DECEMBER 2018 VOL 3 NO 1

A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

Reprints in Dermatology

Facial pigmentation: common causes and how to manage

Nonmelanoma skin cancer – symptoms, signs and treatment

Pruritus: understanding the causes, soothing the itch

Hirsutism: common and a cause of significant anxiety

Dermatological emergencies: how to recognise them and what to do

Diagnosing basal cell carcinoma. What is the role for dermoscopy?

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A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR-IN-CHIEF, DERMATOLOGY COLLECTION

In this fifth issue of *Dermatology Collection* you will find more articles that we consider among the most important published in *Medicine Today* in recent years. Interest in cosmetic dermatology continues to rise and although much of this is focussed on reversing the effect of solar damage, pigmentation of the facial skin is equally problematic. It is very much a female problem, associated with pregnancy and hormonal medications. Hirsutism is another popular subject in the cosmetic area. It is common and anxiety provoking. What can be done?

While on the subject of solar damage, we must be ever mindful of nonmelanoma skin cancer. Issues related to sun damage including skin cancer occupy more than half the practising time of dermatologists. GPs should be up to speed on how to identify and treat and when to refer.

Do you own a dermatoscope? And if so do you think it aids diagnosis of non-melanoma as well as melanoma skin cancer? Read about how it can be used to spot a basal cell carcinoma.

The itchy patient who does not have an obvious rash can be a conundrum and the causes are many: from trivial to serious. Generalised itch should always prompt a search for a cause that can be treated but when none is apparent what to do? Read this article.

Finally, would you be able to identify a problem that is evolving into a dermatological emergency? Early identification of severe drug reactions such as toxic epidermal necrolysis and DRESS syndrome and the skin signs of severe infections such as meningococcal disease and necrotising fasciitis could save your patient's life.

Gayle Fischer MB BS, MD, FACD
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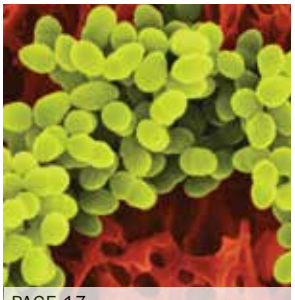
FEATURE ARTICLES PEER REVIEWED



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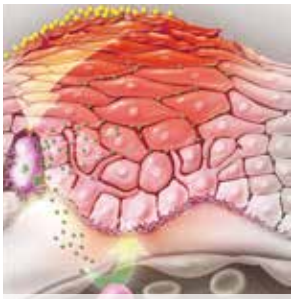

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Facial pigmentation

Common causes and how to manage

THOMAS STEWART BBioMedSc(Hons), MB BS
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Facial pigmentation may be due to a generalised process but most often is localised to the face. Melasma and actinic damage pigmentation are common and tend to be bilaterally distributed and slowly progressive. Irregularly shaped isolated lesions should be viewed with more caution, and biopsy may be required. Treatments include topical and oral medications, peels, intense pulsed light therapy and laser treatment.

KEY POINTS

- Diagnosis of the type of facial pigmentation can be made on clinical grounds in most cases.
- Facial pigmentation is a cause of considerable psychosocial distress for many patients.
- Melasma, the most common facial hyperpigmentation worldwide, is most prevalent in women and people with constitutionally darker skin. It occurs in about 25% of women who are pregnant.
- Hydroquinone-based skin-bleaching preparations remain the gold standard for the treatment of melasma.
- Many patients with facial pigmentation can be managed in the general practice setting but referral for specialist management may be required for refractory cases.

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About 14% of GP consultations are for the management of skin diseases.[1] Pigmentary disorders represent a large proportion of diagnoses in dermatological populations.[2] Melasma, the most common facial pigmentation worldwide, may account for up to 10% of new dermatology referrals,[3] and GPs therefore need to be able to recognise it.

Skin pigmentation normally varies according to racial origin and the amount of sun exposure, and pigmentation disorders are often more troublesome in constitutionally darker skin ('skin of colour'). Facial hyperpigmentation manifests as either localised to the face or part of diffuse disease. Pigmentation localised to the face usually represents a benign condition, although it may be the cause of significant psychological distress because of its high visibility and sociocultural implications (regardless of the nature of the problem, people generally desire uniformity of skin colour). Increased facial pigment can, however, herald underlying systemic disease or malignancy.

Melanin contributes to racial and phenotypic appearance, but also has important roles in protecting from ultraviolet (UV) radiation damage and scavenging of toxins. Several pigment intensifiers have been identified, the most notable of which are UV radiation and, in the setting of melasma, oestrogen and progesterone. The process of pigment intensification is thought to involve an increase in pigment production and/or melanocyte numbers, usually mediated, at least in part, by the enzyme tyrosinase. Several established treatments target this enzyme, although improved understanding of melanogenesis in recent times has seen the emergence of several novel treatment options.

This article reviews the causes of hyperpigmentation and discusses treatment options for facial pigmentation that can be used in general practice.

1. COMMON FACIAL PIGMENTATIONS

- Melasma
- Postinflammatory
- Sun-damaged skin
- Photosensitivity
  - connective tissue disease
  - drugs
- Naevi
  - Ota
  - Hori
- Fixed macules
  - lentigines (solar and other)
  - seborrhoeic keratoses

Generalised versus localised hyperpigmentation

Generalised hyperpigmentation may be drug-induced, nutrition-related, have endocrine or metabolic causes or occur after inflammation. It can also occur with malignancies or have genetic causes. Limited facial pigmentation, the most common presentation of localised hyperpigmentation, typically is part of several common and largely benign skin conditions. Solar lentigines (freckles), melasma and postinflammatory hyperpigmentation are some of the more common facial pigmentations (Box 1).

Generalised hyperpigmentation

The causes of generalised hyperpigmentation are listed in Box 2. Drug-induced hyperpigmentation may occur with use of minocycline and hormonal contraceptives. Nutrition-related hyperpigmentation may be seen with deficiencies of vitamin B_{12} or folate associated with inadequate dietary intake or gastrointestinal malabsorptive disease (e.g. Crohn's disease), and alcoholism is known to deplete folic acid stores. The endocrinopathies and metabolic disorders most commonly associated with systemic hyperpigmentation are Addison's disease, haemochromatosis and hyperthyroidism; although patients may have associated symptoms or a past medical or family history suggestive of these conditions, pigment changes are often among their first signs. Postinflammatory hyperpigmentation is not a common cause of 'generalised' hyperpigmentation. Far less frequently, occult malignancy such as adrenocorticotrophic hormone (ACTH)-producing lung carcinomas and metastatic melanomas may cause generalised hyperpigmentation.

Symmetrical distribution is a hallmark of hyperpigmentation caused by systemic disease. In patients with Addison's disease, hyperpigmentation is most intense on light-exposed areas, in skin creases and flexures, at sites of friction and on mucous membranes; other associated features of this disease are loss of androgen-stimulated hair, such as pubic and underarm hair. Patients with hyperthyroidism may display the Addisonian pattern of pigmentation but involvement of mucous membranes is uncommon and darkening of nipples and genital skin is less striking; the eyelids are occasionally pigmented and some patients show localised 'melasmal' rather than diffuse pigmentation.

2. CAUSES OF GENERALISED HYPERPIGMENTATION*

Drug and toxins
- Analgesics (NSAIDs)
- Antiarrhythmics (amiodarone)
- Antibiotics (tetracyclines [e.g. minocycline], co-trimoxazole)
- Anticonvulsants (phenytoin)
- Antidepressants (imipramine, desipramine)
- Antimalarial drugs (hydroxychloroquine, chloroquine)
- Cytotoxics (bleomycin, busulfan, cyclophosphamide, 5-fluorouracil)
- Heavy metals (arsenic, bismuth, gold, mercury, silver)
- Hormones (oestrogen, progesterone, adrenocorticotrophic hormone)
- Psychotropics (phenothiazines [e.g. chlorpromazine])

Postinflammatory
- Allergic dermatitis
- Autoimmune disorders such as systemic lupus erythematosus/scleroderma
- Inflammatory dermatoses such as acne, psoriasis
- Medication use (e.g. hydroquinone, tretinoin)
- Postinfective (e.g. tuberculosis, malaria, subacute bacterial endocarditis, HIV)
- Ultraviolet light (most frequent postinflammatory cause)

Nutritional
- Kwashiorkor
- Pellagra
- Scurvy
- Vitamin B_{12}/folate deficiency (most frequent nutritional cause)

Endocrine
- Pregnancy
- Addison's/Cushing's disease (one of the most frequent endocrine causes)
- Phaeochromocytoma
- Carcinoid syndrome
- Hyperthyroidism (one of the most frequent endocrine causes)
- Acanthosis nigricans

Metabolic
- Chronic renal failure
- Chronic liver disease
- Haemochromatosis (most frequent metabolic cause)
- Porphyria

Malignancy
- Melanoma (rarely)
- Small cell lung carcinoma (rarely)

Genetic
- Familial (e.g. periorbital hyperpigmentation)
- Chromosomal (e.g. xeroderma pigmentosum; dyskeratosis congenital)
- Racial (e.g. naevi of Ota, Ito, Hori)

* Causes listed in alphabetical order.

Patients with haemochromatosis have slate grey or brownish-bronze skin, mostly in sun-exposed areas and particularly on the face; other associated features include skin and nail changes such as hair loss and koilonychia (twisted nail plate).

Assessing localised hyperpigmentation

Diagnosis of the various facial pigmentations can be made on clinical grounds in most cases. Differential features can be identified using the following diagnostic schematic:

- skin type
- history
  - onset and duration
  - comorbidities
  - medication use
- examination
  - morphology
  - distribution.

Fitzpatrick skin type

Solar lentigines and other hyperpigmentations due to actinic (solar) damage are seen predominantly in people with Fitzpatrick skin types I to III, the predominant skin types in Australia, whereas melasma and postinflammatory hyperpigmentation are seen mainly in people of skin types III to VI (Table 1; Figures 1 and 2).[4,5]

Onset and duration

Naevus of Ota (pigmented dermal 'birthmark') exhibits a bimodal onset, presenting either at birth or puberty, whereas solar lentigines appear during childhood (Figure 3). Melasma onset spans the reproductive years from 20 to 40 years of age. Cutaneous systemic lupus erythematosus and naevus of Hori (also known as acquired bilateral naevus of Ota) similarly have broad spectrums of onset, appearing between the ages of 20 and 50 years, and 20 and 70 years, respectively. Actinic damage and seborrhoeic keratoses become apparent during the fourth decade of life and usually increase in number with age.

TABLE 1. FITZPATRICK SKIN TYPES

Skin type	Skin/hair/eye colour; example ethnicity	Characteristics
I	White; very fair, red or blonde hair; blue eyes; freckles; Celtic	Always burns, never tans
II	White; fair, red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair colour (common)	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin; Asian	Rarely burns, tans with ease
V	Dark brown; mid-eastern skin types; East Indian	Very rarely burns, tans easily
VI	Black; Aboriginal and Torres Strait Islander	Never burns, tans very easily

Comorbidities

A specific history should be sought regarding endocrinological and metabolic conditions associated with skin hyperpigmentation (Table 1).

Medication use

Hormonal contraceptive use commonly triggers melasma in women. Minocycline and phenytoin are other recognised causes of facial hyperpigmentation, and other parts of the body and mucosa may also be involved.[6]

Specific lesional characteristics such as colour (e.g. brown, grey, blue-grey) and distribution depend on the causative agent. In the case of minocycline-induced pigmentation, 'prototype' minocycline degradation products are chelated with iron taken up by macrophages and pigmented drug metabolites deposited in the skin. Minocycline also increases levels of melanin in epidermal and dermal macrophages. Pigment depth varies dependent on the

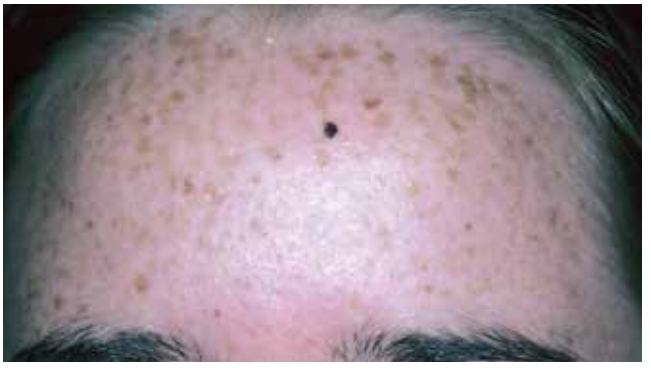

Figure 1. Freckles and an ink spot lentigo (also known as reticulated lentigo; occurs after sunburn in very fair skinned people).

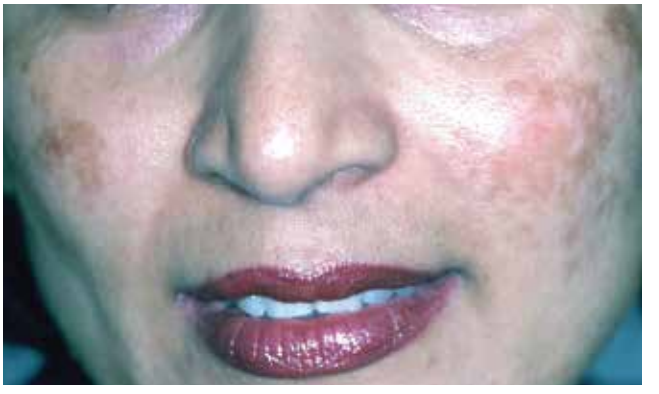

Figure 2. Melasma in type V skin.

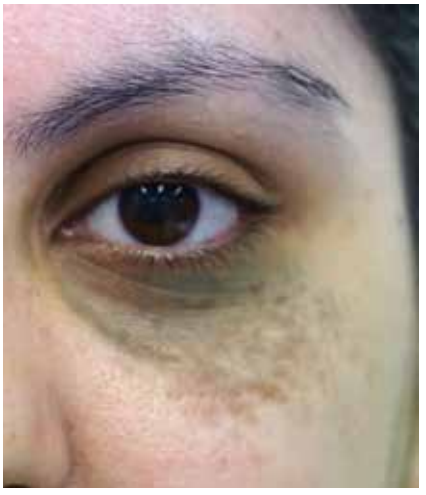

Figure 3. Naevus of Ota.

drug, dose, duration of use and patient factors; biopsy may be useful for assessment.

Morphology

Facial pigmentation diseases may have macules varying in pigment intensity. Lentigines and melasma characteristically produce well-circumscribed lesions, whereas actinic damage and solar lentigines typically give a blotchy or speckled appearance (Figures 1 and 2). Seborrhoeic keratoses can sometimes resemble flat lentigines, but are distinguished by a characteristic waxy/scaly veneer. Naevi of Ota lesions sometimes coalesce forming larger patches (Figure 3).

Melanomas such as lentigo maligna are unilateral irregularly shaped lesions, often variegated in colour and architecture and best appreciated on dermoscopy (Figure 4). Timeline to invasion is variable and even invasive thin melanomas may evolve slowly.[7] Lesions diagnosed as a melanoma or considered a potential melanoma should always be biopsied or referred for confocal analysis.

Distribution

Lentigines (all types), melasma, photosensitive reactions and actinic elastosis are most typically found bilaterally on sun-exposed areas of the face, particularly the forehead and malar regions. Naevi of Ota are distributed unilaterally (rarely bilaterally) in the skin innervated by the first two branches of the trigeminal nerve, whereas naevi of Hori are bilaterally distributed. Naevi of Ota are most commonly found in people of Asian origin, and are uncommon in Caucasians.

Initial investigations for hyperpigmentation

Tests used in the initial investigation of generalised and facial hyperpigmentation are listed in Table 2.

Melasma

Melasma, often referred to as 'chloasma' or the 'mask of pregnancy,' is the most common facial pigmentation presentation worldwide, with a reported prevalence of about 6 to 9% in a Brazilian population-based study.[8] Women are affected nine times more often than men, and it occurs in about 25% of pregnant women. People with constitutionally darker skin (i.e. Fitzpatrick skin types III to VI) are affected more than people with light skin.

Clinically, it is an acquired progressive, nonscaling hypermelanosis of sun-exposed skin, chiefly affecting the face, more specifically the forehead, cheeks and chin regions.

