Endocrinology and the skin

This article discusses various cutaneous features associated with endocrine disease, which are of general medical relevance. Many of these, such as features associated with hypothyroidism, are common, while others, such as features of adrenal insufficiency, are relatively rare but important.

Hormones are essential biochemical enzymes involved in the regulation of various physiological processes in the body, including the skin. Endocrinological abnormalities, through excesses or deficiencies of hormones, result in alteration of the cutaneous morphology and function which can manifest in cutaneous signs and symptoms. Certain features are relatively characteristic, and examination of the skin can therefore provide valuable clues to various underlying endocrine disorders. Additionally, there may be autoimmune manifestations of some endocrinopathies and evidence of other associated autoimmune diseases may also be present. This article reviews the main organ-specific endocrinopathies and their cutaneous features. Some eponymous signs in endocrine disease are listed in *Table 1*.

The skin and thyroid gland

Cutaneous manifestations of thyroid diseases relate to the biochemical and metabolic consequences of the underlying condition. Few signs are disease-specific; thyroid acropachy and pretibial myxoedema (although the latter is not specific) are more reliable as they are associated with the disease per se, rather than with its metabolic consequences.

Hyperthyroidism

Cutaneous signs in hyperthyroidism may be divided into three groups: those that occur in any state of hyperthyroidism as a consequence of increased metabolic state, those which occur in autoimmune Graves' disease, and a miscellaneous group of interesting signs.

Table 1. Some eponymous 'signs' found in endocrine disorders

Jellinek's sign	Hyperpigmented eyelids seen sometimes in hyperthyroidism
Pemberton sign	Facial suffusion in patients with a large substernal goitre
Maroni sign	Erythema (occasionally with pruritus) occurring in the skin overlying a toxic goitre
Hertog's sign	Loss of the outer third of the eyebrow in hypothyroid patients (very non-specific; a common normal feature in elderly patients but notable in younger subjects)
Liddle's sign	Peeling of the skin after being covered with adhesive tape (non-specific but often found in Cushing's patients as a result of skin atrophy)

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Cutaneous signs in hyperthyroidism include warm skin, flushing, palmar erythema and increased sweating. These signs are caused by increased cutaneous blood flow and peripheral vasodilatation which occurs as a consequence of the increased sympathetic flow in hyperthyroid state (Heymann, 1992). Pruritus and urticaria may be associated with hyperthyroidism (Leonhardt and Heymann, 2002); the latter probably reflects autoimmnity rather than being metabolic.

Scalp hair is fine and soft, and diffuse alopecia may occur in up to a third of the patients, although the severity of alopecia is not related to the severity of the underlying hyperthyroidism (Leonhardt and Heymann, 2002). Alopecia areata (*Figure 1*) (well-circumscribed patches of hair loss) and vitiligo (*Figure 2*) may occur in autoimmune thyroid disease although both also occur in isolation.

The nails can be involved with a thin and shiny appearance; onycholysis (distal separation of the nail

Figure 1. Alopecia areata, showing typical 'exclamation mark' hairs. Ask about family history, as this autoimmune disease is associated with several endocrine conditions.

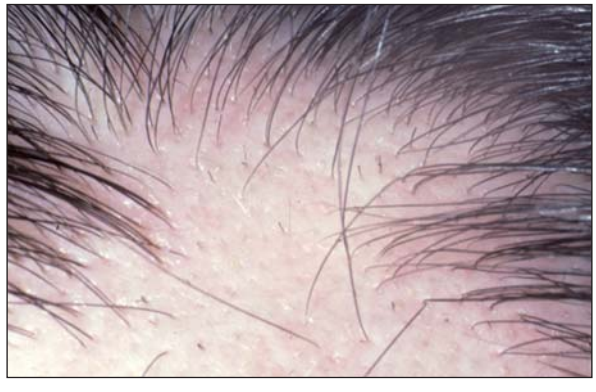


Figure 2. Vitiligo may occur associated with endocrinopathies, especially in thyroid disease.

