DECEMBER 2017 VOL 2 NO 2

A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

Reprints in Dermatology

Therapies for common cutaneous fungal infections

A pigmented macule on the nose – what is your diagnosis?

Hidradenitis suppurativa – debilitating and challenging

Advanced melanoma: a new landscape for treatment

Childhood atopic dermatitis – overcoming parental topical corticosteroid phobia

Xanthelasma palpebrarum

DERMATOLOGY COLLECTION
REPRINTS IN DERMATOLOGY
DECEMBER 2017 VOL 2 NO 2

ISSN 1443-430X

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Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR-IN-CHIEF, DERMATOLOGY COLLECTION

In this fourth issue of *Dermatology Collection* you will find articles that we consider among the most important published in *Medicine Today* in recent years.

Cutaneous fungal infections are common but despite this they are easily misdiagnosed because they can mimic many noninfective dermatoses. This article is a reminder of how easy it is to confirm fungal infections with a simple scraping and how to most effectively manage them.

Corticosteroid phobia is a heartsink condition that leads to familiar discussions between anxious parents and their doctors when they bring their children for management of atopic dermatitis. After years of campaigning, largely by Australian researchers, this topic is gaining international attention in the medical press. It is time for all of us to know and tell the truth about topical corticosteroids. They are absolutely safe if used properly and natural therapy is no substitute for them when it comes to itchy, sleep-deprived children.

Do you think you could identify hidradenitis suppurativa? It is rarely correctly identified because it can look so much like recurrent boils. New effective treatments, including the biologic agent adalimumab, can change its often debilitating course.

Australia is one of the countries where melanoma is a major issue. Advanced melanoma was almost always a death sentence only a few years ago, but new advanced treatments are changing that and patients are living with this disease for long periods. It is early but hopeful days. On the subject of pigmented lesions, brush up your dermoscopy knowledge with this case study.

Finally the humble xanthelasma palpebrum: a very common sign to take note of when considering your patient's lipid status.

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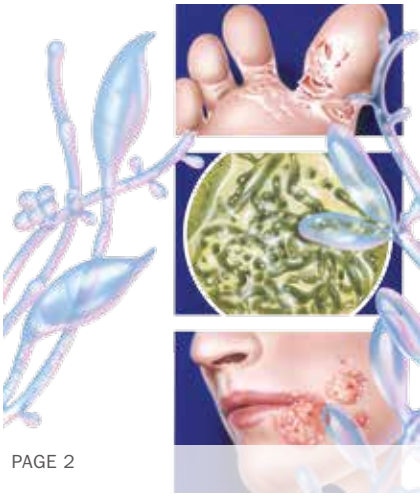

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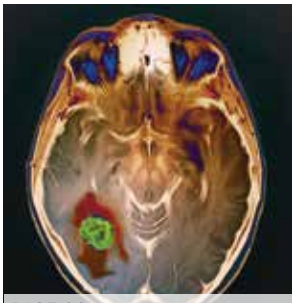

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FEATURE ARTICLES PEER REVIEWED

Therapies for common cutaneous fungal infections

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A practical approach to the diagnosis and treatment of common fungal infections of the skin and hair is provided. Topical antifungal therapies are effective and usually used as first-line therapy, with oral antifungals being saved for recalcitrant infections. Treatment should be for several weeks at least.

KEY POINTS

- Fungal infection should always be in the differential diagnosis of any scaly rash.
- Topical antifungal agents are typically adequate treatment for simple tinea.
- Oral antifungal therapy may be required for extensive disease, fungal folliculitis and tinea involving the face, hair-bearing areas, palms and soles.
- Tinea should be suspected if there is unilateral hand dermatitis and rash on both feet – 'one hand and two feet' involvement.
- Oral antifungal treatments can often be pulsed intermittently, reducing the overall dose required.

MedicineToday Dermatology Collection 2017; 2(2): 2-14
First published MEDICINE TODAY 2014; 15(6): 35-47
Updated November 2017

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Tinea and yeast infections are among the most common diagnoses found in general practice and dermatology. Although antifungal therapies are effective in these infections, an accurate diagnosis is required to avoid misuse of these or other topical agents. Furthermore, subsequent active prevention is just as important as the initial treatment of the fungal infection.

This article provides a practical approach to antifungal therapy for common fungal infections of the skin and hair. It is not intended to be an in-depth treatise on dermatomycoses, and onychomycosis and cutaneous candidiasis are not covered in detail. The initial section briefly reviews the practical pharmacology of commonly used antifungal agents, in order to guide their use. Treatment options are summarised in the Table. The defining features of various dermatophytoses (tinea) and yeast infections and their differential diagnoses and treatments are then discussed.

Antifungal therapies

Topical antifungal preparations are the most commonly prescribed agents for dermatomycoses, with systemic agents being used for complex, widespread tinea or when topical agents fail for tinea or yeast infections. The pharmacology of the systemic agents is discussed first here.

Systemic antifungal agents

Terbinafine

Terbinafine is a highly effective antifungal agent, by virtue of its fungicidal property. It is an allylamine and works by inhibiting

TABLE. TREATMENT OPTIONS FOR COMMON CUTANEOUS FUNGAL INFECTIONS

Fungal infection	First-line therapy	Second-line therapy	General notes
Tinea corporis, Tinea capitis, Tinea cruris, Tinea faciei, Tinea manuum	Topical terbinafine Topical imidazoles	Oral terbinafine 250 mg for 2 to 4 weeks Fluconazole 200 mg weekly for 2 to 4 weeks (off-label use) Itraconazole 200 mg twice daily for 1 week per month for several months Griseofulvin 500 mg daily for several weeks	Keep skin dry Identify and eliminate source
Tinea incognito	Oral agent as above, with topical agent as adjunct		Cease topical corticosteroid use Identify and eliminate source
Tinea pedis – interdigital type	Topical terbinafine or econazole – spray-on lotion Topical miconazole – tincture	Add topical mometasone furoate lotion to reduce inflammation	Dry feet and interdigital spaces thoroughly, e.g. with a hair dryer Add antifungal powders to shoes Wear open shoes whenever possible, go barefoot at home Remove shoes under desk at work
Tinea pedis – moccasin type	Topical terbinafine – cream Topical imidazoles	Typically needs oral agent Oral terbinafine 200 mg daily for 2 to 4 weeks Fluconazole (off-label use) Itraconazole 200 mg twice daily for 1 week per month for several months	
Kerion	Oral terbinafine 250 mg daily until clinically and mycologically cured Antidandruff shampoo daily to reduce shedding of fungal elements Cephalexin 500 mg three times daily to treat secondary bacterial infection	Fluconazole 200 mg weekly until cured Itraconazole 200 mg twice daily for 1 week per month Griseofulvin 500 mg daily until cured Prednisone 0.25 to 0.5 mg/kg daily if significant inflammation or scarring	Treat with oral agent until clinically cured and hairs start regrowing
Seborrhoeic dermatitis	Scalp and body disease: daily antifungal shampoo for scalp and body for 10 days; then twice weekly long-term. Treat top half of body, down to groin; leave shampoo lather on for 10 minutes each time. Change type of shampoo with each new bottle Facial disease: topical imidazoles or topical combination therapy such as hydrocortisone 1% with either miconazole 2% or clotrimazole 1% creams	Fluconazole 200 mg weekly for 4 weeks (off-label use)	Daily scalp shampooing to reduce accumulated scale Always use conditioner to restore moisture to hairs
Pityriasis versicolor	Econazole 1% as a foaming solution over 3 nights or antidandruff shampoo as for seborrhoeic dermatitis, followed by twice weekly antifungal shampoo long-term	Fluconazole 200 mg weekly for 4 weeks (off-label use) Itraconazole 200 mg once daily for 7 to 10 days	Discolouration takes months to even out

squalene epoxidase. It has greater affinity for fungal squalene epoxidase than the human type. Inhibition results in a deficiency of ergosterol (an important fungal cell wall constituent) and the accumulation of squalene, both of which disrupt fungal cell membranes. It is especially effective against infections caused by dermatophytes (*Epidermophyton*, *Microsporum* and *Trichophyton*).