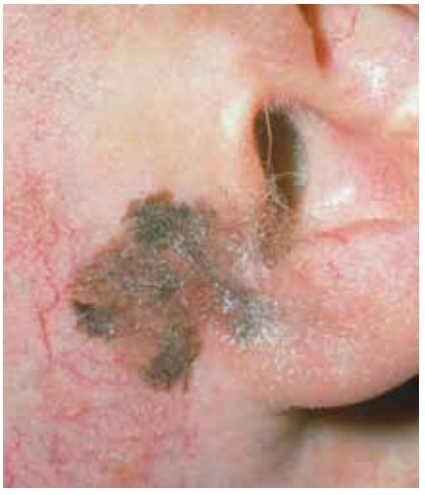

Figure 4. Lentigo maligna (preauricular region).

The pathophysiology of melasma is uncertain but an interplay of multiple inciting and exacerbating factors has been proposed. Genetic predisposition is suggested by a high reported incidence in family members in several studies. UV radiation, oestrogen and progesterone induce melanocyte proliferation, migration and melanogenesis independently and through upregulation of tyrosinase activity (Figure 5).[9] Hydroquinone, the mainstay of systemic treatment for melasma, and several other skin-lightening agents target tyrosinase primarily.

TABLE 2. INITIAL INVESTIGATIONS FOR HYPERPIGMENTATION

Cohort	Clinical suspicion	Indicated tests
Generalised hyperpigmentation without obvious aetiology	Nutritional cause	Measurement of levels of serum vitamin B_{12} and folic acid
	Endocrine cause	Measurement of levels of serum electrolytes, thyroid stimulating hormone, cortisol, adrenocorticotrophic hormone and, possibly, urinary catecholamines
	Metabolic cause	Serum liver and kidney function tests, iron studies
Localised facial hyperpigmentation where diagnosis is uncertain	Melanoma e.g. lentigo maligna	Punch biopsy, or excisional biopsy where possible
	Postinflammatory e.g. systemic lupus erythematosus	Examination for primary cutaneous inflammatory event such as drug reaction, connective tissue disease

Melasma is a chronic condition and recurrence is common, especially after re-exposure to sunlight. Intermittent, long-term topical therapy and strict sun protection are usually necessary to remain in remission. In some patients, areas of hyperpigmentation may never completely resolve.

Treatment of facial pigmentation

The management of the more common facial pigmentation disorders of melasma, lentigines, actinic damage and naevi are considered here. Although solar lentigines are a more common pigmentary problem than melasma in Australia, they are relatively straightforward to treat and so discussion will focus on the treatment of melasma, which remains a therapeutic challenge. All patients with melasma should be counselled about the condition's natural history and the management goals – 'control rather than cure'.

Treatment options for generalised pigmentation are diverse and aimed at managing its multiple causes, as previously listed, once the cause has been confirmed by investigation.

General measures

The first step in managing patients with skin pigmentation is to reduce and/or eliminate any triggers, such as cessation of the hormonal contraceptive in women with melasma.

All patients with facial pigmentation should be instructed to apply a broad-spectrum sunscreen (at least SPF 30+) containing a physical blocking agent (e.g. zinc oxide), backed by other sun-protection measures including wearing a hat and long-sleeved clothing. The appropriate reapplication interval, which may be up to two hourly, should be guided by the risk pertaining to sun exposure and the nature and level of outdoor activity.

Cosmetic camouflage provides photoprotection as well as aiding cosmesis; a few commercially available products are listed in Box 3. When camouflage is not worn, sunscreen should be used.

Topical therapies

Hydroquinone

The main therapy for melasma is the skin-lightening agent hydroquinone. This benzene metabolite exerts multimodal effects through competitive inhibition of tyrosinase-mediated melanin production, degradation of melanosomes and inhibition of nucleic acid synthesis. It is used in varying concentrations, with 4% appearing to be most advantageous. Improvement is usually evident after five to seven weeks, although treatment can be safely continued for up to 12 months.[10] Hydroquinone is most commonly used, and potentially best utilised, in combination with other agents including retinoids (e.g. tretinoin) and corticosteroids (e.g. fluocinolone) to reduce side effects of each individual ingredient.[10]

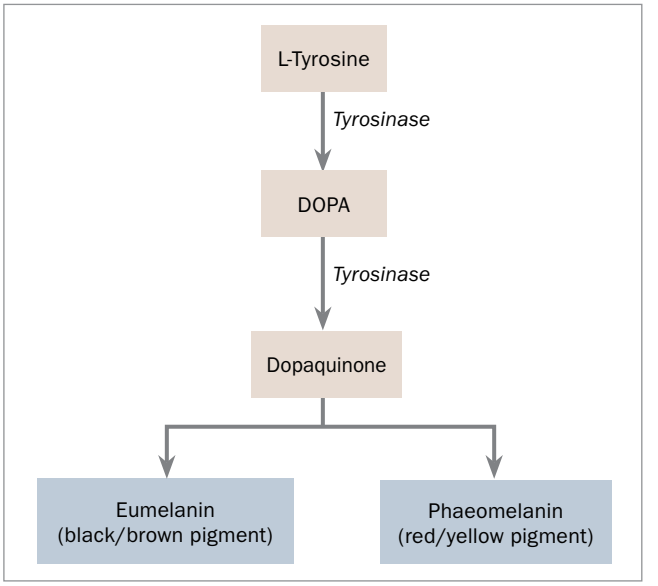

Figure 5. Tyrosinase-mediated reactions in the melanin production pathway.

Side effects reported as mild and transient include irritation, erythema, irritant or contact dermatitis and halo hypochromia. Rarer longer-term reactions include milia and postinflammatory hyperpigmentation. Initial concerns about the breakdown products of hydroquinone causing bone marrow toxicity and anti-apoptotic effects are unsupported by more recent clinical research.[11]

Retinoids

The acne treatments tretinoin and adapalene have been shown to reduce epidermal pigmentation in melasma as monotherapy (off-label use).[12,13] Adapalene is the first choice because it shares similar efficacy with its peers but is generally better tolerated.[13] Tazarotene may offer slightly superior results in postinflammatory hyperpigmentation (e.g. acne).[14] Unfortunately, retinoids can take up to 24 weeks to show effects so are best used in combination with other agents that have quicker effects (i.e. hydroquinone and fluocinolone). Retinoid products should be avoided in pregnancy because of the potential for teratogenicity.

Azelaic acid

Azelaic acid monotherapy has proven value in treating melasma (off-label use) and postinflammatory hyperpigmentation such as that caused by acne. In a randomised, double-blind study, 20% azelaic acid was shown to be as effective as hydroquinone 4% in the treatment of melasma, but without its side effects.[15] In the event of adverse effects, patients might be instructed to reduce dosing intervals and/or cease use temporarily, reintroducing when the effects have resolved.

3. EXAMPLES OF COMMERCIALLY AVAILABLE COSMETIC CAMOUFLAGE PRODUCT BRANDS

- Dermablend (Vichy Laboratories)
- CM Beauty (formerly Covermark)
- Microskin (Microskin International Pty Ltd, Brisbane)
- Cover FX (Cover FX skin care)

Ascorbic acid

Topical ascorbic acid (vitamin C) is modestly effective as monotherapy for melasma but much less so than hydroquinone. Ascorbic acid has a superior safety profile however, and therefore may be of use in people who cannot tolerate hydroquinone.[16] It is available in many over-the-counter cosmeceuticals, both as monotherapy and in combination with other agents.

Combination therapy

Retinoid, hydroquinone and fluocinolone combination therapy produces the best and longest-lasting results of any commercially available topical agents for the treatment of melasma.[17] A combination skin-bleaching product is marketed as Tri-Luma (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) in the US but is not approved for use in Australia. Safety concerns were exaggerated in the early stages of its use, curbing interest.[18] Tri-Luma can be accessed on private prescription through compounding chemists.

Tranexamic acid

Tranexamic acid (TXA) has been reported as a promising potential treatment for melasma. It is thought to inhibit the plasminogen-plasmin system, interfering with the keratinocyte-melanocyte interaction.

TXA is being used in an oral form as limited duration therapy by some dermatologists in Australia for melasma that has not responded to topical agents (off-label use).[10] The most commonly reported side effects are headaches, GI upset and hypomenorrhoea. Rare instances of thromboembolism, pulmonary embolus and myocardial infarction advocate for a cautious approach in people with hypercoagulable states (e.g. smokers, those who are obese, those with a past history of thromboembolic disease) and those with comorbidities (e.g. hypertension) and of advanced age.[19] With future examination, it may become part of the GP's armamentarium for treating melasma but at this stage consideration warrants referral to a dermatologist.

'The main therapy for melasma is the skin-lightening agent hydroquinone.'

Physical therapies

Chemical peels

Chemical peels have variable success in reducing skin pigmentation and multiple treatments are usually required to achieve modest results. They are best used in combination with topical agents such as hydroquinone 4%.

Low concentrations of alpha-hydroxy acids such as glycolic, lactic and salicylic are most commonly used. Glycolic acid (20 to 30%) may be best for solar damage hyperpigmentation and people with types I or II skin.[20] Salicylic acid (20 to 30%) has been shown to be particularly beneficial for melasma and postinflammatory hyperpigmentation in patients with dark skin.[21] Patients must be forewarned about the risks of erythema, irritation, burning and, less commonly, postinflammatory hyperpigmentation and scarring.

Specialist referral is recommended for medium and deep chemical peels like trichloroacetic acid and phenol, respectively.

Dermabrasion

Dermabrasion is not popular as a treatment for facial pigmentation due to long downtimes and poor results.

Light therapies

Phototherapy for skin disorders carries an inherent risk of postinflammatory hyperpigmentation, and light and lasers should be used with extreme caution. Patients must be well versed in the risks. A test patch is recommended prior to initiation of treatment, especially in patients with types IV, V or VI skin. Lasers and energy devices are second-line treatment and only considered when topical therapies have not been suitably effective. In Australia, GPs, specialists, skin clinics and beauticians perform light treatments.

Intense pulsed light therapy. Intense pulsed light (IPL) technology is replacing laser as the standard first-line treatment in photodamage. This transition is credited to improved efficacy coupled with comparatively less downtime. Lentigines are among the many examples of pigmented lesions that have been successfully treated. Concomitant use of a Nd:YAG (neodymium-doped yttrium aluminium garnet) laser provides additional benefit with no additional downtime.[22]

IPL has also been used adjunctively with varied success in melasma; trials have reported almost universal recurrence however, perhaps directing best use at disease refractory to topical therapy alone.[23] Broadband light (BBL), which utilises a spectrum of nonablative and visible light, has shown similar benefits in photodamage, particularly for lentigines and epidermal dyspigmentation. Its effects may be augmented when used in combination with a Er:YAG (erbium-doped yttrium aluminum garnet) laser.[24]

Fractional photothermolysis. Er:YAG and carbon dioxide (CO_2) fractional lasers (the laser beam is divided into thousands of microscopic treatment zones that target a fraction of the skin at a time) are effective for actinic damage and lentigines but should be considered second line, Er:YAG for superficial or mild damage and CO_2 for deeper photodamage.[25]

Fractional lasers are approved in some countries (e.g. the US) for the treatment of melasma but are not routinely used

because any short-term improvement is outweighed by the risk of causing other pigment problems.

Other. Q-switched lasers and combined Er:YAG/CO_2 lasers have either never shown benefit or have been associated with unsatisfactory adverse effects or superseded by more efficacious and/or practical treatments.

Conclusion

Facial pigmentation may be due to a generalised process but most often is localised to the face. The common melasma and actinic damage pigmentations tend to have a bilateral distribution and be slowly progressive. Irregularly shaped isolated lesions should be viewed with more caution, and biopsy may be required to exclude melanoma. Treatments include topical and oral medications and physical therapies such as peels, IPL therapy and lasers. MT

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Nonmelanoma skin cancer

Symptoms, signs and treatment

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GPs are at the forefront of the detection and early management of nonmelanoma skin cancers, which are the most common skin cancers encountered in general practice.

KEY POINTS

- Australia has one of the highest rates of skin cancer in the world.
- GPs play a crucial role in the detection and early management of nonmelanoma skin cancer.
- Actinic keratoses can develop into squamous cell carcinomas.
- Squamous cell carcinomas can metastasise and lesions with histological margins less than 1mm require further treatment.
- Basal cell carcinomas are the most common nonmelanoma skin cancer in Australia; their treatment is determined by site and subtype.

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Australia has one of the highest rates of skin cancer in the world, with nonmelanoma skin cancers (NMSCs) the most common types encountered. Cancer registries do not routinely report NMSC, but the latest age-standardised incidence rates (from 2002) were estimated to be 884 per 100,000 people for basal cell carcinoma (BCC) and 387 per 100,000 for squamous cell carcinoma (SCC). These rates are expected to be increasing.[1] This translates to an estimated cost to Medicare of more than $700 million annually.[2]

GPs are at the forefront of managing this burden. Skin conditions account for 15.9% of GP consultations, and skin cancers are the most common reason for specialist referral.[3] This high consultation rate also presents GPs with the opportunity to educate patients on sun-safe behaviour and to detect skin cancers at the earliest opportunity. Patient education should include information on ultraviolet (UV) light exposure risks and sun-protection measures.

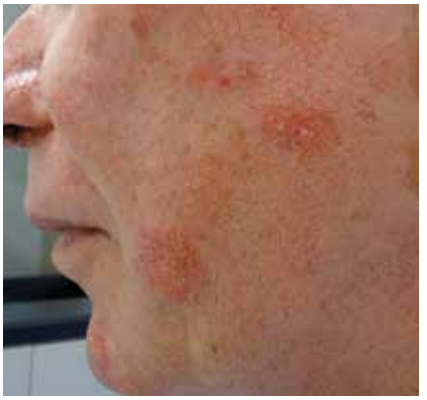
This article summarises the presentation and treatment of actinic keratosis (AK), which is the most common type of precancerous skin lesion, and the two most common types of NMSC – BCC and SCC.

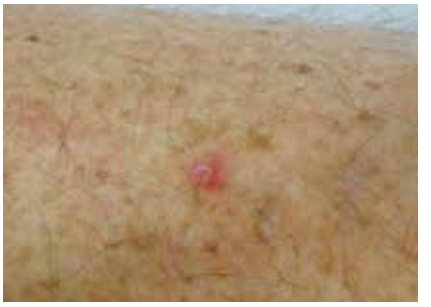
Actinic keratosis

Presentation and diagnosis

AK, also known as solar keratosis, is one of the most common lesions GPs encounter. AKs are precancerous lesions that are often found on sun-exposed areas, such as the face, scalp, ears and back of the hands (Figures 1a and b). AK and SCC are distinguishable by the extent of keratinocyte atypia; in AK, it is confined to the lower portion of the epidermis, but in SCC it occupies the entire epidermis and infiltrates through to the dermis. The reported rate of development from AK to SCC varies widely, between 0.025% and 16%.[4]

AK has varied clinical presentations, with a lesion classically





Figures 1a and b. Actinic keratosis on the left cheek (a, left) and on the forearm (b, right).

described as a scaly macule or papule on an erythematous base that is 3 to 6 mm in diameter, often with rough yellow or white scale. However, AK can also present as hyperkeratotic, pigmented, lichenoid or atrophic lesions. The lesions are often asymptomatic but may sting or itch.

In addition to the concern about its possible progression to SCC, the clinical significance of AK is that the presence of multiple lesions is an indication of significant UV light exposure. This exposure is a risk factor for other nonmelanoma (and indeed melanoma) skin cancers, which should be considered during a patient's consultation and treatment. A full skin check should be regularly undertaken for patients with multiple AK lesions.

The diagnosis of AK is predominantly clinical. The use of palpation is particularly of benefit because of the rough nature of the lesions. A biopsy should be considered if there is concern that the lesion may be an early SCC. Hallmark signs of concern include tenderness, bleeding, inflammation and thickness of the lesion.

Treatment

Treatment of AK may comprise localised treatment or field therapy. To determine the most appropriate treatment, consider the number of lesions, their size and location, and patient factors such as age and compliance with therapy. Lesions may spontaneously regress, especially if strict sun-protection measures are followed, but the clinical course is nevertheless difficult to predict.