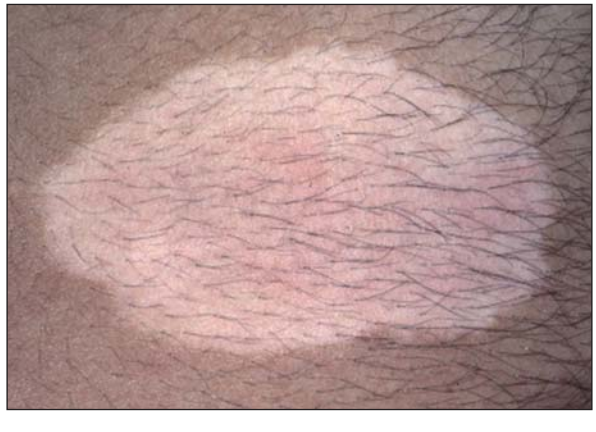


plate from the nail bed) may be present (*Figure 3*). It typically starts on the fourth digit of the hand (Tosti et al, 2001).

Cutaneous signs which may occur with Graves' disease are pretibial myxoedema (*Figures 4* and *5*) and thyroid acropachy (*Figure 3*). Pretibial myxoedema causes localized oedematous and thickened pretibial plaque(s) with a peau d'orange appearance, and can occur in up to 10% of patients with Graves' disease. It is usually a late feature, occurring after ophthalmopathy and in some cases post-treatment when the patient is euthyroid (Fatourechi, 2005). It consists of pink, flesh-coloured or brown nodules or plaques, usually bilateral on the anterolateral aspect of the lower limbs and gradually extending to the posterior side of the legs and feet. An important differential is chronic obesity lymphoedematous mucinosis which arises on the calves and shins of obese people (Tokuda et al, 2006). Treatment for pretibial myxoedema is always controversial. The authors' experience is that corticosteroids (topical, occluded or intralesional) are relatively unhelpful once mucinous change is established; short-stretch bandaging as for lymphoedema does reduce tissue bulk.

Thyroid acropachy consists of the triad: digital clubbing, soft tissue swelling of the hands and feet, and periosteal bone formation (Fatourechi, 2005). It occurs in up to 1% of patients with Graves' disease and is almost always associated with ophthalmopathy and pretibial myxoedema (Diamond's triad). The proximal phalanges and first or second metacarpals are most commonly affected.

Figure 3. Onycholysis (distal separation of the nail plate from the nail bed) and clubbing (thyroid acropachy) are both present here. The horizontal white striations are often mistakenly felt to represent a dietary deficiency, they are actually air spaces in nails caused by minor trauma.

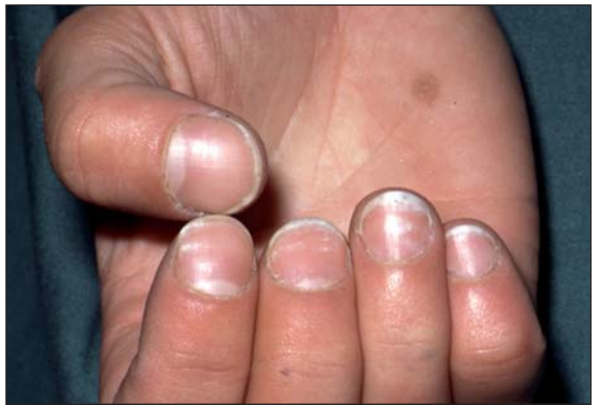
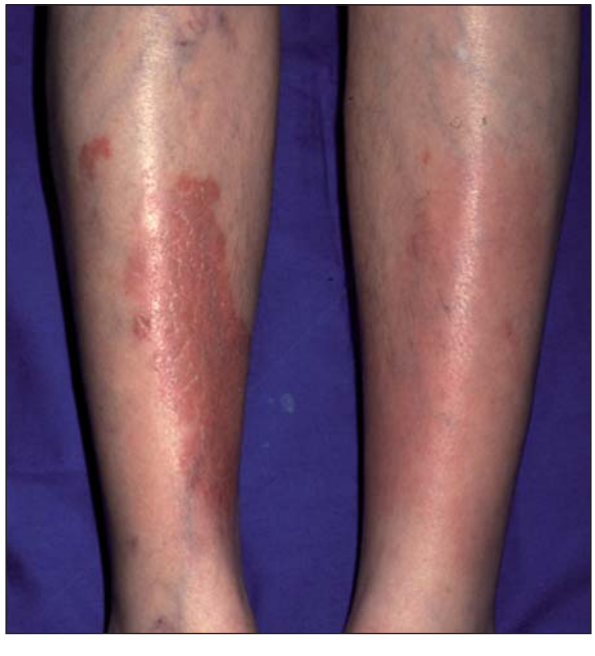