About 80% of an oral dose of terbinafine is absorbed, regardless of food intake, but first-pass metabolism limits bioavailability to 40%. Terbinafine is lipophilic and thus widely distributed, with significant and rapid distribution in skin stratum corneum, sebum, hair and nails.

High concentrations of the medication are reached in the stratum corneum within hours of commencement of therapy. After 12 days of terbinafine 250 mg

daily, there is enough drug in the skin to maintain a minimum inhibitory concentration (MIC) for two to three weeks after cessation of treatment. Terbinafine is found in the distal nail after one week of therapy, and after six or more weeks of treatment it is detectable for at least another 30 weeks (indicating the potential for continued action). It is also found in the hair after one week of treatment, and may be detected for up to another 50 days after just two weeks of treatment.

As terbinafine is metabolised in the liver and the metabolites are excreted in the urine, dose adjustment is required in patients with renal failure where the serum creatinine level exceeds 300 µmol/L. With the exception of those with renal insufficiency, dose adjustment is not required in the elderly.

Terbinafine is generally a very safe agent. The most common adverse effects are headache, gastrointestinal symptoms and drug eruptions; hepatic and haematological complications are quite uncommon. Blood counts and liver function tests should be performed if terbinafine is to be used continuously for more than six weeks. One peculiar side effect is a disturbance, or even loss, of taste in some patients, which can be irreversible.

Terbinafine has no serious drug interactions and there are no contraindications to its use with other drugs. However, because it is an inhibitor of cytochrome P450 2D6, care should be taken when administering it to patients taking tricyclic antidepressants and other drugs metabolised by this isozyme.

Griseofulvin

Griseofulvin was the first important oral antifungal agent available for the treatment of fungal skin infections. Historically its main use was in the treatment of tinea capitis. Being only fungistatic, it is not as effective as the other agents described here.

Treatment needs to be continuous until mycological and clinical cure when griseofulvin is used to treat dermatophyte infections. This often leads to protracted courses (several weeks to months), especially with onychomycosis, for which up to 18 months of treatment may be required. It is important to note that griseofulvin has no activity against the yeasts *Candida* and *Malassezia* (formerly known as *Pityrosporum*).

Typical doses in children are 10 to 15 mg/kg daily, with recalcitrant cases requiring up to 25 mg/kg daily, and in adults, 500 mg to 1 g daily. The medication is best taken with a fatty meal to increase absorption. For children, the tablets can be crushed and administered with, for example, chocolate, full-cream ice cream or peanut butter. The medication is presented to the skin via sweat, concentrating in the stratum corneum. It is quickly cleared from skin and hair after cessation of therapy.

Although well tolerated, side effects are common with the use of griseofulvin and include headaches, photosensitivity, drug rashes, gastrointestinal disturbance, urinary and menstrual disturbances, liver dysfunction and neurological effects (fatigue, mood changes, dizziness, blurred vision). Changes to spermatogenesis occur, and men taking griseofulvin should not father children for at least six months after ceasing treatment.

The use of antacids and H_2-antagonists may reduce absorption of griseofulvin; they should be taken two hours after the antifungal agent. Griseofulvin can increase the metabolism of warfarin and the contraceptive pill. When co-administered with alcohol, patients should be warned about the disulfiram-like reaction that can occur.

Itraconazole

Itraconazole, a triazole, is useful in the treatment of onychomycosis and dermatomycoses. It is also useful for infections caused by *Candida, Malassezia* and some nondermatophyte moulds. It acts by inhibiting 14α-demethylase, resulting in inhibition of ergosterol production from lanosterol.

Being a highly lipophilic drug, itraconazole is best taken with a meal. A low pH gastric environment is also useful to aid absorption. In patients who have relative achlorhydria (i.e. those taking H_2-antagonists, proton pump inhibitors or antacids) or who are taking the drug on an empty stomach, absorption is aided by the coadministration of a cola soft drink. The drug is often used in a pulsatile manner.

Itraconazole rapidly presents into the stratum corneum and persists for three to four weeks after cessation of therapy. In the nail, a MIC is achieved after only one week of 200 mg itraconazole twice daily. After several one-week-per-month pulses of treatment, the drug can persist for months in the nail plate. Appreciable amounts are present in hair after only one week of therapy, with higher concentrations found with longer pulses. Itraconazole can persist for up to nine months after cessation of therapy.

Note that a newer formulation of itraconazole was introduced into the Australian market in 2014, with a much higher bioavailability; thus a 50 mg tablet is equivalent to 100 mg of the older preparations. The doses of itraconazole listed in this article are for the older, original formulation.

Fluconazole

Fluconazole is a commonly used broad-spectrum triazole that, like other azoles, inhibits 14α-demethylase. However, it is much less lipophilic and much less protein-bound than other azoles. It has very high bioavailability and its absorption is not affected by food.

When used as a once-a-week 150 mg pulse, fluconazole is present in the skin after the first dose, and with continuous therapy can persist several days after cessation. It is present in the nail after one dose as well, but after several months of once-weekly therapy, it is still present in the nail after six months.

As the drug is primarily cleared by renal excretion, a dose adjustment is needed when there is renal impairment (creatinine clearance, less than 50 mL/min). There is no need for dose reduction in renally impaired patients receiving a single dose

for vaginal candidiasis.

Fluconazole is very well tolerated. Headache, gastrointestinal upset and mild liver function test abnormalities are uncommon. At very high doses, anorexia and hair loss have been reported.

Ketoconazole

Oral ketoconazole was deregistered and discontinued in Australia and New Zealand in December 2013 because of its risk of hepatotoxicity.

Before its discontinuation, oral ketoconazole was the oldest of the systemic imidazoles available for the treatment of fungal infections but had been largely replaced in clinical practice by terbinafine, griseofulvin, itraconazole and fluconazole. It was, however, considered still useful in the treatment of widespread pityriasis versicolor because of its significant excretion in eccrine sweat, a 10-day course being generally regarded as being reasonably safe.

Topical antifungal agents

Topical antifungals are the most common agents prescribed for dermatomycoses. In general, dermatophyte infections are better treated with terbinafine, and yeast infections with the imidazoles. Regardless of the treatment used, general measures that keep infected areas dry and in good condition are just as important.

Terbinafine

Being both fungistatic and fungicidal, terbinafine is likely to be the most effective topical antifungal therapy. As mentioned earlier, it is highly lipophilic and efficiently absorbs into and binds the stratum corneum, sebum and hair follicles. High minimum inhibitory concentrations are achieved in the skin after a few days of therapy, and its avidity for the keratin layer helps prevent reinfection during treatment.

Creams and spray formulations of terbinafine are available. Creams are effective on the body and can be used with little irritation in the folds. Spray preparations are useful in the interdigital areas, as the sprayed lotion dries on the skin, avoiding maceration. Twice-daily applications are most practical.

Terbinafine is a well-tolerated topical agent and should be considered a first-line therapy for dermatophyte skin infections. It is important to note that it is not effective against *Candida* or *Malassezia* infections.