Liquid nitrogen cryotherapy is usually the first-line localised treatment for AK. The application of liquid nitrogen (stored at -196°C) to the affected area, which causes superficial cellular damage, can be performed using a cryospray or cryoprobe device. The duration of therapy varies depending on lesion size and location, but a freeze of about three to five seconds is usually recommended.[5] Other lesions, such as seborrhoeic keratoses and superficial BCCs, can also be treated with cryotherapy, but may require longer freeze times due to factors such as the thickness of the lesion. Curettage and shave treatments can also be considered for AK, although these are often reserved for larger and thicker lesions.

Field therapies should be considered for areas that contain multiple AKs. The main field therapies are fluorouracil 5% cream (5-fluorouracil), imiquimod cream, ingenol mebutate gel, photodynamic therapy and diclofenac sodium gel (Table).[6] As these therapies work by inducing an inflammatory reaction, including redness, soreness and crusting, counselling patients, including showing them pictures of expected reactions, is recommended before starting therapy.

Squamous cell carcinoma

Presentation and diagnosis

SCC is the second most common skin cancer in Australia, behind BCC (Figures 2a and b). It can arise de novo, develop from AK or be associated with infection (oncogenic subtypes of human papillomavirus), sites of chronic inflammation or previous trauma (Figure 3). The two main risk factors for SCC are cumulative UV light exposure, which damages the keratinocyte DNA and impairs the immune system, and Fitzpatrick skin type, which alters susceptibility to UV effects due to the level of melanin present (types I to III are the most susceptible). The primary concern with SCC is its ability to metastasise, which accounts for about 20% of deaths from skin cancer.[7]

SCCs can be described across a spectrum that starts with in situ SCC (Bowen's disease), then further defined using the TNM (tumour, nodal, metastasis) staging system. Clinically, Bowen's disease presents as an erythematous patch or plaque with scale. It can also be pigmented. The histopathological definition of Bowen's disease is full-thickness epidermal keratinocyte atypia. Once there is involvement of the dermis, the lesion has become an invasive SCC. Without treatment, Bowen's disease progresses to invasive SCC in 2 to 5% of cases. Invasive SCC presents as an erythematous, keratotic papule or nodule, which is often tender.

There is debate about the inclusion of keratoacanthoma in the SCC spectrum, but guidelines from the Cancer Council Australia state that it is likely a form of SCC.[1] Keratoacanthomas have traditionally been thought of as relatively benign squamoproliferative lesions that do not have the ability to metastasise. However, they grow very quickly and are often of concern to patients. Keratoacanthomas present as erythematous crateriform nodules with a central keratin core. Although they can spontaneously resolve within six to 12 weeks, early excision is nevertheless recommended because of their clinical appearance and, more importantly, to definitively rule out an SCC, which can be difficult to do without histological analysis of the entire lesion.

Diagnosis of SCC is confirmed with a biopsy. If invasive SCC is suspected, it is important that the biopsy sample is taken from deep enough to determine the extent of dermal invasion. It is also important to

TABLE. FIELD THERAPIES FOR ACTINIC KERATOSIS

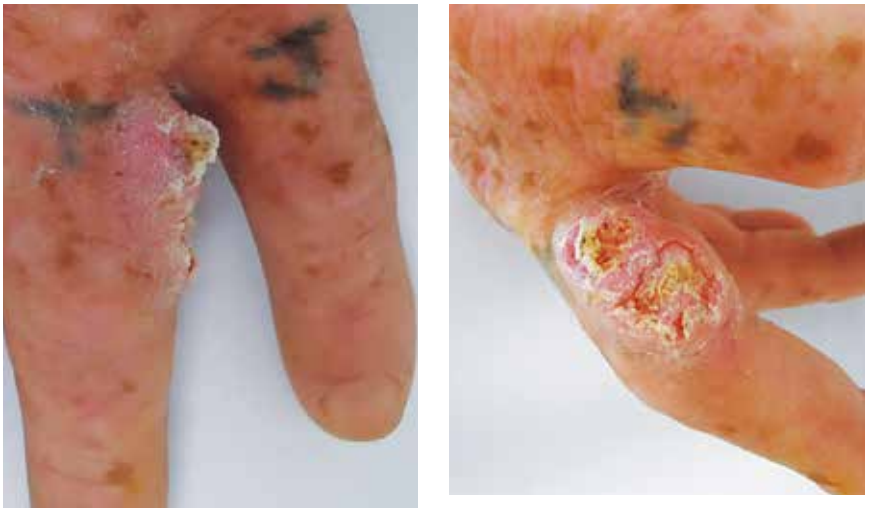
Medication	Action	Treatment regimen	Comments
Fluorouracil 5% cream	Antimetabolite	Applied by patient once or twice daily for two to four weeks (face) or three to six weeks (body)	One of the most common field therapies because of its cost (about $60/tube), ease of use and efficacy
Imiquimod cream	Enhances the local immune system	Applied by patient three nights a week (washed off the following morning) for three to four weeks	Review should be undertaken four weeks after treatment; treatment cycle can be repeated once if required As this immune alteration is achieved through toll-like receptor 7 activation, inflammatory reactions can vary in severity because of varying levels of expression in the population
Ingenol mebutate gel	Plant extract that activates protein kinase C, leading to an immune response and cell death	Applied as a 0.015% gel to face or scalp for three consecutive days, or 0.05% gel to other body regions for two days	The inflammatory response develops rapidly; skin heals in about seven days
Photodynamic therapy with a photosensitising agent (e.g. methyl aminolevulinate)	Apoptosis and necrosis of target cells	The photosensitising agent is applied to the treatment area, then occluded for three hours before being exposed to a dedicated light source	Usually only one treatment required, and the treatment area is reassessed at three months
Diclofenac sodium gel	Nonsteroidal anti-inflammatory agent	Applied by patient twice daily for 60 to 90 days	Used in practice but not included in the *Therapeutic Guidelines* recommendations

Adapted from Dermatology Expert Group. Solar damage and skin cancer [revised November 2015]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2017.[6]

examine regional lymph nodes, with suspected metastases confirmed by fine-needle aspiration. Poor prognostic factors include immunosuppression and lesions arising in scar tissue and ear, lip, mucosal, anogenital, head and neck sites. The four main histological signs for poor prognosis are lesion size greater than 2 cm, poorly differentiated histology, invasion beyond subcutaneous fat and perineural involvement.

Treatment

Treatment of SCC is by margin-controlled surgical excision, with the margins varying between 2 and 10 mm depending on lesion characteristics. Favourable lesions (e.g. those that are well differentiated and less than 2 cm in diameter) are adequately cleared with a margin of 4 mm in 95% of cases.[1] As incomplete excision carries up to a 50% risk of recurrence, lesions with histological margins of less than 1 mm must be considered for further therapy. Mohs surgery can be undertaken at sites where tissue conservation is paramount, such as the nasal tip, and for high-risk lesions. Radiation therapy can be used when there is greater surgical risk (e.g. due to patient comorbidities or lesion site) and as adjuvant treatment for high-risk lesions.



Figures 2a and b. Squamous cell carcinoma. a (left). Dorsal view. b (right). Radial right second finger.

Figure 3. Persistent verruca vulgaris on the right thumb with histological changes overlapping with squamous cell carcinoma.

Topical therapies, such as cryotherapy, imiquimod cream, 5-fluorouracil and photodynamic therapy, can also be used to treat Bowen's disease when surgery is not advised. Further details on therapy duration and high-risk definitions are given in the Cancer Council Australia guidelines.[1] Recommendations on when to refer patients to specialist care are shown in the Box.

Basal cell carcinoma

Presentation and diagnosis

BCC is the most common skin cancer in Australia. As with SCC, Fitzpatrick skin type and UV radiation exposure are the biggest risk factors; however, unlike SCC, risk is associated with intense episodes of burning, not cumulative exposure. BCCs rarely metastasise and the main clinical concern is local destruction.

BCC has multiple clinical presentations, with the most common being nodular BCCs. These are pearly papules or nodules with evident telangiectasia and/or umbilication. They may ulcerate and are most often seen on the head and neck, including areas with little sun exposure, such as the inner canthus or behind the ears. Superficial BCCs present as erythematous patches or plaques, often on the trunk or extremities (Figure 4). BCCs may also be pigmented (Figure 5), leading to a clinical differential diagnosis of melanoma, but an evident pearly edge and vascularity, seen clinically or through the dermatoscope, can aid in the distinction. Less common variations include morphoeic or sclerosing (scar-like), micronodular and basosquamous BCC. Diagnosis of BCC is confirmed with a biopsy.

Treatment

Treatment is determined by the subtype and site of BCC. Superficial BCCs can be treated with topical therapies, including imiquimod cream, cryotherapy, curettage and cautery and photodynamic therapy.[6] Imiquimod treatment for BCC is more intensive than for AKs, with therapy applied by the patient five nights a week for six weeks. It can be used in low-risk sites, such as the trunk and facial areas including cheeks and forehead. Cryotherapy for BCC is performed with a double freeze-thaw cycle of 20 to 30 seconds. This causes a significant blister and can leave hypopigmentation, so it is important to counsel patients before starting treatment. Cryotherapy is not recommended for use on areas where healing is a concern, such as the lower legs. Curettage and cautery can be undertaken for well-demarcated lesions, on suitable patients and sites. Photodynamic therapy can be used for superficial and thin nodular BCCs. It usually requires two treatment sessions, one week apart, with lesions first descaled or debulked, and the sensitising agent applied to a thickness of 1 mm, with a margin of 5 mm.[1]

Surgical treatment is usually first-line therapy for nonsuperficial BCCs, although radiation therapy is an option if surgery is contraindicated. High-risk lesions should be excised with clinical margins of 3 to 4 mm. Histological margins less than 1 mm require further evaluation and potentially further treatment. Favourable BCCs should be excised with 2 to 3 mm margins, and histological clearance of 0.5 mm. Where neither surgery nor curative radiation therapy is an option, oral therapy (e.g. vismodegib) targeting the hedgehog signalling pathway is available on the PBS with authority. Patients requiring this treatment should be under specialist care.

WHEN TO CONSIDER SPECIALIST REFERRAL FOR NONMELANOMA SKIN CANCER

- Uncertainty of diagnosis or doubts about appropriate treatment
- Lesions >1 cm (and certainly those >2 cm)
- Multiple lesions
- Technically difficult sites, such as the ear, tip of nose or eyelid
- Recurrent lesions despite treatment
- Incompletely excised lesions
- Recommended treatment is beyond the skills of the practitioner, or difficulty with technique or anatomy is anticipated
- SCC on the lips and ears
- Infiltrating or scar-like morphoeic BCC
- Cosmetic concerns
- Areas where palpable regional lymph nodes suggest metastatic spread of SCC
- When the GP will be unavailable for regular follow up, especially for an SCC

Adapted from Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia.[1]

Abbreviations: BCC = basal cell carcinoma; SCC = squamous cell carcinoma.

New therapies

Studies and clinical trials are underway to improve treatment options and outcomes for patients with NMSC. Areas of research are focusing on immune pathways, new oral and topical treatments and advances in radiation therapy.

Researchers at The University of Sydney are exploring photoimmunology – the role UV radiation has on altering the immune system. Although at a relatively early stage, the aim of this research is to explore how photoimmunology can be manipulated to treat SCC.[8] Further development of drugs targeting the hedgehog pathway is an area of interest in advanced or metastatic BCC,

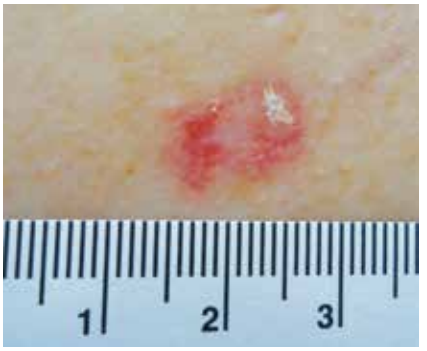


Figure 4. Superficial basal cell carcinoma on the mid-back.

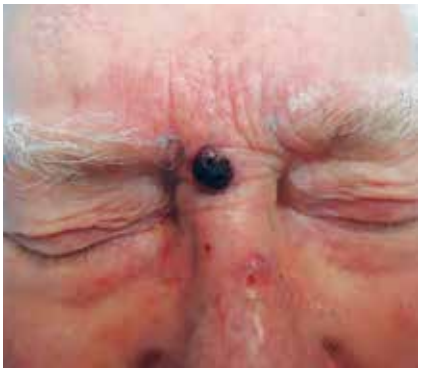


Figure 5. Pigmented basal cell carcinoma.

and therapies targeting the epidermal growth factor receptor are being explored for use with SCC.[9]

Two oral therapies that have begun to be adopted for preventing NMSC in people at high risk are retinoid therapy and nicotinamide (vitamin B_3). Oral retinoid therapy is already recommended for renal transplant patients,[10] and its benefit in reducing the risk of NMSC has been shown in trials. For example, in an Australian crossover study of 23 patients, treatment with the retinoid acitretin reduced SCC development by 144%.[11] Nicotinamide, a cheaper medication with fewer side effects, has shown significant and promising results in reducing the number of new NMSCs and AKs. A recent phase III study in Australia showed a 23% decrease in new NMSCs in high-risk patients taking daily nicotinamide supplements, compared with placebo.[12]

Both these oral therapies are only effective during active treatment and should be considered in consultation with a specialist. Topical therapy with combination low-dose fluorouracil (0.5%) and 10% salicylic acid has been shown to be effective in treating hyperkeratotic AKs.[13] Fluorouracil-salicylic acid is available overseas but not in Australia.

Advances in radiation therapy have led to new treatment modalities that allow for shallower treatment zones, protecting deeper tissues and resulting in fewer side effects and better cosmesis.[14]

Conclusion

NMSC is the most common skin cancer encountered in Australia, and GPs are at the forefront of patient interaction for these conditions. Prevention (through sun-safe education), early detection and appropriate treatment help reduce the impact these cancers have on patients' lives and the healthcare system. MT

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Dermatological emergencies

How to recognise them and what to do

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Emergencies in dermatology are uncommon but can cause significant long-term morbidity or even be life-threatening. Three patients illustrate the need for early recognition and urgent referral for treatment of staphylococcal scalded skin syndrome, toxic epidermal necrolysis and pyoderma gangrenosum.

Emergencies in dermatology are rare but have the potential to cause significant morbidity and a major impact on quality of life. We describe three patients with dermatological emergencies. They illustrate the importance of early recognition and urgent referral to a dermatology service in a tertiary hospital for treatment.

Patient 1. Staphylococcal scalded skin syndrome

A previously well 4-year-old girl presented to the emergency department (ED) of a large teaching hospital with tender erythematous patches affecting the axillae, inguinal folds and flexural aspect of the neck (Figure 1). She was not taking any medication.

On examination, the child was irritable, had a fever and complained of pain on palpation of the affected flexural sites. She had periorificial scaling and erythema as well as superficially eroded patches where the tender erythematous areas came into contact with each other. No lymphadenopathy, organomegaly or mucosal lesions were noted.

KEY POINTS

- Dermatological emergencies are uncommon but can cause devastating complications if not recognised and treated early.
- Many patients require early referral to a tertiary hospital with a dermatology department.
- Staphylococcal scalded skin syndrome is a spot diagnosis in children aged under 5 years and responds well to flucloxacillin.
- In toxic epidermal necrolysis, identification and cessation of the causative drug is key, which requires a careful history of any prescribed and over-the-counter medications the patient is taking.
- In pyoderma gangrenosum, clues to the diagnosis include pain disproportionate to lesion morphology and rapid progression; however, pyoderma gangrenosum is a diagnosis of exclusion and infective causes must be ruled out.

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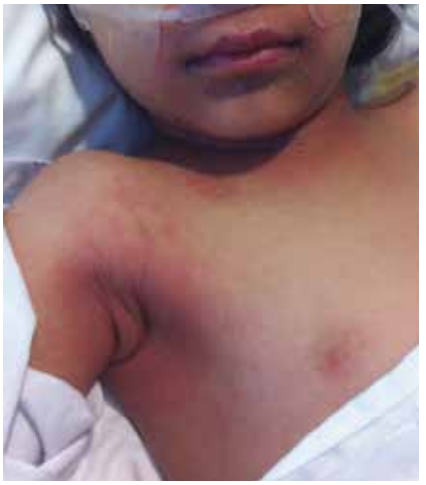


Figure 1. A young child with staphylococcal scalded skin syndrome showing periorificial and flexural scaling and erythema.