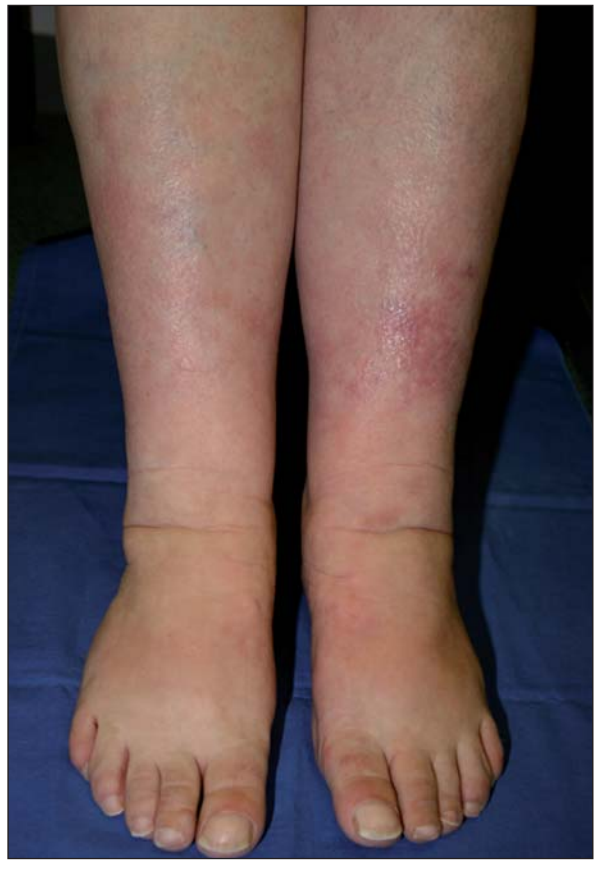
Figure 4. Early pretibial myxoedema is often quite red and superficial (in this case with some scaling on the right leg, but more typical deeper mucinous change on the left).



Hypothyroidism

The cutaneous changes seen in hypothyroidism are either related to the slow metabolism seen in this condition, or to the dermal accumulation of mucopolysaccharides which bind water in the tissue thus leading to the myxoedematous appearance typically seen in hypothyroidism (Bernhard et al, 1996). Myxoedema is most marked in the periorbital area (*Figure 6*) and the hands and is often insidious in development. There is non-pitting swelling and loss of the outer third of the eyebrows and the face lacks expressiveness. A drooping of the upper eyelid may

Figure 5. Longer-established pretibial myxoedema causes localized oedematous and thickened pretibial plaque(s) with a peau d'orange appearance.



occur secondary to decreased sympathetic stimulation. In contrast to the pretibial myxoedema seen in Graves' disease, the myxoedema of hypothyroidism is reversible after treatment with thyroid replacement.

The skin may have a yellowish tinge as a result of a combination of alterations in connective tissue of the dermis and the colour changes of carotenaemia. The latter is attributed to a hepatic defect in the conversion of beta-carotene to vitamin A; increased carotene is excreted in sweat and is retained by the stratum corneum, thus is usually most apparent on palms, soles and axillae. Sparing of the sclerae differentiates carotenaemia from jaundice if this is in doubt (Al-Jubouri et al, 1994).

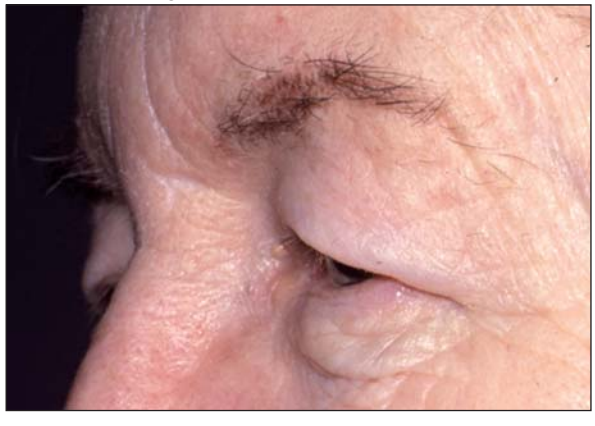
As a consequence of the slow metabolism the skin is generally cold and pale. Dry and rough hyperkeratotic areas may be seen and fine wrinkling may also occur; palmar hyperkeratosis is occasionally the presenting feature of hypothyroidism. Xanthomata may be present secondary to hyperlipidaemia. Capillary fragility, as a result of altered dermal support, may lead to easy bruising. The nails may be brittle, striated and grow slowly (Bernhard et al, 1996).