Imidazoles

The topical imidazole antifungals are the most commonly prescribed antifungal preparations. This group includes ketoconazole, bifonazole, clotrimazole, econazole and miconazole. They are effective against most dermatophytes and against *Candida* and *Malassezia*. Of interest, miconazole and econazole also show modest antibacterial properties and may be serendipitously efficacious in treating erythrasma, ecthyma and mild impetigo.

Practically, the various topical preparations are equivalent in efficacy. They should be used twice daily for dermatophyte infections, to increase efficacy and to ensure that if forgotten occasionally, patients are still getting therapy every day. Clinicians should become familiar with a few products in different bases, i.e. creams, lotions, tinctures, powders and shampoos, allowing different agents to be used in different situations.

Topical imidazoles are often used to treat tinea pedis. The interdigital spaces are often moist with prolonged use of shoes and socks. Thus, putting a cream preparation here can perpetuate the maceration that occurs with tinea infections. Spray-on lotions are useful in this site, as the product can dry on the skin and not leave a boggy mess. Tinctures are also useful in the toe webs, as they dry the area applied to by virtue of the alcohol base (they are also useful under the nail plate). Some commercial tinctures, however, can stain the tissues.

Antifungal powders can be dusted into skin folds, helping dry the area. However, a powder used with any cream can result in a gritty paste, which causes irritation. The author finds powders most useful when placed in shoes; they do not treat the tinea pedis per se, but can reduce the rate of re-infection by reducing the fungal load in the shoes and socks.

Antifungal shampoos are useful in the treatment of seborrhoeic dermatitis. The two key clinical pearls of wisdom are to leave the lathered preparation on for up to 10 minutes before rinsing to allow the antifungal agents to work, and to regularly rotate shampoos to reduce the risk of resistance to one active agent. In extensive tinea capitis, antifungal shampoos are used with a systemic agent in order to reduce the spread of fungal spores from the scalp.

A foaming solution of econazole is useful in the initial treatment of pityriasis versicolor or seborrhoeic dermatitis.

A two-part proprietary treatment kit is available for onychomycosis: a urea-containing ointment that is applied to the nail for one to three weeks to soften it, allowing most of it to be scraped away, and bifonazole cream that is then applied daily for four weeks.

Imidazole preparations formulated with hydrocortisone acetate (as are available for clotrimazole and miconazole) have the added benefit of the corticosteroid's mild anti-inflammatory effect. These are useful where an inflammatory rash or itch accompanies the infection, such as with seborrhoeic dermatitis on the face and when there is irritancy and candidal co-infection in tinea of the skin folds.

Amorolfine

Amorolfine is a broad-spectrum topical antifungal agent that acts by disrupting fungal cell membranes through inhibition of ergosterol synthesis. It is available as an over-the-counter lacquer paint formulation for the treatment of onychomycosis caused by dermatophytes and yeasts. Although early clinical trials showed some benefit, it is relatively expensive, has variable effectiveness and is unlikely to be useful for extensive, deep

onychomycosis; systemic agents are best used for these infections.

Patients are required to file down the affected nail and apply the preparation on a once- or twice-weekly basis until the onychomycosis is cured. Most patients give up with this treatment; of those who do use it for more than a year, less than half will achieve clinical cure. The role of amorolfine may well be only for white superficial onychomycosis.

Role of topical corticosteroids

Traditionally, the use of topical corticosteroids for treating cutaneous infections has been discouraged. When potent topical corticosteroids are used on dermatomycoses, the annular erythema of the rash can be reduced, making it look quite nonspecific. Thus the 'ringworm' loses its classic appearance – tinea incognito – and misdiagnosis can result. Furthermore, topical corticosteroids can reduce the body's inflammatory/immune response to the infection and thus facilitate its spread.

The availability of several combination products, however, is testament to the usefulness of corticosteroids in the adjuvant treatment of infections that have a significant inflammatory component. The key to avoiding misuse of a topical corticosteroid in fungal infections is an accurate diagnosis in the first instance. Tinea should always be considered in any eruption that is scaly or has an annular or serpiginous appearance, and skin scrapings should be taken for fungal microscopy and culture.

Once antifungal therapy has commenced, it is reasonable to occasionally add in a topical corticosteroid, tailoring the potency to the degree of inflammation, to reduce the inflammatory itch and discomfort. Corticosteroids can also help restore the integrity of the skin and improve its barrier function as the fungal infection is being treated. Practical examples include adding a corticosteroid lotion to an imidazole lotion/spray in the treatment of inflammatory interdigital tinea, and using topical or systemic corticosteroids in addition to antifungal therapy in the treatment of highly inflammatory tinea capitis in children to reduce hair loss and scarring.

Common clinical dermatomycoses

Dermatomycoses are caused by dermatophytes and some yeasts. The three classic sources of dermatophyte infections – or tinea – in humans are animals (zoophilic dermatophytes), the soil (geophilic dermatophytes) and other humans (anthropophilic dermatophytes). These infections of skin, hair and nails can present in a similar fashion, although the zoophilic types tend to be somewhat more inflammatory. It may be important to identify the source of the fungus in order to prevent further reinfection or spread to others; for example, a new guinea pig, cat or other pocket pet may be the source of facial tinea in a young child (through cuddling of the pet), and a child with a kerion may well disseminate the tinea to classmates.

Fungal infections of the skin and hair tend to be treated similarly regardless of the specific fungus causing the infection.

One common classification of tinea is based on the body site infected, and this is the classification followed in the discussion below of common dermatophyte infections (tinea infections of the nail – tinea unguium or onychomycosis – are common but beyond the scope of this article). Two *Malassezia* infections are also discussed. The treatments of these fungal infections are summarised in the Table.

Body – tinea corporis

Tinea corporis, classically known as 'ringworm', presents as erythematous patches with scales on the trunk, arms or legs (Figure 1). There should be an 'active' border with accentuation of the clinical findings; this is the spreading edge of the patch of tinea. Patches may be quite large and extensive with long-term infections, but the classic features of scale and activity at the border should be present. Multiple patches may be found, and tinea in other body sites should be sought.

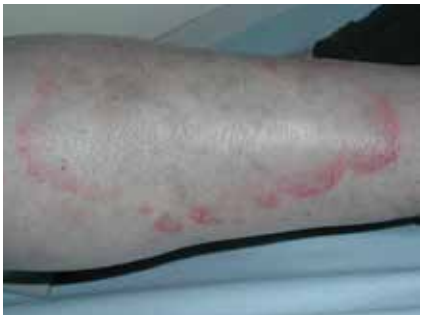

Figure 1. Tinea corporis on a leg. Note the active, advancing border, central clearing and scale. Skin scrapings should be performed from the edges.

Tinea incognito. Patches of tinea inadvertently treated with topical corticosteroids will look less impressive, with less erythema and little scale. This disguises the true nature of the dermatophyte reaction, hence the term 'tinea incognito'. Rashes that are spreading or poorly responsive to topical corticosteroids should prompt the consideration of corticosteroid-modified tinea.

Fungal folliculitis. Fungal folliculitis can occur in hair-bearing skin, manifesting as follicular pustules in an area of tinea. It can be accentuated by the use of topical corticosteroids.

Differential diagnoses

The many differential diagnoses for the annular or discoid rash of tinea corporis include the following:

- discoid eczema – the dry and scaly rash is rounded but not often annular (i.e. no central clearing); it can be intensely itchy, whereas tinea corporis may not be
- psoriasis – is typically a thicker plaque than tinea corporis, with thicker silvery scales, and not annular; it should be sought on the extensor surface of the elbows and knees
- granuloma annulare – is also ring-like, but occurs much more slowly and insidiously; there is never scale, as it is a deeper dermal eruption

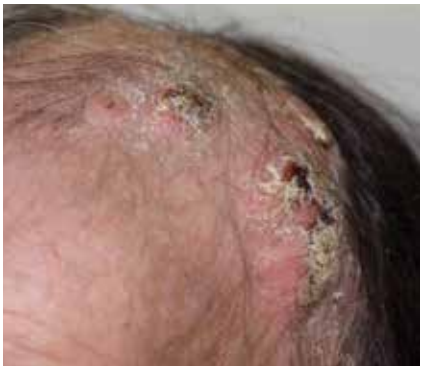

Figure 2. Kerion of the scalp.