Investigations

Results of routine blood tests were normal, including full blood count, measurement of serum urea, electrolytes and creatinine levels and liver function tests. Blood cultures, urine cultures, chest x-ray and bacterial microscopy, culture and sensitivity tests of swabs from affected skin also gave normal results. Polymerase chain reaction (PCR) tests of axillary swabs were negative for herpes simplex virus.

Management

A provisional diagnosis was made of staphylococcal scalded skin syndrome (SSSS). The differential diagnosis included:

- streptococcal toxin-mediated erythema
- drug reaction
- viral exanthema.

The patient showed clinical improvement within 24 hours of commencing oral flucloxacillin. She rapidly improved over the following two to three days and was subsequently discharged from hospital. The septic focus was found to be undiagnosed otitis externa.

Discussion

SSSS is a toxin-mediated dermatosis that presents with erythematous, tender, flexurally distributed skin lesions, commonly associated with periorificial involvement. Practice points about SSSS are summarised in Box 1.

Pathophysiology

The epidermal changes of SSSS are produced by exfoliative toxin secreted by a strain of *Staphylococcus aureus* infecting the skin, eye, throat or mucosa. SSSS is seen mostly in children but can affect adults in rare cases, particularly if they have compromised renal function. The initial event is usually a localised staphylococcal infection, often quite trivial, which may be on the skin or at a distant site. A few days later, the patient develops fever, irritability and skin tenderness, which progresses without treatment to erosive lesions. The condition usually heals within seven to 14 days of commencing antibiotic treatment for the staphylococcal infection.[1]

Diagnosis

SSSS is a unique condition that should be a spot diagnosis. The differential diagnoses listed above relate only to a patient in the early stages where the disease has not yet declared itself. The hallmarks of SSSS are:

- patient age usually under 5 years
- recent staphylococcal infection
- severe pain
- lack of mucosal lesions
- flexural erythema with superficial erosions.

Treatment

Management of SSSS includes:

- oral flucloxacillin 50 mg/kg daily in four divided doses (intravenous flucloxacillin may be required if the patient is not taking oral fluids)
- oral or intravenous clindamycin may be considered in addition to or instead of flucloxacillin to stop the production of exotoxin from bacteria ribosome[2]
- minimal handling and avoidance of dressings (if possible) to avoid causing pain
- analgesia with regular paracetamol with or without oxycodone
- cultures to determine the source of the septic focus, including culture of samples taken from any obvious skin lesions, ears, throat and the conjunctiva.

1. STAPHYLOCOCCAL SCALDED SKIN SYNDROME PRACTICE POINTS

- Staphylococcal scalded skin syndrome typically presents with:
  - skin pain, flexural erythema and superficial blistering
  - periorificial erythema and scaling
  - irritable and/or febrile child
- Negative skin swabs do not exclude the diagnosis
- Treatment does not always require intravenous flucloxacillin unless the child is not taking oral fluids; the condition responds well to oral antibiotics

Patient 2. Toxic epidermal necrolysis

A 33-year-old woman presented to the ED with tender, violaceous, targetoid macules in association with 'gritty-feeling' eyes, pharyngitis and painful vulval erosions. Two weeks before the onset of symptoms, she had begun taking clarithromycin to treat sinusitis. Over the 24 hours after her arrival in the ED, she developed blisters involving 75% of her body surface area (Figure 2).

Investigations and management

A skin biopsy confirmed confluent epidermal necrosis consistent with toxic epidermal necrolysis (TEN). The patient was transferred to the intensive care unit (ICU) for high-dependency nursing care and appropriate analgesia, eventually requiring intubation and an induced coma for pain management.

In the ED, the patient was immediately commenced on intravenous immunoglobulin 1 g/kg. She received a second

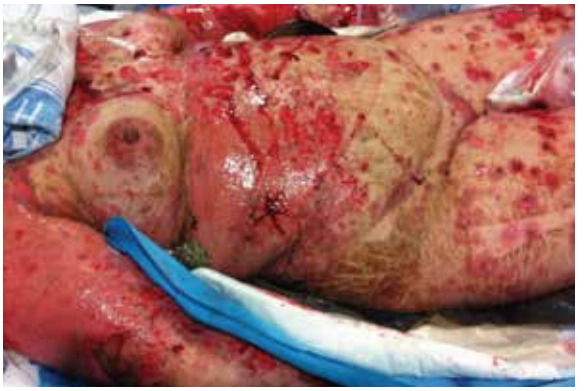


Figure 2. A woman with toxic epidermal necrolysis showing Nikolsky-positive generalised erosions affecting more than 75% of the body.

immunoglobulin dose the following day, as well as intravenous hydrocortisone 100 mg daily for three days.

The patient was reviewed daily by dermatology and ophthalmology specialists and the burns team. She was commenced on daily vaginal dilatation and intravaginal prednisolone suppositories to prevent vaginal fusion.

The patient's hospital stay was complicated by *Pseudomonas aeruginosa* pneumonia and staphylococcal bacteraemia. She required ICU treatment for three weeks. She recovered and was discharged home after 31 days.

Discussion

TEN is an acute life-threatening mucocutaneous reaction characterised by extensive necrolysis and detachment of the epidermis. It is almost invariably a drug reaction, and involves more than 30% of the body surface area.[3]

Although survival rates in patients with TEN have improved over the past 20 years, some long-term sequelae may occur and are often devastating, including vision loss, oesophageal strictures and vaginal stenosis. Patients' quality of life may be severely compromised. Practice points about TEN are summarised in Box 2.

Pathophysiology

The pathophysiology of TEN remains unclear, but it is well established that drugs are the most important aetiological factor, with more than 100 different drugs being reported as possible causes. The drugs with the highest risk of TEN include antibacterial sulfonamides, aromatic anticonvulsants, allopurinol, oxicam NSAIDs, lamotrigine and nevirapine. A significant but much lower risk has also been reported for nonsulfonamide antibiotics, such as aminopenicillins, quinolones, cephalosporins and tetracyclines.[4] The reaction usually occurs on first exposure to the medication.

Clinical signs and symptoms

TEN typically begins within eight weeks (usually four to 30 days) of first exposure to the drug. Nonspecific symptoms, including fever, pharyngitis, headache, rhinitis and myalgia may precede the mucocutaneous lesions by one to three days. The initial skin lesions are characterised by irregularly shaped erythematous, dusky red, purpuric macules that progressively coalesce. The Nikolsky sign (dislodgement of the epidermis by lateral pressure) is positive on erythematous zones. At this stage, the lesions evolve to superficial flaccid blisters that spread with pressure and break easily. The necrotic epidermis is easily detached at pressure points or by frictional trauma, revealing large areas of exposed, erythematous dermis.[3]

Treatment

The most important element of the treatment of patients with TEN is cessation of the causative drug. If a diagnosis of TEN is suspected then any potential causative medications should be ceased and the patient should be immediately referred to a tertiary hospital with a dermatology department and a burns unit.

Intubation is often necessary for pain management and dressing changes, and most patients spend some time in the ICU in an induced coma because of pain. Patients should also have regular specialist ophthalmology review, nanocrystalline silver dressings of wounds and supportive care, including mouth care. Nanocrystalline silver dressings have an important role through their antibacterial and anti-inflammatory properties.

Intravenous immunoglobulin has been found to arrest progression of the disease, allowing re-epithelialisation. Treatment with systemic corticosteroids and other immunosuppressive agents, particularly ciclosporin A, has been described but is controversial because of a possible increased risk of sepsis and the lack of grade A supporting evidence. Recently, tumour necrosis factor (TNF)-alpha blockers, specifically infliximab and etanercept, have been shown to be effective at halting disease progression.[5]

Infection is the most common cause of death in TEN, with *S. aureus, P. aeruginosa* and *Candida* spp. being the most

2. TOXIC EPIDERMAL NECROLYSIS PRACTICE POINTS

- Toxic epidermal necrolysis (TEN) is an acute, life-threatening, mucocutaneous drug eruption with extensive necrolysis and detachment of the epidermis
- If there is any suspicion of TEN, patients must be urgently referred to a tertiary hospital; a multidisciplinary team approach is necessary with dermatology, burns, ophthalmology, gynaecology and sometimes intensive care involvement
- Cessation of the causative drug, wound care and pain management are the cornerstones of treatment
- Intravenous immunoglobulin is frequently used to arrest progression of the disease, allowing re-epithelialisation

typical isolates.[6] Other potentially fatal complications include pulmonary embolism, adult respiratory distress syndrome, gastrointestinal haemorrhage and cardiac and renal failure.[7]

Follow up involves ensuring that the offending medication (and closely related medications) are never readministered to the patient as this could lead to a recurrence of TEN. Long-term morbidity is often related to ocular, dermatological, gynaecological and renal complications.

Patient 3. Pyoderma gangrenosum

A 52-year-old woman with a history of type 2 diabetes and hypertension presented to her private dermatologist with a two-week history of very painful, rapidly enlarging ulcers on her left foot, a toe on her right foot and her calves (Figure 3a).

Investigations and management

Swabs were collected from the ulcers for microscopy and culture and the patient was commenced on oral antibiotics. A biopsy was also performed, which showed a neutrophilic dermal infiltrate consistent with pyoderma gangrenosum. Cultures were negative for bacteria, mycobacteria and fungi.

The patient was referred to the dermatology department at her local hospital where she was commenced on prednisolone 60 mg daily and cyclosporin 5 mg/kg daily. She was advised to apply simple dressings daily to existing ulcers and betamethasone dipropionate 0.05% ointment to any new ulcers.

Initially she was managed as an outpatient. However, she developed osteomyelitis as a complication and required hospital admission to receive intravenous antibiotic treatment.

Within weeks of the patient commencing treatment, the ulcers improved significantly (Figure 3b). The patient was able to mobilise and perform activities of daily living independently. Prednisolone was withdrawn, but cyclosporin was continued until all ulcers had healed completely. The patient was at risk for below-knee amputation because of the osteomyelitis but fortunately responded well enough to antibiotic treatment to avoid this.

Discussion

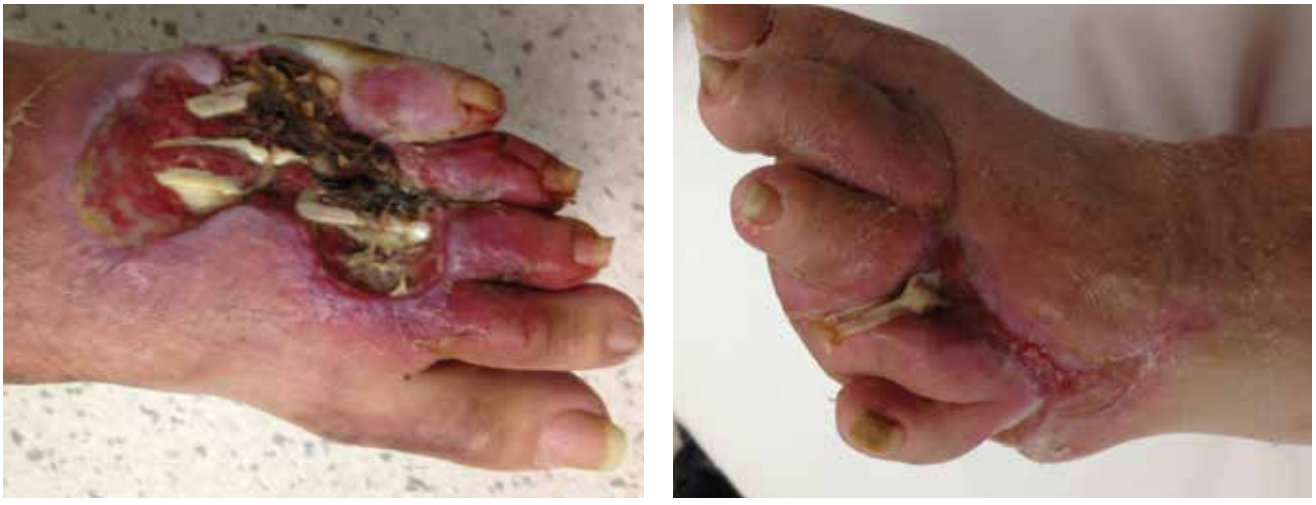
Pyoderma gangrenosum is a rare, non-infectious neutrophilic dermatosis, which is associated with underlying systemic disease in 50% of cases. Diagnosis is based on typical clinical features and the exclusion of other cutaneous ulcerating diseases, including infection, trauma and cancer.[8]

Common associations of pyoderma gangrenosum include inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, haematological malignancies and monoclonal gammopathies. The exact aetiology of pyoderma gangrenosum is unknown, but it is best thought of as an autoimmune process characterised by a sterile neutrophilic infiltrate. Practice points about pyoderma gangrenosum are summarised in Box 3.

Clinical signs and symptoms

Clinical features of pyoderma gangrenosum include:

- rapid progression of painful, necrotic ulceration with an irregular, undermined, violaceous border, often preceded by a papule, pustule or bulla, and causing severe pain out of proportion to the size of the ulcerated area
- history of pathergy (lesions occurring at sites of mild trauma)
- cribriform (crater-like) scarring as the ulcer heals



Figures 3a and b. An older woman with pyoderma gangrenosum affecting the left foot. a (left). At initial presentation, showing deep ulceration of the foot with a violaceous edge. b (right). After treatment with oral prednisolone showing the healing ulcer.

- an underlying condition, particularly inflammatory bowel disease.

There are four main clinical subtypes of pyoderma gangrenosum, comprising:

- classic/ulcerative
- pustular/superficial
- bullous
- vegetative.[9]

Diagnosis

Histopathological findings in patients with pyoderma gangrenosum are often variable and nonspecific, but typical findings include central necrosis and ulceration of the epidermis and dermis, surrounded by an intense, acute inflammatory cell infiltrate consisting of neutrophils.[10] A skin biopsy is not diagnostic of pyoderma gangrenosum but can rule out other conditions, particularly infection and malignancy.

Diagnosis of pyoderma gangrenosum is essentially based on clinical characteristics. PCR tests and microscopy with specific histopathology stains for mycobacteria, fungi and bacteria should be performed to exclude an infectious aetiology before commencing immunosuppression. Tissue should be sent for mycobacterial and fungal culture but treatment should not be delayed while waiting for culture results if there is no histopathological evidence that the ulcer could be caused by an infection.

Treatment

In patients with early or mild cases of pyoderma gangrenosum, topical therapy such as potent corticosteroids or tacrolimus 0.1% ointment can be used. Minocycline and dapsone have also been used in milder cases. More severe or resistant disease responds quickly to oral corticosteroids (1 to 2 mg/kg daily).

A number of immunosuppressive agents have been found useful in corticosteroid-unresponsive pyoderma gangrenosum, either given alone or as corticosteroid-sparing agents, and should be commenced immediately in a patient in whom oral corticosteroids present a relative risk. Cyclosporin has been widely used in the past because of its rapid onset of action. It is not ideal for long-term therapy, but this is usually not needed as the drug can be ceased when the ulcers heal.

Other corticosteroid-sparing options include methotrexate, azathioprine and mycophenolate mofetil. There have also been several reports of TNF-alpha blockers being efficacious in the treatment of patients with pyoderma gangrenosum, including etanercept, adalimumab and infliximab, and other case reports of intravenous immunoglobulin and plasmapheresis.[1]

Treatment of pyoderma gangrenosum can usually be discontinued after complete healing of lesions. Recurrences may occur but are unpredictable and do not justify prolonged maintenance therapy.