Scalp hair is coarse, brittle and dry, in part as a result of diminished sebum production. Diffuse hair loss may be a feature of the disease (*Figure 7*). Other associations with hypothyroidism are urticaria, pruritus, vitiligo and dermatitis herpetiformis. In chronic urticaria associated with thyroid antibodies and a euthyroid state, a trial of thyroxine replacement may resolve the symptoms (Grattan and Humphreys, 2007).

Parathyroid diseases

Skin changes and signs are not a prominent feature of parathyroid disease. Pruritus has been described related to hyperparathyroidism, but the most important dermatological aspect is when hyperparathyroidism occurs secondary to chronic renal failure, as it leads to subcutaneous calcification and potentially the severe necrotic ulceration of calcific uraemic arteriolopathy (calciphylaxis) (Walsh and Fairley, 1995).

Figure 6. Myxoedema of the periorbital area causing puffy eyelids; note the eyebrow thinning and attempt to disguise it using make up (same patient as* Figure 7*).



Hypoparathyroidism is associated with dry, scaly and hyperkeratotic skin. Nails may be brittle and ridged and develop transverse ridges. Chronic mucocutaneous candidiasis is frequently associated with hyperparathyroidism, in particular when it occurs as part of the polyglandular autoimmune syndrome (see below).

Pituitary dysfunction and the skin

Cutaneous signs in pituitary dysfunction relate to the glands and/or hormones involved and their effects on the skin.

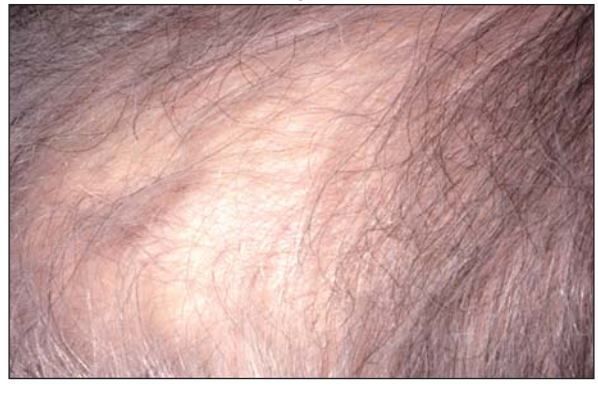
Acromegaly

Growth hormone causes an increase in serum levels of insulin-like growth factor-1, both of which stimulate the synthesis of collagen and glycosaminoglycan in the skin and skeleton (Freinkel, 1993). This leads to the typical features seen in acromegaly which include acral and soft tissue overgrowth, an enlarged jaw (macrognathia), thickened lower lip and eyelids. The skin is generally thickened and has a doughy feel with accentuated creases on the forehead and nasolabial fold, with prominence of the supraorbital ridge giving the patient coarse features and a sombre expression. Fingers may elongate and thicken. Numerous skin tags and seborrhoeic keratoses may be seen. Acanthosis nigricans, which is associated with insulin resistance, is found in around 10% of patients (Melmed, 1998). Hyperhidrosis and hyperpigmentation (as a result of an increase in melanocyte-stimulating hormone; MSH) can be found in around half the patients. Hair growth may be increased and some women may complain of hirsutism. The nails are wide and thickened and may grow fast.

Hypopituitarism

The physical and cutaneous signs in hypopituitarism are similar to those that occur with a primary deficiency of the affected gland. Thyroid-stimulating hormone (TSH) deficiency results in symptoms and signs of hypothyroidism. Adrenocorticotropic hormone (ACTH) deficiency results in adrenal insufficiency; however, whereas Addison's disease is characterized by hyperpigmentation (compensatory

Figure 7. Scalp hair in myxoedema may be sparse, coarse, brittle and dry, as here (same patient as in* Figure 6*).



ACTH secretion being accompanied by pituitary production of MSH, as described below), this is not the case when the cause is pituitary failure. Thus the presence or absence of hyperpigmentation aids in differentiating a pituitary *vs* an adrenal cause of adrenal failure.