- fixed drug eruptions – tend to have a peculiar pigmented, red or purple appearance, and scale is not often a feature; new lesions occur with continued medication use, and older ones reactivate in the same spot
- subacute cutaneous lupus erythematosus – can present as an annular and polycyclic eruption that is scaly and may have the appearance of an active border, thus looking very much like tinea; however, it is found in a photodistributed area, with worsening after solar exposure. Arthritis, facial rash and other manifestations of cutaneous lupus should be sought
- annular lichen planus – although typically occurring on the genitals, this can inadvertently have an annular appearance on the body. The rash is made up of small purple, raised papules with a characteristic lacy scale (Wickham's striae) on the top of the papules; itch is often a feature
- erythema annulare centrifugum – is one of several rare annular rashes that represent a 'reaction pattern' to a variety of stimuli; in most cases no cause is found. These lesions start as a small patch or papule that evolves slowly to a larger annular patch, with a characteristic rim of scale that has the free edge on the inner side of the ring.

Treatment

Unless the clinician is absolutely certain of the diagnosis, skin scrapings from the edge of an annular rash should always be taken to diagnose tinea corporis. Microscopy should show fungal elements, and culture will identify the variant of fungus and sensitivities to aid treatment. A skin biopsy can be useful to rule out the more sinister differential diagnoses.

As mentioned previously, identification of the infection source is important to reduce reinfection. Tinea corporis in an individual may be due to autoinoculation from another body site; tinea pedis, tinea cruris and onychomycosis should be sought.

General measures such as fastidious drying of skin folds is important. Treatment with topical terbinafine is generally more effective than with an imidazole. Treatment should occur twice daily for several weeks, until the rash disappears completely. Any other sources in a patient should be treated, and strategies for preventing reinfection may be needed (such as improving personal hygiene, taking more care in public showering facilities or having the family pet treated for fungal skin infections).

Fungal folliculitis, extensive tinea corporis, tinea incognito, kerion or any other atypical fungal infection should be treated additionally with an oral antifungal agent. Treatment should continue until clinical cure is achieved. Oral terbinafine is highly effective (250 mg daily for at least two to four weeks until the rash settles). It is not on the Pharmaceutical Benefits Scheme for this indication, but generics are available that make it a viable option. Fluconazole 150 to 200 mg weekly for up to four weeks is therapeutic and economical (off-label use). Itraconazole 200 mg twice daily for one week per month is an alternative (original formulation), but the cost in Australia is prohibitive. Oral griseofulvin 500 mg daily is a traditional treatment, but less efficacious than other agents. With any prolonged oral therapy, liver function tests may be appropriate every six weeks or so to exclude hepatotoxicity.

Figure 3. Extensive inflammatory scarring and resultant hair loss around a kerion of the scalp.

Scalp – tinea capitis

The clinical presentation of tinea capitis can vary greatly. Typically there is a patch of hair loss with easily extractable hairs but different species of dermatophyte will cause differing degrees of scaling and inflammation. The variants are:

- alopecia areata-type – discreet patch of hair loss with dull-grey hairs coated with the fungal spores (ectothrix infection)
- black dot tinea – linear patches with the hair shafts broken at skin level (endothrix infection); there is minimal scale, although a low-grade folliculitis is often seen
- agminate folliculitis (diffuse pustular-type) – a sharply-defined dull red plaque studded with follicular pustules
- kerion – a large, boggy, erosive, pustular, inflammatory mass that resembles an abscess (Figure 2)
- favus – a rare variant that has a characteristic 'cup-shaped' scale at the base of the hair shaft.

Scarring from excessive inflammation can lead to permanent hair loss (Figure 3).

Differential diagnosis

Although it is important to recognise other scalp disorders that can have scale and hair loss, differentiating tinea capitis is usually straightforward. Alopecia areata has no scale associated, nor does trichotilomania. Seborrhoiec dermatitis should have no hair loss. Psoriasis has thicker,

adherent scale, and alopecia is not common. Other scarring alopecias such as folliculitis decalvans, lichen planopilaris and dissecting cellulitis of the scalp are chronic conditions, each with a different quality of inflammation.

Treatment

Skin scrapings and hair plucks should be sent for fungal microscopy and culture to confirm the diagnosis and help guide therapy.

As for other types of tinea, other body sites of fungal infection should be sought in an attempt to identify a source. Use of an oral antifungal agent is mandatory because of the involvement of hair follicles. Terbinafine is often the first choice, given at 250 mg daily for several weeks until clinical and mycological cure is achieved. The author's empirical habit is to review treatment after six weeks, including a liver function test and looking for settling of the inflammation and regrowth of hairs; further therapy may be required. In children, the daily dose of terbinafine is adjusted to body weight: for children weighing up to 20 kg, use 62.5 mg (i.e. a quarter of a tablet); for those weighing 20 to 40 kg, use 125 mg (half a tablet); and for those above 40 kg, use the full adult dose (250 mg; one tablet).

Griseofulvin is a traditional agent and is now typically used as a second-line treatment for tinea capitis, at a dose of 500 mg daily for adults and 10 mg/kg daily for children for six weeks or longer. Higher doses may be required in children (15 mg/kg daily) or recalcitrant cases (up to 1 g). A recent Cochrane review found griseofulvin may be more effective for *Microsporum canis* infections, whereas terbinafine may be superior for *Trichophyton tonsurans*. However, the authors of the review advise individualised treatments may well vary from the results of the meta-analyses.[1]

Should either terbinafine or griseofulvin be contraindicated, the use of fluconazole (off-label use) or itraconazole is reasonable. The doses would be as for tinea corporis but treatment should be continued until clinical and mycological cure is achieved.

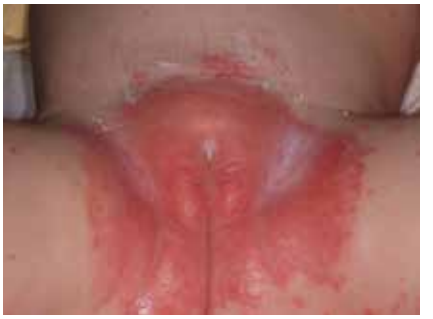

Figure 4. Candidiasis in the inguinal region. Note the satellite lesions away from the main infection.

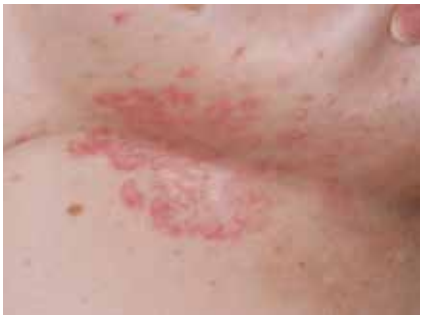

Figure 5. Submammary psoriasis. This can be difficult to differentiate from tinea and seborrhoeic dermatitis.

The daily use of an antidandruff shampoo is also useful to reduce the continued shedding of spores from the patient's scalp. Furthermore, it may be important to keep a child away from school for the first two weeks of the infection, reducing the risk of spread to his or her schoolmates.

