes to carcinoma have been described (58).

Recently, another disease has been proposed as an early clinical marker for MEN type 2A: *Notalgia paresthetica*, an isolated sensory mononeuropathy (59). It is a benign cutaneous disorder in the mid-upper back, a papulous and pruriginous lesion with dermal melanosis and deposits of amyloid in the dermis at the histological examination. Patients with a familial history of notalgia paresthetica or with an onset of notalgia paresthetica in childhood should be screened for MEN type 2A.

Cutaneous metastases from thyroid neoplasia are not frequently seen in daily practice; however, patients having follicular (60) and medullary (61) carcinomas presented solitary nodules in the head and neck. As we mentioned before, there is a rise in histaminase activity in the metastases of medullary carcinomas, and it has been suggested that the intradermal histamine test might be used for the detection of that metastases (32).

A single case of multiple pilomatrixomas associated with myotonic dystrophy, frontotemporal *alopecia*, Raynauds phenomenon, acrokinesia and medullary carcinoma of the thyroid has also been reported (62)

CONCLUSIONS

There is a wide range of skin disorders which reflects several degrees of harmfulness coming directly or indirectly from thyroid abnormalities. Their manifestations are so varied that they become amazing for both endocrinologists and dermatologists as well as for general clinicians. This review is an attempt to approach most of these dermopathies and to update the current knowledge on the relationship between the thyroid and the skin. We have proposed a primary classification of the skin disorders, regarding the thyroid involvement, in two main groups: 1) dermopathies associated with thyroid abnormalities, mainly to autoimmune thyroid diseases, like dyschromias, Sjögren's syndrome, *alopecia*, idiopathic hirsutism, pre-menstrual acne, bullous or connective tissue diseases, hamartoma syndrome, atopy, leprosy and DiGeorge anomaly; and 2) dermopathies depending on the nature of the thyroid disorder, in which the endocrinological treatment leads to the cure or amelioration of the dermatological symptoms in most of the patients. The skin alterations, seen in hyper and hypothyroidism, are good examples of the strong influence of the circulating levels of thyroid hormones on the dermic tissue.

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