Conclusion

This article outlines some dermatological emergencies that are important for GPs to be able to identify as possible differential diagnoses and to refer on appropriately. MT

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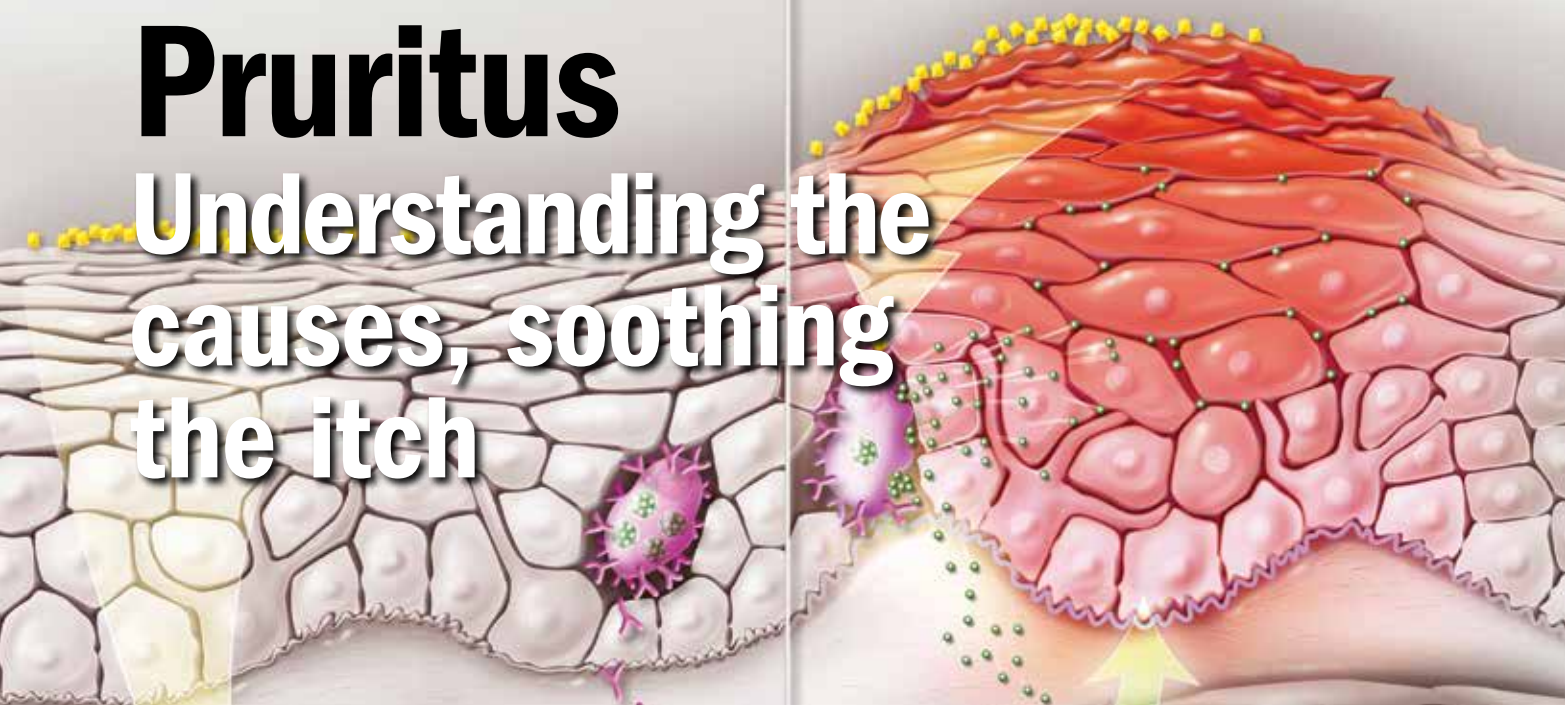
Pruritus

Understanding the causes, soothing the itch



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A careful structured approach to the diagnosis and management of pruritus, with the application of simple intensive topical treatment regimens, at least initially, helps patients with pruritus.

KEY POINTS

- Pruritus is extremely debilitating and prompt management is essential.
- A phone call to a dermatologist regarding a desperate patient should ensure prompt review.
- Dry, sun-damaged skin is itchy and the application of moisturiser, and avoidance of soap and overheating, will help all patients with pruritus.
- A careful history and examination is essential.
- Investigations are only indicated if the diagnosis is not obvious or simple treatments fail.
- Printed patient information and treatment instruction sheets are essential.

Pruritus (itch) is a common reason for presentation to a GP and is a source of misery to the patient and a challenge to the doctor. It is a feature of many diseases, including allergic, contact, irritant and nummular eczema, idiopathic itch, psoriasis, tinea, systemic disease and urticaria, and it may be a symptom of adverse drug reactions (Figures 1 to 3a and b).

An approach to the diagnosis and management of pruritus is discussed in this article. As it is not possible to discuss in detail the treatment of all the conditions that can produce pruritus, the causes highlighted are those responsible for most cases and those that it is important not to miss. Some rarer conditions present more challenging management problems, including systemic diseases, neurodermatitis and delusions of parasitosis.

Pathophysiology

Control and elicitation of pruritus involves a complex interaction between skin receptors, the peripheral and central nervous system, and a range of cytokines and neuromodulators produced in the dermis and in keratinocytes.

The sensation of pruritus is transmitted through the primary afferent nerve type C fibres (which, being unmyelinated, are slow conducting) and possibly also through type A-delta fibres (myelinated and therefore fast conducting), with the free nerve endings – the nociceptors – located near the dermoepidermal junction

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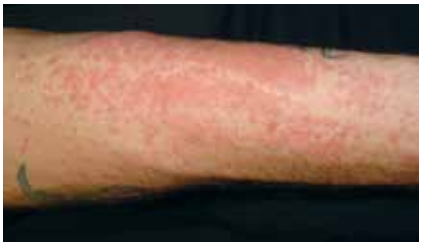


Figure 1. Allergic contact dermatitis due to epoxy resin exposure. Note the vesicular dermatitis.

or in the epidermis. Activators of the polymodal (chemical, mechanical and thermal) C nociceptors include histamine, neuropeptide substance P, serotonin, bradykinin, proteases (such as mast cell tryptase) and endothelin (which stimulates the release of nitric oxide). A-delta nociceptors are activated by mechanical and thermal stimuli. The sensitivity of these nerve fibres to temperature explains the well-recognised phenomenon of a lowered itch threshold when the skin temperature is raised.

Opioids are known to modulate the sensation of pruritus, both peripherally and centrally. Although pruritus is an entirely separate sensory modality from pain, the neural pathways both follow the same overall route from the dorsal route ganglion to the spinothalamic tract and eventually to the thalamus and cerebral cortex.

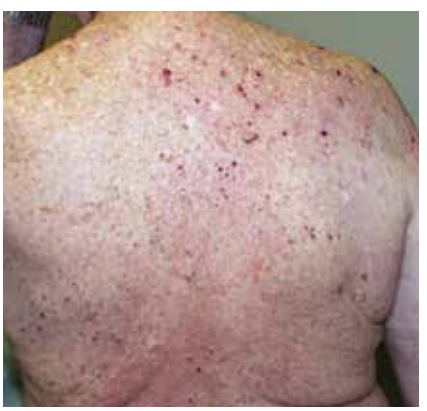
Under pathological conditions such as tissue damage and nerve injury, the sensation of itch can increase markedly, such that a normally insignificant stimulus can produce itching sensations (alloknesis). Moreover, a normally pruritic stimulus can elicit a greater than normal duration and/or magnitude of itch (hyperknesis).

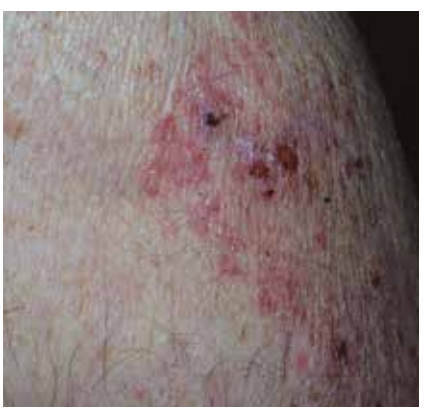
Diagnosis

At the outset, it is important to know whether the itch is associated with a rash. This is not as easy as it sounds, as sometimes the skin may be covered in excoriations, or even small ulcers, without any other features. Is the itch localised to a particular area of the body or generalised? Is the skin dry or does it look otherwise normal?

Diagnostic lists based on a simple division of clinical features, determined by the presence or absence of the rash and how much of the body is affected are presented in the Flowchart. The diagnostic clues and the appropriate investigations and management of the conditions are summarised in the Table.

Scratching the skin can eventually produce secondary changes such as lichenification (thickening of the skin), which can be chronic, intensely itchy and treatment resistant (Figure 4). It is essential to reverse the itch-scratch cycle for these patients to get better.





Figures 3a and b. Tinea corporis. a (left). The very extensive rash on the back was undiagnosed and treated as eczema for a long time, altering the appearance – 'tinea incognito'. b (right). The 'tell-tale' well-demarcated border of tinea.

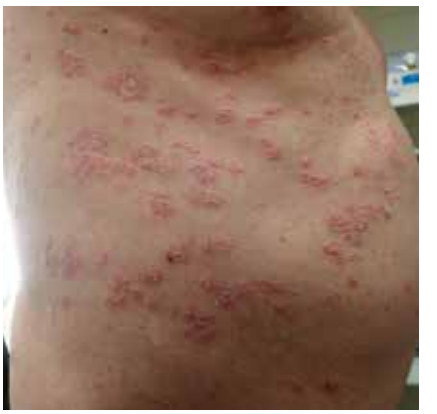


Figure 2. Typical psoriasis. Patients sometimes present because of itch but may only be worried about the appearance.

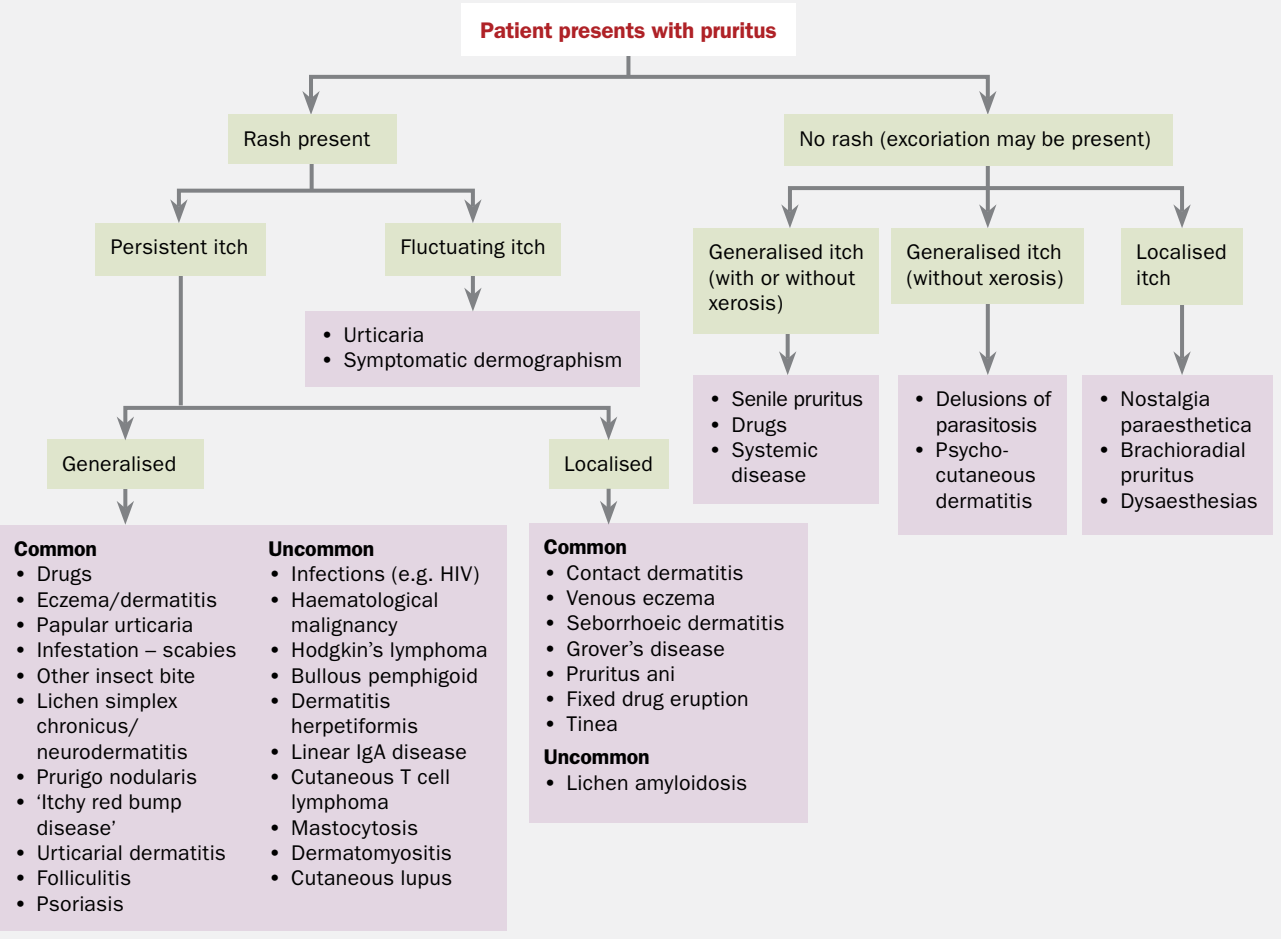
Lichen simplex chronicus is a localised, well-demarcated area of lichenification. It is sometimes termed neurodermatitis. The scratching and/or rubbing appears to heighten the skin sensitivity and alter the itch perception of local nerve endings. Lichenification occurs in many different dermatoses, when there is scratching and rubbing.

Careful examination may reveal dry, slightly scaly xerotic skin without any inflammation. This is a feature of some systemic diseases and is common in the elderly. In Australia, many patients have significant sun damage to their skin, and this is prone to produce dry, itchy excoriated patches on the arms, shoulders and upper back.

In patients with scabies there may be little to find on examination unless the examination is very thorough. Favoured sites for infestation with the scabies mite that should always be checked include the wrists, web spaces, soles of the feet, the genitals in men and the chest in women.

Some patients, especially older men, develop atypical dermatitic eruptions with no obvious underlying disease but severe itch that is poorly responsive to treatment (Figure 5). Several diagnostic terms for variants have been used, including urticarial dermatitis and 'itchy red bump disease'.

A DIAGNOSTIC APPROACH TO PRURITUS



Patients with urticaria often have no visible wheals at presentation but the history is highly suggestive of the diagnosis. Stroking or rubbing the skin can produce the linear wheals of dermographism, which can be intensely itchy. Some patients may not get a rash unless they rub or scratch, and this is an urticarial variant know as symptomatic dermographism.

The area to which a rash localises can offer important clues for diagnosis, but inflammatory dermatoses such as eczema can 'systemise' once the immune system is primed. A good example of this is venous eczema (also known as stasis eczema or gravitational dermatitis), which may be present on the lower legs for months and then spread to the arms and trunk (Figures 6a and b). Grover's disease is occasionally surprisingly widespread.

Systemic disease

When no other cause is obvious for pruritus, a systemic cause is possible.

Renal pruritus

Renal pruritus is most often seen in patients receiving haemodialysis. The condition is not due to elevated serum urea levels, and the actual pruritogenic substance has yet to be identified. Xerosis greatly exacerbates the condition and raises the 'itch threshold' and moisturiser can be very helpful. Fine tuning the dialysis procedure and taking 300 mg gabapentin after dialysis has been reported as being useful.

Cholestatic pruritus

Cholestatic pruritus is more common in patients with intrahepatic cholestasis than in those with extrahepatic cholestasis. It does not appear to relate to bile salt or bilirubin levels. The accumulation of endogenous opioids seems to be involved because opioid antagonists such as naltrexone have been shown to partially relieve cholestatic pruritus. Narrow-band UVB phototherapy can be very effective in some patients.