Although kerion may resemble an abscess, incisional drainage is not useful as there is no cavity, only inflammatory granulation tissue. Often, however, there is a coexistent bacterial infection. If this is the case, an oral antifungal agent and a broad-spectrum antibiotic such as cephalexin should be used. Antifungal therapy is prolonged, typically at least six weeks. Excessive inflammation may lead to scarring alopecia; dermatologists may use oral corticosteroids in some cases to limit this inflammatory scarring.

Skin folds – tinea cruris

A typical site for flexural tinea is the inguinal fold. Tinea cruris is easily diagnosed and presents as a flexural erythematous rash with an active border; there may not be a lot of scale, given the occluded nature of the groin, but the rash is often itchy. Although most commonly ascribed to adult men, tinea cruris can occur in teenagers and women. Once again, there may be tinea at other sites, and the feet and nails should be checked. Scrapings for fungal microscopy and culture confirm the diagnosis.

Note that chronic tinea corporis often involves skin folds and can be rather recalcitrant to therapy.

Differential diagnosis

Infectious differential diagnoses for tinea cruris are candidiasis and seborrhoeic dermatitis:

- candidiasis – wet, macerated erythematous folds with whitish discharge may be due to candidiasis, which is characterised by the presence of 'satellite lesions', red papules or pustules further away from the main front of the erythematous rash (Figure 4). The submammary fold is a common site for candidiasis. It is important to remember that terbinafine is not effective in the treatment of candidiasis and that the imidazole antifungals work for both candidiasis and dermatophyte infections
- seborrhoeic dermatitis – can present in the flexures (the axillae and pubic areas are common sites), although it more often occurs in the scalp and eyebrows and on the face and chest. The rash is pale pink with friable, loose small scales.

Noninfectious differential diagnoses for tinea cruris are flexural psoriasis and irritant contact dermatitis:

- flexural psoriasis – has no scale, involves the depth of the fold and has

Figure 6. Tinea faciei. The source of the infection was a new kitten.

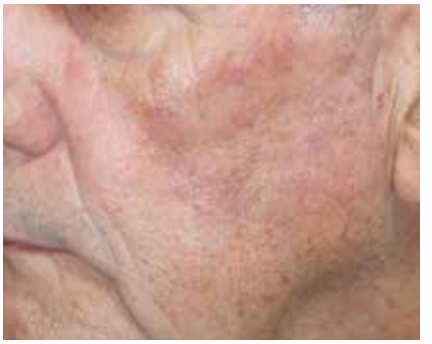

Figure 7. Tinea incognito. Treatment of tinea faciei with topical corticosteroid has obscured its classic features.

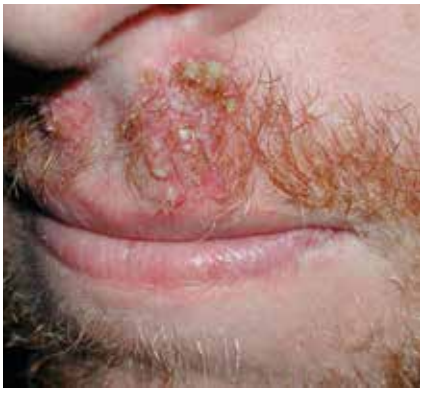

Figure 8. Kerion of the moustache area.

a characteristic glazed appearance; the submammary and the inguinal folds are typical sites of involvement (Figure 5)

- irritant contact dermatitis – dermatitis secondary to urine in the folds can be seen in infants as napkin dermatitis and in the elderly as an ammoniacal dermatitis. This eczematous rash typically spares the depths of the folds, although not always.
  Co-infection with *Candida* or the incidental presence of a dermatophyte should always be considered.

Treatment

Tinea cruris should be treated the same way as tinea corporis, with deliberate drying of the folds being particularly important. A change in underwear style that avoids skin-on-skin contact in the depth of the folds can help aerate the fold and reduce sweating (i.e. a style where there is a layer of fabric on the thigh as well as the genital area; boxer shorts may be too loose and allow the fold to occlude so there is skin against skin).

Face – tinea faciei, tinea barbae

Tinea faciei often presents in an annular pattern similar to tinea corporis (Figure 6). However, topical corticosteroids are often prescribed initially, leading to tinea incognito (Figure 7). Solar exposure can worsen the inflammation. As mentioned earlier, pets may be the source of facial tinea, and the possibility that a new pet is the source of fungus should be explored. Although much less commonly recognised than tinea elsewhere, the clinical features of an annular rash with an active border should help with the diagnosis.

Fungal folliculitis of the beard (tinea barbae) may be quite inflammatory and can present as a kerion; hairs are easily extracted (Figure 8).

Differential diagnosis

There are multiple differential diagnoses to be considered with a facial rash. A skin scraping should make the diagnosis of tinea easier. Occasionally a biopsy can be performed, though the clinician needs to consider the legacy of a small scar.

Differential diagnoses include the following:

- seborrhoeic dermatitis and facial psoriasis – as well as being difficult to distinguish from tinea faciei, these two conditions can be difficult to distinguish from each other. Both have an erythematous rash with greasy, loose scales but seborrhoeic dermatitis is typically found on the mid-face, over the eyebrows and paranasal sinuses (and as dandruff on the scalp) whereas psoriasis is found on the rest of the body and on the margins of the scalp
- atopic dermatitis and contact dermatitis – atopic dermatitis is common on the face, with the eyelids affected most often in adults. The skin tends to be drier than with tinea faciei, with ill-defined edges to the rash. Contact dermatitis may look similar to atopic eczema; if contact dermatitis is suspected, a history of possible exposure needs to be explored
- rosacea – typically affects the convexities of the mid-face (cheeks, nose, chin). Flushing and blushing are common historical features, and the rash is of telangiectasias, background erythema, papules and pustules. There is no active border per se, and rosacea often spares the nasolabial folds. Perioral dermatitis typically occurs around the perialar lip, and extends to the skin around the rest of the cutaneous lip and chin, including the nasolabial folds. Papules and pustules accompany the rash. It is associated in many cases with the use of potent topical corticosteroids on the face
- cutaneous lupus erythematosus – if the rash is photosensitive, lupus should be suspected as it can be quite inflammatory, scaly, scarring and annular. Rash should be sought in other parts of the skin, especially the photoexposed areas, and systemic illness also. A biopsy is mandatory if the patient does not respond to antifungal therapy or if there is systemic illness.

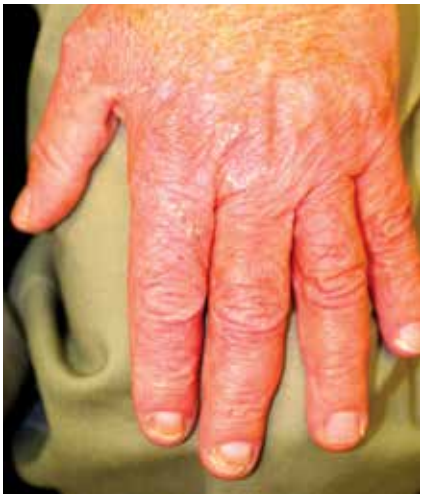

Figure 9. Tinea manuum. Note the scaly, serpiginous superior border just above the metacarpophalangeal joints. Diagnosis is made difficult due to prior topical corticosteroid use.

Treatment

Therapy is as for tinea corporis; a systemic antifungal is likely to be required for extensive disease, folliculitis and beard kerion.

Hands – tinea manuum

Tinea of the hands can be difficult to diagnose and is often confused with pompholyx, hand dermatitis, psoriasis and keratolysis exfoliativa. A scaly rash that has an active border should be easily diagnosed as tinea (Figure 9). More often, the presentation is a dry, slightly scaly and peeling erythema of the palmar surface that can be confused with dermatitis. It can also be quite inflammatory, with blisters at the edge, like pompholyx. The rash can affect both the palmar and dorsal surface in continuity with each other. A classic description is that only one hand is involved; the above-mentioned differential diagnoses are often symmetrical.