Pallor of the skin with a slight yellowish tinge is a prominent feature, but mucous membranes retain their normal colour unless anaemia is present (Braverman, 1998). The skin is generally dry and soft, although the dryness is not as marked as in primary hypothyroidism, because of autonomous production of thyroid hormones by the thyroid. The face may be puffy and lacks expressiveness. Thinning of the skin and subcutaneous tissue around the eyes results in fine wrinkling, giving the patient a prematurely aged appearance (Geller and Braunstein, 2006).

Loss of secondary sexual hair occurs in all patients as a result of decreased gonadotrophin secretion, and scalp hair tends to be fine and dry. Sweating and sebaceous secretions are both decreased. Onycholysis and longitudinal ridging of the nails may also be noted (Lamberts et al, 1998).

Adrenal syndromes

The cutaneous signs and symptoms observed in patients with adrenal disease relate to the effects of corticosteroids or their deficiency.

Cushing syndrome and disease

This entity is defined as the constellation of clinical signs and symptoms resulting from chronic glucocorticoid excess. Cushing syndrome can be caused by pituitary hypersecretion of ACTH (Cushing disease), ectopic secretion of ACTH by non-pituitary tumours, adrenal hypersecretion of glucocorticoids, or exogenous administration of corticosteroids. The cutaneous manifestations are similar regardless of the underlying cause of glucocorticoid excess, although some additional effects mediated by androgens are found in patients with adrenal disease.

The striking and most apparent feature of glucocorticoid excess is the change in the appearance and body habitus. The most common feature is progressive centripetal obesity which can also involve the face, neck, trunk and the mesentery. Fat deposition caused by the effect of corticosteroid on fat metabolism appears in the cheeks, resulting in the 'moon facies' which is often accompanied by plethora of the cheeks. The deposition of fat in the dorsocervical area results in what is known as the 'buffalo hump'. Retro-orbital fat deposition may result in exophthalmos. The fat redistribution results in wasting of the extremities (Orth, 1998).

Corticosteroids inhibit epidermal cell division and decrease collagen synthesis (Shibli-Rahhal et al, 2006). This alteration in skin physiology results in skin atrophy, which is often prominent in chronic glucocorticoid excess. The skin is fragile and bruises easily.

An almost pathognomic sign of Cushing syndrome is the presence of broad (more than 1 cm) purple striae commonly seen on the abdomen and lower flanks. These violaceous striae can be distinguished clinically from those seen in obese and pregnant people, which are pink or silvery, less pigmented and narrower (Newell-Price et al, 2006). Hyperpigmentation can be seen and is dependent on both the duration and the degree of increase in ACTH secretion. It occurs most often in patients with ectopic ACTH syndrome, less often with pituitary hypersecretion and is not a feature of adrenal Cushing syndrome (Orth, 1997). Acanthosis nigricans can be found as a result of the insulin resistant state caused by hyperinsulinism.

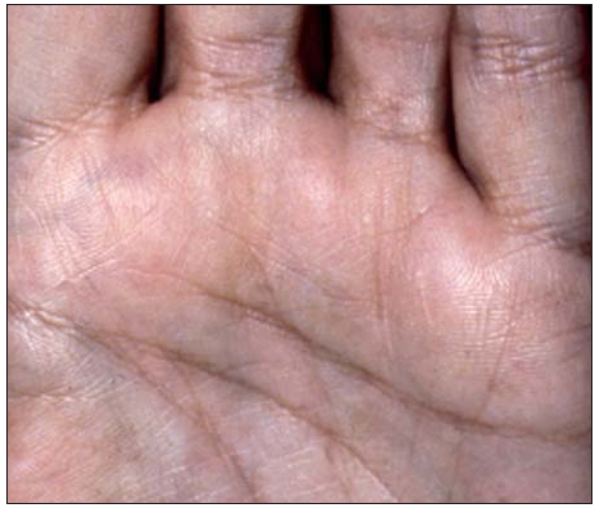
Concomitant excessive androgen secretion, a frequent feature in those in whom Cushing disease is caused by carcinoma of the adrenal glands, causes hirsutism, greasy skin, an acneiform eruption on the face, neck and shoulders, temporal baldness and signs of virilization (Yanovski and Cutler, 1994).