Haematological pruritus

Patients with pruritus and iron deficiency

TABLE. PRURITUS: CAUSES, DIAGNOSIS AND MANAGEMENT

Condition	Diagnostic clues	Investigations	Management
Itch with rash			
Generalised, common			
Drugs	Rash may be morbilliform or eczematous, can be very extensive Usually 'new' medication	Careful history most helpful, if sick or extensive rash FBC, UEC and LFT	• Stop drug, intensive topical treatment • If unwell, consider oral corticosteroids
Eczema/dermatitis	Erythema, scale, papules and patches	Biopsy will show 'spongiotic dermatitis'	• Intensive topical treatment • If no response, refer
Folliculitis	Follicular pustules	Swab for bacteria	• Cephalexin or other appropriate anti-staphylococcal antibiotic • May be due to rubbing in ointments and irritating hair follicles
'Itchy red bump disease'	Extensive erythematous papules worst on the trunk	Biopsy may show some spongiosis, often just dermal lymphocytes with some eosinophils	• Intensive topical treatment • If no response, phototherapy or systemic treatment
Lichen simplex chronicus/ neurodermatitis	Dry thickened skin, sometimes plaques especially limbs, upper back	Clinical diagnosis	• Intensive topical treatment with occlusion
Papular urticaria (can be localised or generalised)	Erythematous papules in location that reflects type of bite, e.g. flea bites on legs Once sensitised, itches all over	Clinical diagnosis, biopsy may show intense dermal perivascular inflammation and eosinophils	• Protect from insects, high-dose antihistamines, intensive topical treatment • If no response, refer
Prurigo nodularis	Excoriated nodules that may resemble an SCC Especially on limbs	Clinical diagnosis, but biopsy may be required	• Intensive topical treatment with occlusion, intralesional triamcinolone 5 to 10 mg/mL • If no response, refer
Scabies	Burrows in wrists, web spaces, instep of foot, genital papules in men, breasts in women	Clinical diagnosis, use dermatoscope to look for 'black dot' of scabies mite at end of burrow	• Permethrin two treatments six days apart, can use ivermectin 200 mcg/kg immediately, repeat at one week • Treat all contacts
Urticaria	Typical history of dermal wheals, flare lasting up to 24 hours	Clinical diagnosis, history may be the only clue, 'smartphone photos'	• Nonsedating antihistamines in doses up to four times recommended dosage, combine different types; oral corticosteroids five days 0.5 mg/kg in emergency situations • If no response, refer
Urticarial dermatitis	Erythematous papules and dermal urticarial looking plaques, especially lower trunk	Biopsy shows dermal inflammation	• Very poor response to intensive topical treatment or antihistamines • If responds to prednisolone but quickly rebounds, refer
Psoriasis	Typical plaques, scalp, natal cleft, nail pitting, elbows and knees	Clinical diagnosis	• If extensive, refer for systemic treatment including phototherapy

Abbreviations: FBC = full blood count; LFT = liver function tests; SCC = squamous cell carcinoma; UEC = urea, electrolytes and creatinine.

continued on next page

TABLE. PRURITUS: CAUSES, DIAGNOSIS AND MANAGEMENT *continued*

Condition	Diagnostic clues	Investigations	Management
Itch with rash			
Localised, common			
Contact dermatitis	Erythematous papules, patches sometimes vesicles localised to area of skin contact	Usually clinical history indicative Biopsy shows spongiosis	• Intensive topical treatment plus oral corticosteroids, if severe tapering over several weeks • Refer for patch testing
Grover's disease	Scaly, eroded papules on upper abdomen or back in men and between breasts in women	Clinical diagnosis or confirm with skin biopsy	• Intensive topical treatment • If no response, phototherapy or acitretin (oral retinoid)
Seborrhoeic dermatitis	Scalp scale, erythema with scale ears, central face occasionally central chest, upper back, axillae and groins	Clinical diagnosis	• Combined hydrocortisone and antifungal cream, occasionally use a more potent topical corticosteroid • Oral fluconazole 200 mg once or twice a week
Venous eczema	Erythematous, scale, swelling, crust on lower legs, can 'generalise'	Clinical diagnosis	• Intensive topical treatment with wet dressings • Grade II compression stockings
Itch without rash			
Generalised			
Psychogenic pruritus	Extensive excoriations, sometimes ulcers Healed 'porcelain' scarring on upper back and arms	Clinical diagnosis	• Intensive topical treatment with occlusion, explanation, amitriptyline • Psychological support
Senile pruritus	Very dry skin	Clinical diagnosis	• Good skin care and moisturiser
Systemic disease	May have xerosis, excoriations or no obvious rash	Consider if no other explanation for pruritus and patient clinically unwell, blood tests as suggested in text	• Treat underlying disease, moisturiser, can try topical corticosteroids • Phototherapy
Localised			
Brachioradial pruritus	Intense formication (crawling itch) forearms or upper arm, most often unilateral, relieved by ice	Clinical diagnosis	• Capsaicin cream, osteopathy or manipulative physiotherapy, acupuncture, plus sun protection
Notalgia paraesthetica	Intense itch on back usually localised to unilateral scapula	Clinical diagnosis	• Capsaicin, can try topical corticosteroid, upper thoracic mobilisation

may not be anaemic, suggesting that pruritus may be related to iron and not haemoglobin. Pruritus can be a feature of myelodysplasia. Mastocytosis is generally very itchy due to the high number of mast cells in the skin and sometimes systemically. Polycythaemia rubra vera can also produce very intense pruritus and is associated with aquagenic pruritus, where the itch is precipitated by water exposure.

Endocrine pruritus

Hyperthyroidism and hypothyroidism both produce pruritus, the latter especially due to the associated xerosis. Diabetes mellitus is generally included on the list of causes but is unproven.

Pruritus and malignancy

Pruritus has been linked to almost every type of malignancy in numerous reports

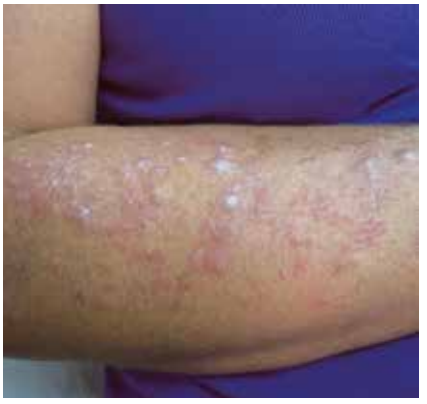


Figure 4. Lichen simplex with prurigo, caused by chronic scratching.

but in practice is not a common presenting symptom of malignancy. It is, however, a common feature of Hodgkin's lymphoma. The author has seen it present as severe papular urticaria and prurigo following an exaggerated insect bite reaction.

Cutaneous T cell lymphoma, although rare, is one of the more common T cell lymphomas and can present with intractable pruritus and what looks like an extensive eczema or psoriasis (Figure 7).

Psychogenic pruritus

Patients may present with severe itch that is so intense that only breaking the skin seems to provide relief. They sometimes admit to scratching when stressed.

The repetitive scratching results in excoriations, erosions and sometimes frank ulcers. Skin that is torn can heal with characteristic white 'porcelain' scars, especially on the upper arms and upper back. The itch may be concentrated to single or multiple areas of lichenification that may then go on to form prurigo nodules.

It is essential to reverse the itch-scratch cycle for these patients to get better.

Delusions of parasitosis

Patients with delusions of parasitosis may have pruritus but essentially are convinced that their skin is being infested with insects or other parasites. The descriptions can be bizarre and they may bring containers filled with 'evidence' of their infestation containing skin debris. Family members may collude with the diagnosis or describe similar problems.

This is regarded as a psychosis – a psychocutaneous disorder – and is a very serious illness with significant morbidity. Psychiatric referral should be a priority if the patient can be persuaded.

Investigations

Skin biopsy

If a rash is present, a skin biopsy may be helpful in confirming a diagnosis. Punch biopsies (3 mm) should be taken from two or three locations. Inflammatory patches or papules will give the most information; biopsying ulcers and excoriations should be avoided.

Generally, the pathologist will give a description of a 'reaction pattern'. The diagnosis can only be made from a clinicopathological correlation between the history, examination and careful interpretation of the biopsy findings. It can be worthwhile discussing the results with the pathologist.

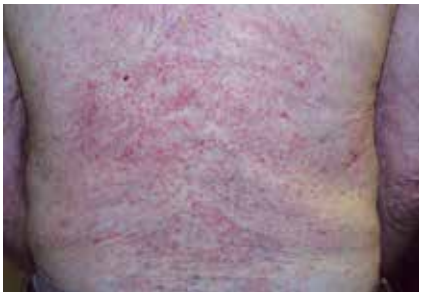
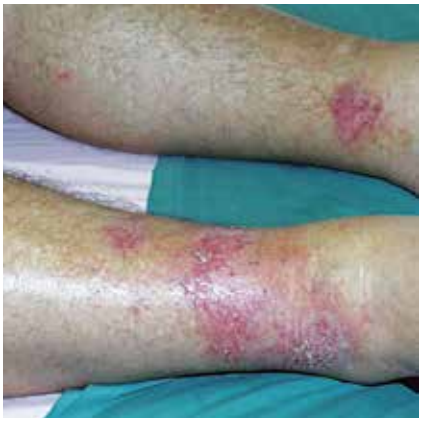
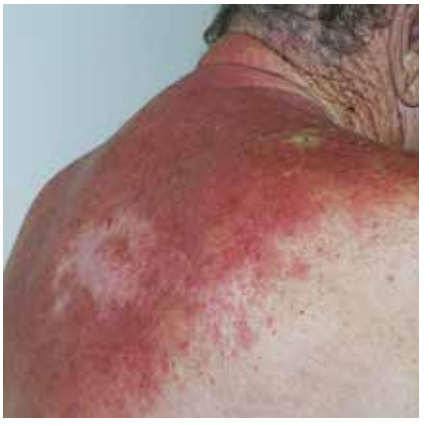


Figure 5. Urticarial dermatitis. A classic case of an intensely itchy erythematous papular rash on the back with a nonspecific biopsy result and topical treatment resistance.

Blood tests

The author generally orders blood tests when an underlying systemic disease is suspected as the cause of pruritus, and also investigates patients whose inflammatory rash has proved completely refractory to intensive topical, and sometimes systemic, treatment. The diagnostic yield from these tests is low.





Figures 6a and b. Venous eczema (also known as stasis eczema and gravitational dermatitis). a (left). On the leg. b (right). 'Generalised' to the body.

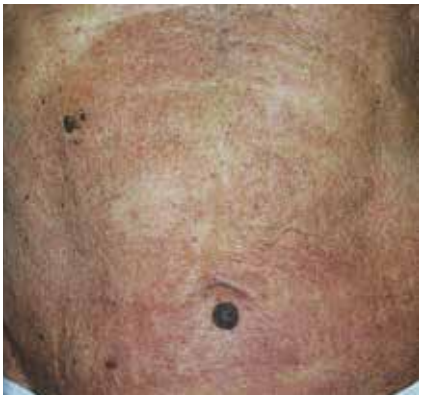


Figure 7. Cutaneous T cell lymphoma, a rare condition that can present with what looks like extensive eczema or psoriasis.

1. INVESTIGATION FOR SYSTEMIC CAUSES OF PRURITUS

- Full blood count
- Erythrocyte sedimentation rate
- C-reactive protein
- Liver and renal function tests
- Thyroid-stimulating hormone level measurement
- Ferritin
- Fasting blood glucose
- Electrophoresis or immunoelectrophoresis
- IgE antibody measurement if atopy or allergy suspected and no clear cut history or clinical clues

2. WHEN TO REFER PATIENTS WITH PRURITUS

- Patient not getting better or deteriorating despite treatment
- No effective diagnosis
- Blistering or extensive vesicular rash evident
- Erythroderma, or any 'sick' patient
- Diagnostic tests indicate a disease you have never managed
- If you or the patient are unhappy with progress

3. RESOURCES ON PRURITUS AND PRECIPITATING CONDITIONS

- **Australasian College of Dermatologists**
  - www.dermcoll.edu.au
- **New Zealand Society of Dermatologists**
  - www.dermnetnz.org

'Googling' a specific skin disease that has pruritus as a symptom will usually bring up DermNet New Zealand in the search results; adding 'ACD' to the topic search will bring up Australasian College of Dermatologists pages.

The basic screening tests for investigation of pruritus are listed in Box 1. More specific screening such as HIV antibody test, connective disease serology, full thyroid function testing, full iron studies, anaemia screen and hepatitis serology would be predicated by clinical features and the results of initial tests.

Treatment

Simple treatment regimens should be developed. Treatments can be time consuming, and regimens that involve at the most twice daily application can help compliance. Patients should be reviewed after one or two weeks of treatment, and moved on to the next step if there is no progress. Referring a distressed patient early if they are no better is a sign of a conscientious physician and will be appreciated by patients (Box 2).

Printed patient information and treatment instruction sheets are useful. Reliable online sources of information for patients with pruritus are provided in Box 3.

Intensive topical treatment

The backbone of all treatment for pruritus is intensive topical treatment. Dry skin is itchy skin. Patients should be encouraged to avoid overheating, which is a problem especially for the elderly and those who are ill. Central heating and slow combustion fires dehumidify the atmosphere, and electric blankets and doonas may increase nocturnal itch. Long hot showers and baths should be avoided.

Soft, synthetic fabrics are kinder to irritable skin than wool or rough natural fibres. Similarly, sand, carpets and upholstery will aggravate atopic dermatitis in small children.

If possible, provide patients with written instructions on skin care and keep regimens reasonably simple. If there is only dry skin and no inflammatory changes then moisturiser is a good starting point, especially in xerosis of the elderly. Always advise the avoidance of alkaline soaps and washes; sorbolene soaps, goat's milk-based soaps and soaps containing moisturisers are suitable if patients cannot afford proprietary non-soap cleansers.

Moisturiser in tubs should be used, as it is thicker than moisturiser in pump packs. It should be applied when the skin is wet as water is a good humectant but will worsen skin dehydration if allowed to evaporate. Always smooth on in direction of hair and do not rub because this can cause folliculitis.

If topical corticosteroids are to be used, the author prefers ointment-based more potent corticosteroids such as betamethasone dipropionate, mometasone furoate or methylprednisolone aceponate, provided they are not contraindicated. If patients have an aversion to ointments then a cream may be used. Ointments are more moisturising, better absorbed and significantly more potent. With streamlined authorities, a reasonable amount is easily prescribed on the PBS. The author always instructs patients to apply moisturiser over the corticosteroid. Recommending moisturiser to be used twice a day and topical corticosteroid at night should increase compliance.

Wet dressings can be applied over the applied corticosteroid ointment and moisturiser. For localised areas, cotton bandaging (wet then dry over the top) can be used; for the whole body, use pyjamas wetted with tap water and wrung out and then worn. The bandages can be worn overnight; for the whole body dressings, wrapping in a cotton blanket may be needed for comfort and the wet dressings only applied for an hour once or twice a day. An alternative to wet dressings is a 'soak treatment': the patient has a 15-minute oil or oatmeal bath, the topical corticosteroid and moisturiser is applied to the skin without drying and the patient then dresses in light pyjamas and retires for the night.

The rationale for using potent corticosteroids is to achieve good control quickly. Patients should be encouraged to use topical corticosteroids regularly until the skin inflammation has settled and then maintain the skin in that condition with a moisturiser and occasional use of corticosteroid.

The topical calcineurin inhibitors pimecrolimus and tacrolimus (off-label use of tacrolimus, as a compounded ointment) are an alternative to topical corticosteroids. These immunomodulators are similar in

potency to hydrocortisone 1% but more expensive. Their advantage is that they do not cause epidermal atrophy, and may therefore be more appropriate for use on the face or longer term in the flexures.

If a patient has had no response after a few weeks of treatment then re-evaluation and consideration of systemic treatment is generally required.

Systemic treatments

Antihistamines are the primary treatment for pruritus when histamine is the principle mediator, as occurs in urticaria. Non-sedating antihistamines are preferable in urticaria, and up to four times the normal recommended dosage may be required.

The sedation provided by traditional antihistamines and by tricyclic antidepressants (TCAs) such as doxepin may give patients some extra relief at night. Both sedating antihistamines and low-dose TCAs (e.g. 10 mg doxepin or amitriptyline) are often used in patients with nonspecific itch. Mirtazapine at a maximum dose of 15 mg has been reported as useful when combined with gabapentin titrated to doses of 300 to 600 mg daily.

Narrow-band ultraviolet B phototherapy can be extremely helpful in a variety of diseases precipitating pruritus, including urticaria, psoriasis, eczema, idiopathic itch, systemic disease and urticarial dermatitis.

Prednisolone can be used to gain control of very acute dermatitis in patients in whom topical treatment has failed. A moderate dose of about 0.5 mg/kg is adequate to provide relief for almost all patients with pruritus. Start at 25 mg daily and reduce by 5 mg daily every five to seven days; stop at 5 mg daily and review progress. Reducing the dose slowly reduces the risk of rapid flaring below the immunosuppressive level of about 15 mg daily.

Diabetes is not an absolute contraindication for a short course of oral corticosteroids but the patient will need careful monitoring. The prednisolone can be taken in a single morning dose and patients warned of the possibility of disturbed sleep.

When all else fails patients with pruritus may need immunosuppressive medication, at least in the short term, to gain control of the disease precipitating it. The medications that have been shown to work well include azathioprine, ciclosporin, methotrexate and mycophenolate (off-label use for skin conditions). Oral retinoids (such as acitretin) and dapsone can be effective in intractable Grover's disease and dermatitis herpetiformis, respectively (both off-label uses). Immunosuppressive medications are best prescribed by physicians with relevant experience of prescribing and monitoring these agents.