Other areas of co-infection are possible, and the feet should always be checked as often there is 'one hand, two feet' involved with tinea. Onychomycosis can be seen on the fingernails.

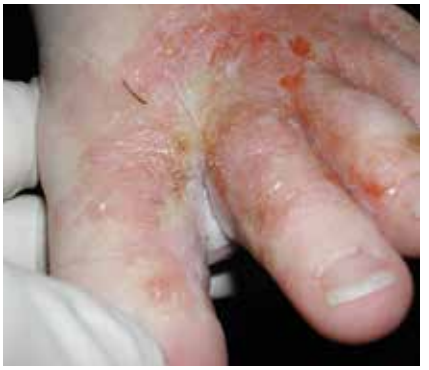

Figure 10. Interdigitial tinea pedis. Note the white, boggy macerated skin in the depth of the fold, and the associated inflammatory tinea pedis on the adjacent skin.

Treatment

Skin scrapings, fungal microscopy and culture is key to a diagnosis. Topical antifungal agents can be used for small areas. However, given that tinea manuum can be extensive and commonly coexists with other areas of dermatophyte infection, an oral agent may be appropriate (see tinea corporis). Once again, treatment is until clinical cure, which can take several weeks.

Feet – tinea pedis

The feet are an exceedingly common site for dermatophyte infections. Spots of ringworm on the dorsum of the feet are easy to diagnose, but there are several variants that clinicians should recognise:

- interdigital tinea ('athlete's foot') – often occurs in the setting of a wet, macerated webspace, which often has broken, boggy, white skin (Figure 10). This should be seen as an infected irritant intertrigo, where there is both an inflammatory irritant dermatitis as well as the dermatophyte infection. The ringworm component of interdigital tinea may spread to the adjacent dorsum of the foot
- moccasin tinea – describes an erythematous, scaly fungal infestation of the plantar surface of the feet, as if the patient was wearing a pair of 'fungal moccasins' (Figure 11). Moccasin tinea is common, and often missed as many older patients have dry scaly feet. An active margin at the sides of the feet, where the erythema and scale appear to stop, should be looked for. It may coexist with interdigital tinea. Skin scrapings should be at the edge of the erythema for the greatest yield of hyphae
- inflammatory tinea – highly inflammatory tinea pedis can have vesicles, pustules, erosion and maceration.

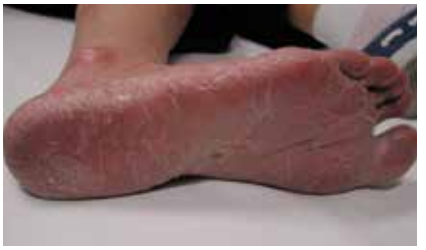

Figure 11. Moccasin tinea pedis. Note the dry scaly fissured infected skin involving the entire sole.

Differential diagnosis

Differential diagnoses may include bacterial cellulitis, pustular psoriasis and secondarily infected pompholyx. Once again, fungal scrapings for microscopy and culture are useful, but also bacterial swabs to rule out a secondary or co-infection.

In patients with recurrent cellulitis of the legs, it is important to look for and treat tinea pedis. The chronic dermatophyte infection creates broken skin, which is the portal of entry for the bacteria responsible for cellulitis.

Treatment

General measures are important to keep the feet as dry as possible. These measures include:

- fastidious drying of the feet and the toe webs after showering – using a hair dryer on a low heat setting can help
- wearing open shoes when possible, to air the feet – if appropriate, desk-bound office workers should remove their shoes when seated to reduce sweating

- regular changes of socks, and laundering at above 60°C to decontaminate them of fungus
- use of antifungal powders in shoes – to help prevent reinfection in the future.

With interdigital tinea, therapeutic lotions/sprays (e.g. terbinafine spray-on lotion, econazole spray-on lotion or miconazole tincture) should be used as they dry on the skin, whereas cream-based products may encourage more maceration and wetness. If there is excessive inflammation, a topical antifungal can be used in conjunction with a topical corticosteroid lotion, such as mometasone furoate 0.1% drops.

Moccasin tinea and tinea with inflammatory changes can be recalcitrant to topical therapy. Should regular use of terbinafine or an imidazole cream fail, then a systemic antifungal agent should be considered.

Seborrhoeic dermatitis

Seborrhoeic dermatitis is probably due to an inflammatory response to *Malassezia*. This yeast is a commensal organism on human skin but appears to overgrow in some individuals, leading to an inflammatory reaction.

Seborrhoeic dermatitis presents as a pale pink, ill-defined erythematous rash characterised by loose, flaky scale. Dandruff is seborrhoeic dermatitis on the scalp. The mid-face, along the eyebrows, nasolabial folds, and cheeks and beard areas are classically affected. The rash may also be present on the central chest, upper back and in the axillae (Figure 12). Seborrhoeic dermatitis is more common in people who are psychologically stressed, fatigued or in poor general health. HIV infection and other immunodeficiencies are a common association, as are Parkinson's disease, stroke and other neurological diseases.

Differential diagnosis

Psoriasis is the most common differential diagnosis for seborrhoeic dermatitis. Psoriasis, however, has a more chronic course, more intense erythema and a thicker layer of scales. Rash should be looked for on more pathognomonic sites, such as elbows, knees and affected nails. Sometimes it is not possible to differentiate seborrhoeic dermatitis and psoriasis, and the term sebopsoriasis is used.

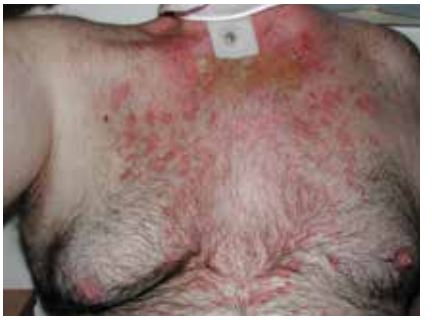

Figure 12. Seborrhoeic dermatitis.

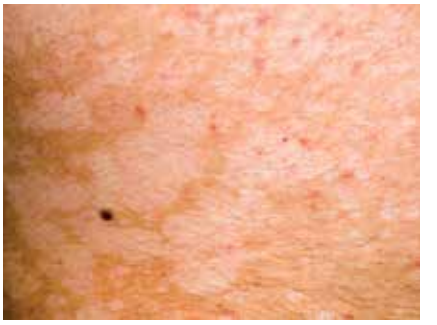

Figure 13. Pityriasis versicolor.

Treatment

As the putative cause of this rash is the overgrowth of a commensal organism, treatment is aimed at reducing the skin's yeast load as well as targeting the inflammation.

Facial dermatitis will usually respond to a mild topical corticosteroid/imidazole combination such as hydrocortisone 1%/miconazole 2% cream or hydrocortisone 1%/clotrimazole 1% cream used two to three times daily. Alternatively, ketoconazole 2% cream can be used alone. For more severe inflammation, a mid-potency corticosteroid can also be used, such as desonide 0.05% lotion.