Adrenal insufficiency

The hallmark cutaneous change seen in patients with chronic primary adrenal insufficiency is hyperpigmentation. This occurs in over 90% of patients and is often the first sign of the disease (Ten et al, 2001). It is caused by increased melanin content in the skin as a result of the increase in MSH activity, as hypersecretion of the common precursor pro-opiomelanocortin causes overproduction of both ACTH and MSH. The hyperpigmentation is generalized but is most conspicuous in sun-exposed areas, palmar creases (*Figure 8*), mucosal surfaces and areas exposed to chronic pressure such as elbows and knees. Pigmentation in mucous membranes is often patchy rather than diffuse. Scars acquired after the onset of Addison's disease are permanently pigmented, unlike other areas of pigmentation which gradually improve with corticosteroid replacement.

Hair may darken and the nails may have linear pigmented streaks, called linear melanonychia. Decreased axillary and pubic hair are common in women, in whom androgen production primarily occurs in the adrenal glands.

Figure 8. Palmar crease hyperpigmentation in Addison's disease, a characteristic feature.



Vitiligo can occur in patients with autoimmune adrenal disease but not in those with other causes of adrenal insufficiency (Zelissen et al, 1995).

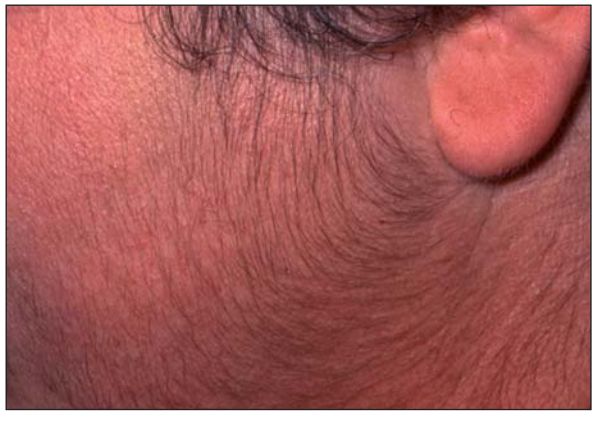
Hyperandrogenism

This is a term used to describe a state of excessive androgen production. The cutaneous and physical signs referred to here relate to polycystic ovarian syndrome (PCOS) which is the commonest cause of hyperandrogenism in females of reproductive age (Lowenstein, 2006). A precise definition for PCOS is lacking and some authors prefer to refer to it as 'functional ovarian hyperandrogenism'. It represents a complex phenotype with heterogeneous signs and symptoms that vary over time. Symptoms typically begin to manifest around menarche with oligomenorrhoea as the most common presenting complaint affecting nearly three-quarters of patients. Amenorrhoea is less prevalent, seen in around 30% of affected patients. Insulin resistance, dyslipidaemia, microvascular disease and hypertension are all prevalent in PCOS.

The cutaneous signs seen in PCOS are related to hyperandrogenism and may include acne, hirsutism (*Figure 9*) and a greasy skin. Hirsutism is caused by the transformation of vellus hairs into terminal hairs under the influence of androgen, and presents clinically with excessive hair on 'androgenic areas' such as the face, chest and abdomen (Schmidt et al, 1986). This should be distinguished from hypertrichosis, where hair growth is not mediated by androgens and hairs are not distributed in an androgen-sensitive pattern. Treatment options for hirsutism, except for treatment of the underlying condition, are through laser therapy or a relatively new topical cream named eflornithine (Vaniqa, Shire Pharmaceuticals, Basingstoke, UK).

An important issue in patients with PCOS is that a proportion of women (estimated at around 40%) may not have androgenic symptoms on presentation, despite ultrasound evidence of PCOS (Falsetti et al, 2002). However, women who present with a more complete phenotype tend to present at an earlier age with evidence of high serum androgen levels.

Figure 9. Hirsutism – increased hair growth in a male pattern. In this case, the cause was an androgenic drug rather than of internal endocrine origin.



Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN) refers to a group of inherited disorders (autosomal dominant) marked by the presence of neoplasia or hyperplasia in two or more endocrine organs, often in association with mucocutaneous findings.

MEN1 is an autosomal dominant disorder in which tumours characteristically develop in the parathyroid glands, pancreatic islet cells and anterior pituitary. Carcinoids and tumours of the thyroid and adrenal glands may also be seen.