Treatment of psychogenic pruritus

It is essential to break the itch-scratch cycle for patients with this condition. Topical treatments may help but systemic measures are often required. The GP is the ideal person to provide counselling, support and medication for any underlying depression or anxiety.

Treatment of delusions of parasitosis

Patients with delusions of parasitosis need support without measures that will reinforce the delusion. Referral is essential and should include a dermatologist and a psychiatrist. Several psychoactive medications have been reported as useful, including risperidone, selective serotonin reuptake inhibitors and olanzapine.

Conclusion

Pruritus is an extremely debilitating sensation and prompt management is essential. A careful structured approach to its diagnosis and management, with referral early rather than late, will yield rewards. Review is important to gauge treatment efficacy and reconsider the diagnosis. It is also an opportunity for consideration of systemic treatment and eventual referral if there is no progress. MT

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COMPETING INTERESTS: None.

Diagnosing basal cell carcinoma

What is the role for dermoscopy?

HELENA COLLGROS MD
PASCALE GUITERA MD, PhD, FACD

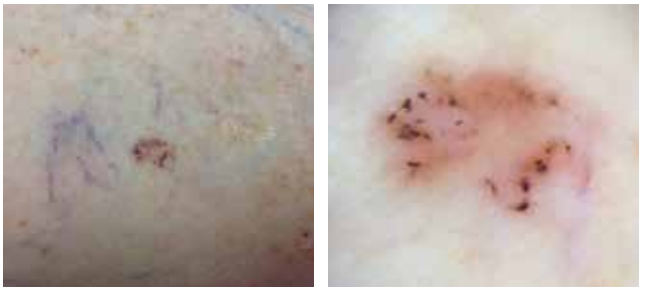
Dermoscopy has a role in the diagnosis of basal cell carcinoma (BCC) and may give clues to discern between superficial BCCs and other subtypes. Histopathology, however, remains the gold standard for diagnosis of these common skin cancers.

Basal cell carcinoma (BCC) is the most common form of skin cancer. Intermitent sun exposure appears to be the most important risk factor but there are others, such as fair skin phototype, that play an important role. BCCs usually develop on skin that contains pilosebaceous units, most commonly on the face, but the lesions also occur on locations that are not exposed to the sun. Although it rarely metastasises, a BCC may be locally aggressive and lead to serious morbidity if not correctly diagnosed and treated.

Case presentations

Case 1: Superficial BCC

A 73-year-old woman with no past history of skin cancer presented with a new lesion on her right thigh (Figure 1a). On clinical examination, a brown and pink macule, 1.5 cm in diameter, was observed. The differential diagnosis included BCC, melanocytic naevus and seborrhoeic keratosis. Dermoscopy showed short and thin telangiectasia, incomplete maple leaf-like areas and blue-grey globules (Figure 1b). A biopsy was performed and confirmed a diagnosis of superficial BCC. The patient received nonsurgical treatment with imiquimod 5% (applied five times per week for six weeks). At follow up three months later, dermoscopy revealed no signs of remnant superficial BCC.



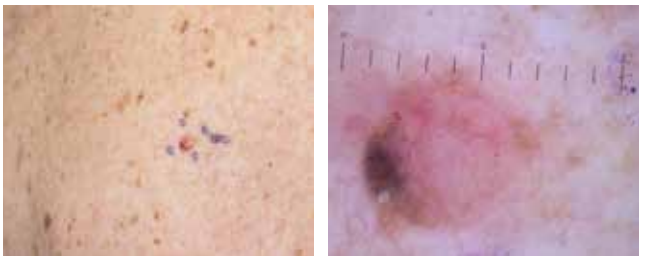
Figures 1a and b. Case 1. a (left). The lesion on the woman's leg at presentation. b (right). Dermoscopy showing short and thin telangiectasia, incomplete maple leaf-like areas and blue-grey globules.

Case 2: Nodular BCC

A 70-year-old woman presented for a full skin check. She had sun-damaged skin and a past history of nonmelanoma skin cancer. On clinical examination, a 1 cm shiny papule with telangiectasia and some brown pigment was noted on her back (Figure 2a). Dermoscopy showed arborising telangiectasia and blue-grey ovoid nests (Figure 2b). The findings were suggestive of nodular BCC and the patient was referred for surgical excision of the lesion.

Case 3: Infiltrative BCC

A 51-year-old woman presented with a lesion that had been growing on her left preauricular area for more than a year (Figure 3a). On clinical examination, a 0.8 cm flat, shiny, white and pink lesion with ill-defined margins was noted. Dermoscopy showed multiple thin arborising telangiectasia distributed in a stellate



Figures 2a and b. Case 2. a (left). The lesion on the woman's back at presentation. b (right). Dermoscopy showing arborising telangiectasia and blue-grey ovoid nests.

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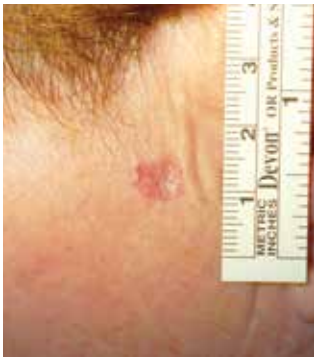
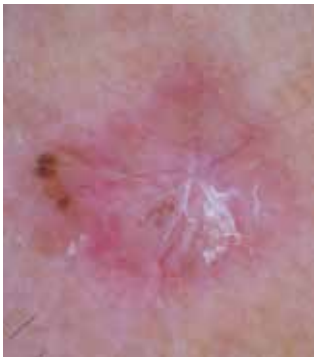
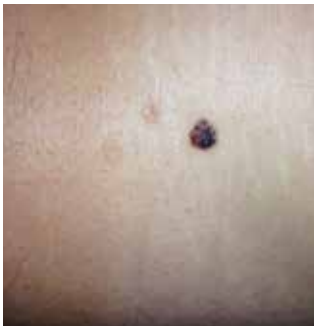
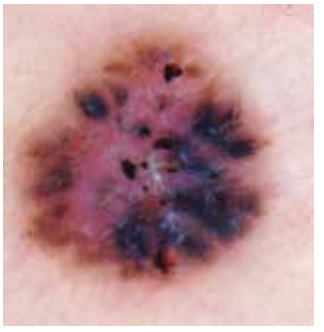



Figures 3a and b. Case 3. a (left). The lesion near the woman's ear at presentation. b (right). Dermoscopy showing multiple thin arborising telangiectasia, white-pink areas, blue-grey dots and concentric brown structures.

Figures 4a and b. Case 4. a (left) The lesion on the man's abdomen at presentation. b (right). Dermoscopy showing milky-red areas, multiple focal ulcerations, blue-grey ovoid nests, chrysalids and brown pigment on the periphery, resembling maple leaf-like areas or concentric structures.

pattern, white-pink areas, blue-grey dots and concentric brown structures (Figure 3b). The dermoscopic pattern was suggestive of an infiltrative BCC, but a diagnosis of melanoma had to be considered because of the brown pigment. After surgical excision, a diagnosis of infiltrative BCC was confirmed by histopathology.

Case 4: Pigmented nodular BCC

A 48-year-old man presented after recently observing a pigmented lesion on his abdomen (Figure 4a). On clinical examination, a 1 cm slightly elevated, shiny and intensively pigmented papule was noted. Dermoscopy showed milky-red areas, multiple focal ulcerations, blue-grey ovoid nests, shiny white streaks and brown pigment was present on the periphery, resembling maple leaf-like areas or concentric structures. No pigment network was observed (Figure 4b). The findings were suggestive of pigmented BCC, but melanoma remained a possibility. Histopathology confirmed a diagnosis of pigmented nodular BCC.

Discussion

Diagnosis

Histopathology remains the gold standard for diagnosing BCC and for differentiating BCC subtypes. Dermoscopy is helpful in the diagnosis of BCC and gives clues to discern between superficial BCC and nonsuperficial BCC, which are managed differently. Dermoscopy has been shown to be effective for discriminating BCC from other skin tumours, with a sensitivity of 95 to 97% and a specificity of 87 to 96%.[1-6] The dermoscopic characteristics of BCC are summarised in Table 1.

Subtypes of BCC

There are five major clinicopathological subtypes of BCC: nodular, superficial, infiltrative, morpheaform and fibroepithelial. Several other histopathological subtypes have been identified.[7]

Most subtypes of BCCs, particularly nodular BCC, can be pigmented, containing aggregates of melanin, melanocytes and melanophages. Pigmented BCCs are more common in people with olive skin (50% of all BCCs) than in those with fair skin (<10% of all BCCs).[8] For a pigmented BCC, the differential diagnosis must include melanoma and other pigmented lesions such as naevi and seborrhoeic keratoses.[9]

Nodular BCC is the most common subtype of BCC (about 50% of all BCC subtypes) and is usually located on the face. Clinically, lesions appear as pearly papules of pinkish colour with arborising telangiectasia and occasional presence of brown colour or ulceration.

Superficial BCC is most frequently located on the trunk and extremities. Clinically, it presents as a well-defined erythematous plaque with focal scale or ulceration. On some occasions a slightly prominent border may be seen. A superficial BCC initially has a horizontal growth but it may develop an invasive component if not treated.

Infiltrative BCC is usually located on the face. Lesions usually present as pinkish, shiny, flat lesions with arborising vessels and poorly defined margins.

Morpheaform BCC is less common than the previously described subtypes. Lesions are usually located on the face and resemble a scar, presenting as a hypopigmented or pink indurated area of ill-defined margins. Arborising telangiectasia, brown pigment and nodular areas may be present. Desmoplastic melanoma is a differential diagnosis.

Fibroepithelial BCC (Pinkus tumour) is a rare subtype of BCC and tends to occur on the sacral area and lower back.[7] It presents clinically as a pink or skin-coloured pedunculated papule or plaque, resembling a fibroma or an intradermal naevus.

Dermoscopy can give clues to discern between superficial BCC and nonsuperficial BCC.[10] In a 2014 study of dermoscopic criteria for discriminating superficial BCC from other subtypes

of BCC, the most potent predictors of superficial BCC were short fine superficial telangiectasia, maple leaf-like areas, multiple small erosions and shiny white-red structureless areas.[11] The authors found the presence of the first two criteria (short fine superficial telangiectasia and maple leaf-like areas) in the absence of blue-grey ovoid nests, arborising vessels and ulceration to be predictive of superficial BCC with a sensitivity of 81.9% and a specificity of 81.8%. By contrast, the presence of blue-grey ovoid nests, arborising vessels and ulceration increased the probability of nonsuperficial BCC. Blue-grey ovoid nests was the most potent predictor for invasiveness. Brown pigment located in the dermis appears blue (Tyndall effect),[12] so the presence of blue colour in a BCC should indicate that the lesion is located in the dermis and is therefore invasive. However, blue-grey dots or globules are found in both superficial and nonsuperficial BCCs. A flat clinical presentation does not imply that a BCC is superficial: 46.5% of flat lesions were found to be superficial whereas 53.5% were not.[11] The presence of blue-grey ovoid nests, even in a flat lesion, should exclude the diagnosis of superficial BCC and lead to surgical management of the tumour.

A study of BCC subtype classification by means of dermoscopy and reflectance confocal microscopy had similar findings.[13] The most frequent dermoscopic criteria of superficial BCC were superficial fine telangiectasia (70.5%), shiny white-red structureless areas (68.2%) and multiple small erosions (38.6%). Maple leaf-like structures were also a positive criterion for superficial BCC (31.8%). In nodular BCC, arborising vessels were the main feature (86.4%), followed by blue-grey ovoid nests (54.5%) and ulceration (27.3%). In invasive BCC, the most common criteria were shiny white-red structureless areas (72.7%) and arborising vessels (50%) of smaller calibre and less tendency to branch compared with those seen in nodular BCC.[13] Features of superficial BCC and nonsuperficial BCC are summarised in Tables 2 and 3.

In another recent study, a stellate peri-tumour dermoscopy pattern was described as a clue for diagnosis of infiltrating BCC.[14] This dermoscopic feature was defined as a geometric star-shaped pattern extending outwards from the circumferential peripheral edge of the tumour, and identified by white lines, vessels or uneven skin surface morphology. It was hypothesised that ulceration, present or past, could be an explanation for this pattern. Further studies are needed to assess the applicability of this dermoscopic feature.[15]

TABLE 1. DERMOSCOPIC FEATURES OF BCC

Absence of pigment network	
Superficial fine telangiectasia	
Linear and arborising telangiectasia	
Maple leaf-like areas on the periphery of the lesion	
Blue-grey ovoid nests or blotches	
Blue-grey dots or globules	
Specks of brown and grey pigment	
Spoke wheel areas (radial projections from a well-circumscribed dark central hub)	
Concentric structures (globular-like structures of brown, grey or black colour, with a darker central area)*	
Focal or multifocal ulceration	
Multiple small erosions	
Shiny white-red structureless areas	
Shiny white streaks (chrysalids)†	

* Considered to be precursors of spoke wheel areas.
† Only with polarised dermoscope.

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Management

The management of patients with BCC is well described in the Australian guidelines, which includes practical information about decision making for specialist referral.[16] The approach taken to treatment will depend on BCC subtype as well as other factors (e.g. tumour location, size, recurrence after prior excision). Dermoscopy allows a better delineation of margins than naked eye examination and should be used when planning surgery. The first-line treatment for nodular and other invasive BCC subtypes is complete excision with 2 mm margins. Mohs micrographic surgery is recommended for infiltrative BCC on specific locations on the face where it is associated with a lower recurrence rate

TABLE 2. SUPERFICIAL BCC: DERMOSCOPIC PREDICTIVE FEATURES

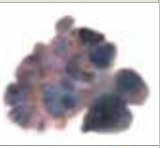
Positive predictive features		Negative predictive features	
Maple leaf-like areas		Blue-grey ovoid nests or blotches	
Superficial telangiectasia (short and thin)		Arborising telangiectasia (long and thick)	
Multiple small erosions		Ulceration	

TABLE 3. MOST FREQUENT DERMOSCOPIC CRITERIA OF BCC SUBTYPES[13]

Superficial BCC
Superficial telangiectasia (70.5%)
Shiny white-red structureless areas (68.2%)
Multiple small erosions (38.6%)
Maple leaf-like areas (31.8%)
Nodular BCC
Arborising telangiectasia (86.4%)
Blue-grey ovoid nests (54.5%)
Ulceration (27.3%)
Invasive BCC
Shiny white-red structureless areas (72.7%)
Arborising telangiectasia (50%)

than conventional surgery;[17] further information about Mohs surgery is provided in the Australian guidelines.[16] For invasive BCC where a surgical approach is not possible or when margins are involved after excision the treatment options include radiotherapy and (rarely) imiquimod; these should be discussed in a specialised environment.[18-20] A recently introduced systemic drug targeting the Hedgehog signalling pathway, vismodegib, is available for treatment of locally advanced or metastatic BCC.[21]

Superficial BCCs may be managed with nonsurgical treatments, such as imiquimod 5%, photodynamic therapy, electrosurgery or cryotherapy, or with second-line treatment with excision.[18-20] For some topical medications, confirmation of the diagnosis by biopsy is a PBS requirement. Patients who have numerous superficial BCCs can be treated with topical medications without the requirement for multiple biopsies. However, pigmented lesions that are suspicious for pigmented BCC but with a differential diagnosis of melanoma will need to be sampled.

KEY POINTS

- Dermoscopy has demonstrated utility in the diagnosis of BCC. It may also be helpful in discriminating superficial BCC from other subtypes of BCC.
- The presence of blue-grey ovoid nests in a BCC, even if the lesion is flat, should exclude the diagnosis of superficial BCC and lead to surgical management of the tumour.
- For a lesion containing elements of pigment, the differential diagnosis must always include melanoma and other pigmented lesions.
- Dermoscopy can inform decision making about the need to perform a biopsy for a lesion, the best location for the biopsy (sampling where the lesion looks most likely to be invasive) and the margins of the lesion before surgery.
- Histopathology remains the gold standard for diagnosis and classification of BCCs.