To treat scalp and skin disease as well as reduce the overall yeast load, an antidandruff shampoo is used. Ciclopirox olamine solution has the greatest in vitro fungicidal activity, but in practice all antifungal shampoos are equally effective. Patients are advised to wet the scalp and entire skin, and then turn the shower off. The shampoo is used to lather up the scalp hair and as a bodywash to cover the top half of the body, including the face, beard, chest, back, axillae and pubic region. The treatment rationale is that these areas are where the reservoir of yeast is greatest. Patients should wait for about 10 minutes before rinsing off the shampoo, to allow it time to work. Initial treatment with the shampoo is every day for seven to 10 days to eliminate the yeast. Subsequently, a long-term, twice-weekly, all-over body shampoo regimen limits further fungal overgrowth. Patients should buy a different shampoo (with a different active ingredient) each time, thus preventing the development of antifungal resistance. Any flare of disease should trigger a change in shampoo and another seven to 10-day course of therapy.

Recalcitrant cases can be treated with a short course of oral antifungal agent. Various regimens are available but a simple one involves fluconazole 200 mg once a week for four weeks. The above antidandruff regimen should then be used twice weekly as well.

Pityriasis versicolor

Pityriasis versicolor is another yeast infection caused by *Malassezia*. It manifests as a salmon-pink spotty, scaly rash on fair skin, and as a paler or white spotty, scaly rash on darker or tanned skin (Figure 13). It is distributed mainly over the back, shoulders, trunk and upper limbs. The infection is most prevalent in the warmer months as the hot, humid, sweaty conditions favour fungal proliferation.

Differential diagnosis

Pityriasis versicolor may be confused with guttate psoriasis. However, the rash of pityriasis versicolor is macular and the scales are powdery and fine, and that of

guttate psoriasis consists of small plaques with thicker scales.

Treatment

Topical antifungals are effective for pityriasis versicolor, but need to be used over a large area. Econazole is available as a 1% foaming solution specifically for this purpose. This is distributed on wet skin after an evening shower and left on overnight; the top half of the body is treated, including the scalp. Thereafter, a twice-weekly antidandruff shampoo regimen is instituted to reduce the rate of relapse (as for seborrhoeic dermatitis, see above).

Alternatively, recalcitrant cases can be treated with fluconazole (off-label use) or itraconazole.

The characteristic scaling of pityriasis versicolor is a good indication of continued activity, as it disappears with effective fungal clearance. The pink spots disappear over a few weeks, but repigmentation may take months. Patients are advised that should they subject themselves to a suntan within the next few months, the previously affected spots can look very obviously pale. When the next summer does come, patients can use the twice-weekly antidandruff shampoo regimen to reduce the risk of the yeast repopulating their skin.

Conclusion

The key to the effective use of antifungal agents is an initial accurate diagnosis of the fungal infection. The classic finding of the active border and fine scale is pathognomonic of tinea, and dermatophyte infection should always be in the differential diagnosis when dealing with red, scaly rashes.

Topical antifungal preparations are usually adequate treatment for simple tinea but systemic antifungal treatment should be considered with complex, widespread tinea or when topical agents fail. A relatively dry skin is an important general treatment measure. MT

Reference

1. Chen X, Jiang X, Yang M, et al. Systemic antifungal therapy for tinea capitis in children. Cochrane Database Syst Rev 2016; (5): CD004685.

Further reading

Mycology Online. University of Adelaide. http://mycology.adelaide.edu.au/mycoses/cutaneous (accessed November 2017).

UpToDate. Dermatophyte infections. http://www.uptodate.com/contents/dermatophyte-tinea-infections (accessed November 2017).

DermnetNZ. http://dermnetnz.org/fungal/tinea.html (accessed November 2017).

COMPETING INTERESTS: None.

Childhood atopic dermatitis

Overcoming parental topical corticosteroid phobia

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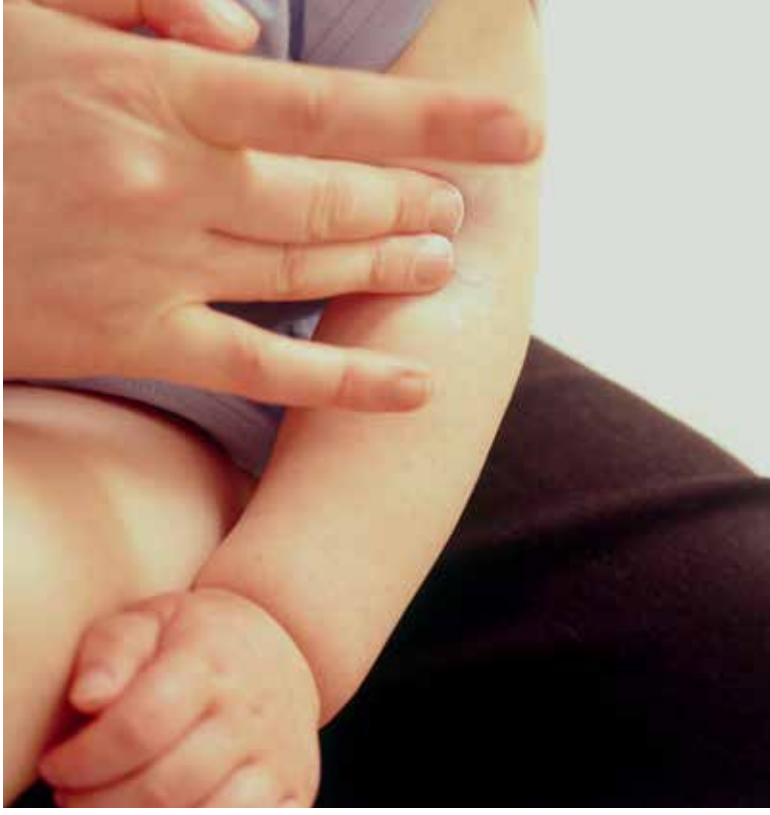

Topical corticosteroids are the mainstay of management of atopic dermatitis, the most common skin condition in children. When used appropriately under medical supervision, they are safe and have been shown not to cause cutaneous atrophy.

Atopic dermatitis, or eczema, is the most common paediatric dermatological condition worldwide. It is also one of the most treatable with the correct management, the criterion standard being topical corticosteroids (TCS). Although severe atopic dermatitis is disabling and highly disruptive for patients and their families, fear and anxiety regarding the use of TCS is a significant barrier to effective treatment.[1-7] This fear and anxiety relating to TCS use is often referred to as 'corticosteroid phobia'.

Corticosteroid phobia can be linked to a preference for 'natural therapies'.[7] Patients and their parents often have a poor understanding of the predominantly genetic basis of atopic dermatitis, which may lead to the pursuit of 'cures' that often focus on a search for offending allergens that can be eliminated.[7] The abandonment of evidence-based medical therapy can have potentially detrimental outcomes for the paediatric patient.[8-11] Parents frequently cite 'skin thinning' as the side effect they most fear.[7] This concern is entrenched in parents in Australia, and is also seen around the world.[4-6] Although cutaneous atrophy is a well-documented side effect of TCS, it is likely to occur only when potent products are used inappropriately, such as under plastic occlusion or on macerated skin of the flexures for extended periods of time. The fear of atrophy in the medical and general communities has become so pronounced that many parents receive grossly exaggerated warnings and as a result find it difficult to treat their children appropriately.[8,9] Contrary to popular perceptions, TCS use in paediatric cases of atopic dermatitis does not cause atrophy, hypopigmentation, hypertrichosis,

KEY POINTS

- Atopic dermatitis has significant biopsychosocial impacts on the patient and family unit, particularly when it is severe.
- Topical corticosteroids (TCS) are the mainstay of its management. Used appropriately, these preparations are safe and do not cause cutaneous atrophy.
- Topical corticosteroid phobia is a significant hurdle to effective treatment.
- Education and information regarding appropriate use and safety of TCS increases confidence in and adherence to such treatment.
- Key strategies are providing safety information on TCS, demonstrating the use of TCS and moisturisers, explaining the genetics and chronicity of atopic dermatitis, addressing allergy concerns and acknowledging the impact on the patient and the family unit