Cutaneous findings include angiofibromas (previously only thought to be related to tuberous sclerosis), collagenomas, lipomas, café-au-lait macules and gingival papules. Angiofibromas in patients with MEN1 tend to be smaller and fewer in number than those seen in severely affected patients with tuberous sclerosis. They are also often found on the upper lip and the vermilion border of the lip, areas that tend to be spared in patients with tuberous sclerosis (Darling et al, 1997).

MEN2A is characterized by the presence of medullary thyroid carcinoma, hyperparathyroidism and phaeochromocytoma. It typically lacks the cutaneous findings of mucosal neuromas and lipomas of MEN1 and MEN2B (Kousseff, 1995). An interesting cutaneous sign in MEN2A is a symmetrical pruritic papular eruption called macular amyloidosis, which has a rippled appearance and muddy brown colour. This presents typically with pruritus in the inter-scapular area (T2–T6), with the amyloid deposition thought to be secondary to repeated scratching (Weyers et al, 1997).

MEN2B is also associated with medullary thyroid carcinoma and phaeochromocytoma; however, the medullary thyroid carcinoma presents at an earlier age and runs often an aggressive course. Unlike MEN2A and MEN1, hyperparathyroidism is a much less common feature (Holloway and Flowers, 1995). MEN2B is associated with mucosal neuromas which present at a very early age and manifest as asymptomatic, soft, flesh-coloured papules or nodules. They cause a characteristic facial appearance with soft, lumpy, protuberant lips and everted and thickened eyelids. Neuromas typically affect mucosal surfaces, especially the anterior border of the tongue and the buccal mucosa inside the commissures of the lips; gingival and pharyngeal surfaces may also be affected. Patients with MEN2B may have other physical characters such as a tall and slender stature with muscle weakness and musculoskeletal anomalies. These are often referred to as 'marfanoid features'.

Autoimmune polyglandular syndrome type 1

Autoimmune polyglandular syndrome type 1 (APS1) is a rare recessively inherited disorder which is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. It is caused by mutations in the autoimmune regulator gene, and is characterized by autoimmune destruction of endocrine tissues, chronic

mucocutaneous candidiasis, and dystrophy of the dental enamel and nails (Collins et al, 2006).

Mucocutaneous candidiasis is frequently the first manifestation of APS1 and occurs at an early age. The severity can range from intermittent angular cheilitis to widespread inflammatory, hyperplastic and leucoplakia-like variants associated with carcinoma of the oral mucosa. Candidal peri-anal dermatitis and vulvovaginitis are also common manifestations (Perheentupa, 2002), as is chronic candidal paronychia. Chronic hypoparathyroidism is the commonest associated endocrine dysfunction, affecting nearly 90% of patients (Myhre et al, 2001). Autoimmune adrenal insufficiency presents usually in the teenage years in APS1 patients.

The 'ectodermal dystrophy' in APS1 includes abnormalities of ectodermal-derived tissues. Ectodermal structures encompass hair, teeth, nails and sweat glands. Ectodermal changes observed in APS1 include enamel hypoplasia of permanent teeth, pitted nail dystrophy and calcium salt deposits in the tympanic membrane (Perheentupa, 2002).

Alopecia areata affects nearly a quarter of patients with APS1 and vitiligo affects up to 10%. The difference between the vitiligo associated with APS1 and other autoimmune conditions is the presence of complement-fixing melanocyte antibodies (Howanitz et al, 1981).

APS types 2 and 3 have few dermatological manifestations and are therefore not discussed in this article.

Conclusions

Cutaneous signs and symptoms can be a valuable clue to an underlying endocrine disorder and may prompt further investigations to establish a previously undiagnosed condition. Certain features such as alopecia areata and vitiligo occur in the setting of autoimmune diseases, some other features (such as pretibial myxoedema) may be strongly associated with a particular endocrinopathy, and others relate directly to altered endocrine function. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Cutaneous features may be the presenting sign of endocrine disease.
- The 'classical' skin sign associated with thyrotoxicosis is pretibial myxoedema but it is an autoimmune phenomenon, and is not associated with the degree of hyperthyroidism.
- Disorders of pituitary dysfunction are often insidious in onset, and the skin signs are relatively non-specific.
- Polycystic ovarian disease is part of a complex series of endocrine and metabolic conditions and is best evaluated by an endrocrinologist.