Conclusion

Dermoscopy has been shown to be effective for discriminating BCC from other skin tumours, and it can give clues to discern between BCC subtypes. Patients with lesions that are clearly classified as invasive after dermoscopic examination may be referred directly for surgery. In situations where a lesion is clearly classified as superficial by a very experienced dermoscopist and managed with nonsurgical treatment without a previous biopsy, follow up is mandatory to confirm resolution of the lesion. There are important potential pitfalls of not performing a biopsy, such as missing an invasive component of a mixed pattern superficial BCC or a rare collision tumour (BCC and melanoma). In doubtful cases, either a biopsy or surgical excision is required. Melanoma should always be included in the differential diagnosis of a lesion that contains elements of pigment. Key points regarding the role of dermoscopy in the diagnosis of BCC are listed in the Box. MT

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COMPETING INTERESTS: None.

Hirsutism

Common and a cause of significant anxiety

SUSAN DAVIS FRACP, PhD, FAHMS

Hirsutism is a common problem for women and associated with considerable psychological distress. Although it may indicate a significant metabolic disorder, it is often idiopathic. Cosmetic management is sufficient for most affected women but medical treatment may be needed when hair growth is severe.

The removal of facial and body hair has been intertwined with social and cultural practices for millennia. Cleopatra is reported to have 'threaded' her eyebrows, while classic nudes were generally lacking in any body hair.[1,2] Hairiness is still often viewed as a masculine characteristic whereas hairlessness may be linked with various ideas of femininity, attractiveness and sexuality. Little wonder then that hirsutism can be associated with considerable psychological distress.[3,4]

What is normal body hair?

Hair follicles exist on every part of the body except the lips, palms and soles of the feet. Body hair is usually fine and not pigmented. The term hirsutism is used to describe the growth of excessive, thick, dark hair in androgen-dependent areas in women (above the lip, chin, chest, upper arms, upper abdomen, lower abdomen, upper back, lower back and thighs).[5]

There are wide ethnic differences in the normal range of visible facial and bodily hair. Rating scales such as the modified Ferriman-Gallwey scale can help to determine whether hair growth fits ethnic norms (Figure 1).[5]

Causes

Idiopathic hirsutism is the most common cause of excessive hair growth in women (Box 1). In such cases, women do not always have normal serum androgen levels and some may have irregular menstrual cycles.

Polycystic ovary syndrome (PCOS) is the most common medical condition underlying hirsutism. However, hirsutism may be the first manifestation of other major endocrine disorders such as Cushing's syndrome, growth hormone excess and non-classical congenital adrenal hyperplasia (NCCAH), a rare cause that is not clinically distinguishable from PCOS.

Androgen-secreting tumours of the ovaries or adrenal glands are very rare. They are usually associated with a sudden and significant increase in hair growth and other signs of masculinisation (such as deepening of the voice or clitoromegaly).

Several medications may be associated with the growth of excess body hair. These include phenytoin, glucocorticoids, diazoxide, minoxidil, ciclosporin, tibolone and exogenous androgens.

Clinical assessment

A careful medical history should provide the diagnosis in most instances. The key points to elicit include the following.

- **Onset in relation to puberty.** Hirsutism that is idiopathic or related to PCOS typically develops soon after puberty or in the late teens. Menstrual irregularity increases the likelihood of PCOS. Acne and oily skin are often associated features.
- **Family history.** A family history of hirsutism is common in women with idiopathic hirsutism. A family history of PCOS or type 2 diabetes supports a diagnosis of PCOS in women presenting with hirsutism.
- **Rate of onset.** Sudden onset of hirsutism, particularly beyond the teenage years, raises suspicion of a major endocrine disorder or a hormone-secreting tumour as the cause.
- **Severe virilisation.** Deepening of the voice and clitoral enlargement are indicative of substantially elevated androgen levels and raise concern of a severe endocrine disorder such as Cushing's syndrome or an androgen-secreting tumour.

Physical examination should include assessment of weight and height to calculate body mass index, a baseline assessment of the

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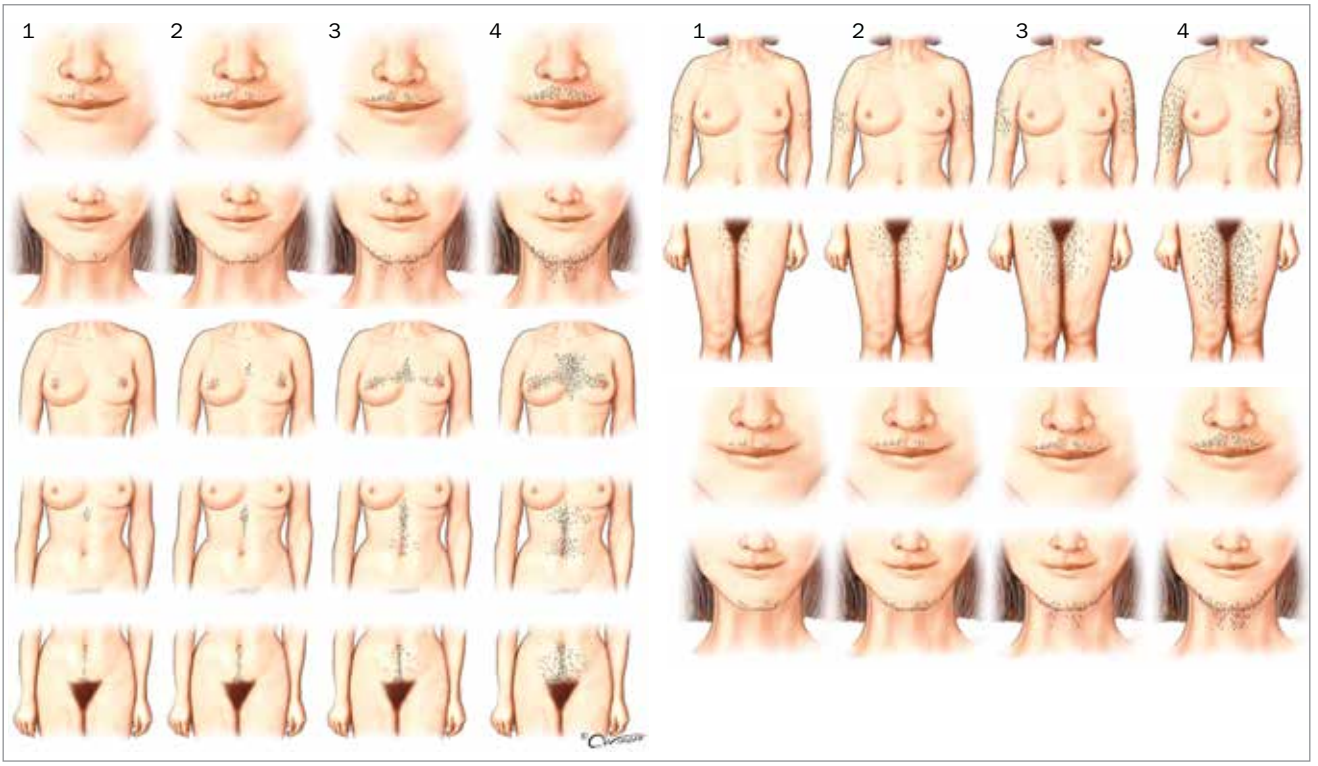

Figure 1. The modified Ferriman-Gallwey scale. Hair growth is rated from 1 (few hairs) to 4 (complete and heavy cover) in nine locations, giving a maximum score of 36. Hirsutism is defined when the total score is greater than 7.

degree of hirsutism and other features of virilisation – specifically male-pattern hair loss, acne, deepening of the voice and clitoromegaly. The latter can be determined by using the clitoral index, which is the product of the vertical and horizontal dimensions of the glans. A clitoral index greater than 100 mm^2 is definitely pathological.[6]

Acanthosis nigricans indicates insulin resistance and, although rarely present, is a cardinal sign of PCOS.

Abdominal examination should be performed to assess for adrenal masses and either pelvic examination or ultrasound to exclude ovarian masses as clinically indicated.

Elevated blood pressure and signs of Cushing's syndrome should be sought. Although hirsutism can be graded by the Ferriman-Gallwey scoring system,[7] this has limited utility in clinical practice. However, the severity of hirsutism should be noted. In addition, documenting how the patient is managing her hirsutism provides a good gauge of severity and documenting this is helpful to evaluate treatment response. For example, if a woman is shaving or plucking daily then this indicates severe hirsutism and a reduction in shaving/plucking frequency indicates a response to intervention.

What tests should be performed?

Young women with mild-to-moderate increased hair growth that has developed very gradually and who have regular menstrual cycles do not need any investigations. Although late-onset congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency may present in this way, the diagnosis is academic, as long-term adrenal suppression with steroids is not used in this setting.

Women with more severe hirsutism and regular menses should have both total testosterone and sex hormone-binding globulin (SHBG) levels measured.

Women with severe hirsutism and irregular menses should also have levels of testosterone precursor hormones (androstenedione and dehydroepiandrosterone sulfate [DHEAS]) as well as follicle stimulating hormone (FSH) and luteinising hormone (LH) measured. They should also have a pelvic ultrasound (ideally transvaginal and performed by a gynaecological sonographer) to identify polycystic ovaries. When NCCAH is suspected, patients should be referred to a specialist for measurement of an early morning 17-hydroxyprogesterone level.

An elevated DHEAS indicates an adrenal contribution to androgen excess. DHEAS and androstenedione are often elevated in women with PCOS. When the level is more than twice the upper limit of normal, the possibility of an adrenal tumour must be excluded. In this instance, an adrenal CT scan is indicated. If any pathology is found, the patient requires referral to a specialist endocrinologist for

further investigation. A very low SHBG level indicates insulin resistance and should be followed up with a fasting insulin and glucose level. An elevated basal early morning 17-hydroxyprogesterone level is highly predictive of late-onset CAH. Rapid onset of hirsutism in a mature woman who has not previously been hirsute raises concern about a sinister cause of the symptom.

When to refer

Women with hirsutism should be referred when:

- the diagnosis remains unclear
- NCCAH is suspected (although this is extremely rare in Australia)
- there is any suspicion of an androgen-secreting tumour (sudden onset, virilisation)
- hirsutism has not improved after six to 12 months of standard therapy.

Management of hirsutism

The aim of any treatment for hirsutism is to achieve an acceptable cosmetic outcome. For women with PCOS, weight loss may result in improvements in menstrual cycles and a reduction of hair growth, although this is usually modest. Therefore, obese women with high androgen levels should follow a sensible low-calorie, low-fat diet and also exercise regularly. Discussion of pharmacotherapeutic interventions for PCOS is beyond the scope of this article.

Cosmetic treatments

Common cosmetic approaches for hirsutism include bleaching hair with peroxide, applying heavy make-up, shaving, plucking, waxing and using depilatory creams. These approaches are effective for mild hirsutism.

Electrolysis and laser therapy for hair removal should be provided only by trained personnel, need to be repeated and are expensive and practical only for treating limited areas. Electrolysis requires repeated visits but the effects are usually long-lasting. It is also effective for nonpigmented hair. Lasers and intense pulsed light (IPL) treatment target melanin in the hair bulb, which absorbs the light emitted by the laser. Therefore, they are effective for pigmented, but not fair hair. Laser therapy allows larger areas to be treated over a short time period. Therefore an advantage of electrolysis over laser therapy is that it can be used on both dark- and light-skinned patients and those with fair hair.

Topical medication

Eflornithine hydrochloride cream (13.9%) has been approved for treatment of facial hirsutism. It is a specific, irreversible inhibitor of ornithine decarboxylase, an enzyme present in the hair follicle that is involved in hair growth. It is applied twice daily to affected facial areas and has demonstrated efficacy in clinical trials.[8] Its use is restricted to the face, as the efficacy and safety with respect to use on other areas of the body have not been studied. Women need to be advised that efficacy is only seen after six to eight weeks of regular use. It complements the use of oral therapies. Some women experience mild skin irritations such as redness, stinging, burning, tingling, acne or rash, but these are usually transient. When used in combination with laser therapy for the treatment of facial hirsutism, eflornithine enhances the efficacy of the laser.[9] It is contraindicated in those with severe renal impairment and is not recommended in pregnant or breastfeeding women.

Oral medication

Oral drug treatment can be recommended when hirsutism is bothersome and/or when cosmetic measures have failed. Six to 12 months of treatment is required before the full effect can be judged.

Oral contraceptives

The combined oral contraceptive pill (OCP) suppresses ovarian androgen production. It also elevates SHBG levels and therefore increases the proportions of testosterone and its potent androgenic metabolite dihydrotestosterone that are protein bound (and therefore less available to have a cellular effect).

The OCP is ideal for women requiring menstrual cycle regulation or contraception. The progestin component of most oral contraceptives is androgenic and may rarely exacerbate hirsutism. However, various OCPs contain nonandrogenic progestins and others contain the antiandrogenic progestins drospirenone and cyproterone acetate, each in combination with ethinyl oestradiol. The OCPs containing cyproterone acetate and drospirenone have been shown to significantly decrease hair growth over six months.

CAUSES OF HIRSUTISM

- Idiopathic
- Polycystic ovary syndrome
- Cushing's syndrome
- Growth hormone excess
- Nonclassical congenital adrenal hyperplasia
- Androgen-secreting tumours of the ovaries or adrenal glands
- Medications, including phenytoin, glucocorticoids, diazoxide, minoxidil, ciclosporin, tibolone and exogenous androgens

Antiandrogen therapy

Women of childbearing age must have effective contraception when using antiandrogens because there is a risk of feminisation of genitalia in the male fetus. Antiandrogens may impair libido. There is no evidence that any one antiandrogen is better than another.

- **Spironolactone.** Spironolactone inhibits androgen production and blocks the androgen effect at the hair follicles. It is a common first-line treatment for hirsutism, being as effective as cyproterone acetate.[10,11] The recommended starting dose is 100 mg daily; the maximum dose is 100 mg twice daily. In previously eumenorrhoeic women, spironolactone may cause irregular bleeding,[12] whereas in women with oligomenorrhoea, menstrual regularity may be restored.[10,13] Spironolactone can be used

as monotherapy or combined with the OCP for added efficacy and/or cycle control. Women should have their electrolyte levels checked shortly after commencing therapy (6 to 12 weeks) and at least annually thereafter to ensure hyperkalaemia does not occur.

- **Cyproterone acetate.** Cyproterone acetate suppresses pituitary FSH and LH secretion, and thus ovarian androgen production, and inhibits the binding of androgen at the hair follicle androgen receptor. It is available as low-dose therapy (2 mg daily) as part of an OCP. When efficacy is not achieved at this dose it can be prescribed in conjunction with an OCP. A starting dose of 50 mg daily with the first 10 days of active OCPs is recommended, with reduction to 25 mg for 10 days per month when efficacy is achieved.

Cyproterone acetate is prescribed as single therapy for postmenopausal women (20 days per calendar month), because it is taken up by fat tissue and then re-released into the circulation. This regimen is not advised for premenopausal women because without cyclical oestrogen menstrual cycle irregularity occurs.

The most common side effects include suppressed libido, diarrhoea, nausea, weight gain, breast tenderness and headache. Most women have no side effects when cyproterone acetate is taken as part of the OCP.

- **Flutamide.** Flutamide is a nonsteroidal antiandrogen that acts by directly blocking the androgen receptor. One study demonstrated that low-dose flutamide (62.5 mg daily) reduced hair growth by 70% after 12 months of treatment.[14] Discontinuation is common with higher dosages.[15] Liver toxicity is rare but worth noting.[16] Abnormal liver function tests were seen in 9.4% of women treated with low-dose flutamide over 12 months.[17] Flutamide is not currently available for the treatment of hirsutism in Australia.
- **Finasteride.** Finasteride is a potent inhibitor of the enzyme 5-alpha reductase-2 and hence blocks conversion of testosterone to dihydrotestosterone. A daily dose of 2.5 mg finasteride decreases hirsutism by 50% after one year.[18] Efficacy has also been demonstrated with dosing every third day.[19] The efficacy of finasteride compared with other antiandrogens is not clearly established with conflicting findings in different studies.[5,20,21] Side effects have not been commonly reported but may include headache, depression, breast tenderness and decreased libido. Finasteride is prescribed by specialists with caution off-label in Australia for hirsutism.

Conclusion

Excessive hair growth is a common problem for women. Cosmetic management is sufficient for most women but medical treatment is a reasonable option when hair growth is severe. For most, drug treatment is only a temporary measure to alleviate symptoms while a long-term cosmetic program is established. MT

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