MedicineToday Dermatology Collection 2017; 2(2): 15-21
First published MEDICINE TODAY 2013; 14(6): 47-52
Updated November 2017

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1. POTENCIES OF TOPICAL CORTICOSTEROIDS USED IN CHILDHOOD ATOPIC DERMATITIS*

Mild potency
- Hydrocortisone 1%
- Hydrocortisone acetate 1%
- Desonide lotion 0.05%
- Clobetasone butyrate 0.05%

Medium potency
- Betamethasone valerate 0.02% and 0.05%
- Triamcinolone acetonide 0.02%

Potent
- Methylprednisolone aceponate 0.1%
- Betamethasone valerate 0.1%
- Betamethasone dipropionate 0.05%
- Mometasone furoate 0.1%

Superpotent
- Betamethasone dipropionate 0.05% in optimised vehicle

* Preparations available in Australia.

osteoporosis, purpura or telangiectasia when used appropriately.[12]

Education of parents whose children have atopic dermatitis helps to deconstruct this complex issue and dramatically increases treatment compliance. Clinicians play a crucial role as 'health educators', but they themselves must have confidence in the safety and appropriateness of TCS before they can recommend these medications to patients.

Health burden of atopic dermatitis

The prevalence of symptoms of atopic dermatitis in children under 5 years of age in Australia is about 20%, a figure that has more than doubled over the past three decades.[13,14] A similar increase in prevalence has been found in the USA.[15] It is not well understood why this increase has occurred; however, environmental and socioeconomic factors appear to play an important role in disease prevalence.[16]

Atopic dermatitis can be managed and usually remits with age, but still places a significant burden on patients and their family unit. It has been shown that a child with atopic dermatitis has a significantly higher biopsychosocial impact on the family unit than a child with diabetes, owing to problems such as itching, sleep loss, problems at school and mood and behavioural changes.[2,3,5,17]

A 1997 Australian study calculated conservative estimates of the annual personal cost of managing mild, moderate and severe atopic dermatitis as $330, $818 and $1255, respectively.[17] Costs included doctor visits, hospitalisations, medicines, over-the-counter therapeutic preparations, time off work and transport. The study found that the personal financial cost of managing atopic dermatitis was greater than that for asthma. Other practical difficulties that occur when caring for a child with atopic dermatitis include skin care, feeding, shopping, washing and cleaning, psychological pressure, physical exhaustion and restriction of the family's lifestyle.[18]

Treating atopic dermatitis

Management of atopic dermatitis involves a combination of environmental modification, infection control, identification and management of triggers and, in some children, investigation of allergy.

A key component of the treatment of the condition is restoration of barrier function with emollients. Emollients are the basis of management and should be used even when the skin is clear (i.e. has no evidence of active atopic dermatitis).[20] They should be applied to the skin very liberally, and fears related to the reality that most of them are derived from 'petrochemicals' need to be allayed by facts about their excellent safety record and lack of evidence that they are in any way dangerous.

TCS are the mainstay of medical therapy for atopic dermatitis. Some of the TCS preparations available in Australia, and their relative potencies, are listed in Box 1. The calcineurin inhibitor pimecrolimus is a useful adjunct to treatment when there is chronic eyelid involvement. However, it is of low potency as an anti-inflammatory agent and is not a substitute for TCS in the acute treatment of atopic dermatitis. TCS have been successfully used to treat atopic dermatitis for more than 50 years. There is no convincing evidence that they pose a risk if used correctly, and overwhelming evidence that they are effective.[19]

Using topical corticosteroids safely

The type of corticosteroid used is usually tailored to the severity of the atopic dermatitis:
- for mild disease, use a mild potency TCS (e.g. 1% hydrocortisone acetate)
- for moderate atopic dermatitis, use a medium potency TCS (e.g. 0.02% betamethasone valerate)
- for severe atopic dermatitis, use a potent TCS (e.g. 0.05% betamethasone dipropionate).

The TCS used also varies depending on the part of the body involved (Box 2). The principle behind selecting TCS based on anatomical site is to initially select weaker corticosteroids for skin where the epidermis is thinner or where maceration is common (for example, the axilla). If there is a clinical failure to respond, higher potency TCS should then be considered. Ointment-based preparations are preferred for two reasons: firstly, ointments are more moisturising to the skin, which optimises the delivery of TCS to the skin; and secondly, creams contain higher amounts of preservatives, which may cause stinging when applied to the broken skin of acute atopic dermatitis.

In general, the principle of using TCS is to treat early at maximum potency and reduce when improved. Most patients with moderate to severe atopic dermatitis should gain control of a flare after using a potent TCS once or twice daily for one week (if applied properly), and can then change to a less potent TCS for maintenance.

Figure. A fingertip unit is a convenient measure of how much of a topical corticosteroid to prescribe a patient. The size of the fingertip unit, and hence the dose of active ingredient, varies with the age of the patient (infant, child, adult).

When describing their experience of using TCS it is not unusual for parents to say they feel as if they are 'smothering' their child in these medications, which suggests a level of anxiety about using corticosteroids. Furthermore, it is commonplace for pharmacists to insert the term 'Use sparingly' on the labels of TCS tubes, even when the doctor has not written this on the prescription. This can be both alarming and confusing to parents, who as a result may apply minute amounts.

Parents require information on how much of a TCS to use, and it is helpful to demonstrate application of the products to parents. A useful rule of thumb is that a 'fingertip unit' (as measured using the patient's index finger) of a corticosteroid ointment or cream should be used to cover a skin area about twice the size of the palmar surface of the patient's hand (i.e. the palm and fingers; Figure). It is also useful to inform parents that the palmar surface of the hand represents 1% of body surface area, so they have a realistic appreciation of how much product they are actually using. In most cases this is much less than they had assumed.

A recent study has demonstrated the safety of TCS in a paediatric dermatology setting.[21] This cross-sectional observational study assessed 70 children with atopic dermatitis or overlapping atopic dermatitis and psoriasis who had used TCS regularly for at least three months. The researchers found that excellent disease control was achievable using TCS, without causing cutaneous atrophy: 93% of patients in the study group were using a combination of potent, moderate and weak TCS as appropriate to severity and site of application and did not show any evidence of cutaneous atrophy over the observation period. Their conclusion was that parents, medical practitioners and pharmacists should have a high degree of confidence in the use of TCS.

Dealing with topical corticosteroid phobia

Corticosteroid phobia is expressed by between 40 and 73% of dermatology patients and/or their parents.[8,22-24] This phenomenon is also seen by paediatricians attempting to manage asthma with inhaled corticosteroids.[7-11]

A phobia is an irrational fear. However, calling the fear associated with using TCS a 'phobia' may well be a misnomer as there are some rational reasons for parents to fear TCS. Parents are often warned of the dangers of TCS not only by friends, relatives and the media but also by traditionally trusted sources, including their family doctor and pharmacists.[7] This often unsolicited advice offered by family and friends helps to create a negative cultural environment for parents of children with atopic dermatitis as they contend with the demands of managing their child's illness and may also contribute to treatment nonadherence.[25] Pharmacists have been cited as one of the main contributors of misinformation leading to TCS phobia in particular regarding excessive and long-term use, supporting the removal of the words 'use sparingly' from TCS prescriptions.[26-28] A recent systematic review concluded that clinicians should target the source from which patients with TCS phobias are receiving information about corticosteroids to increase adherence to treatment regimens.[29]

2. TOPICAL CORTICOSTEROID SELECTION FOR CHILDHOOD ATOPIC DERMATITIS*

Topical corticosteroids are selected for use based on the severity of the atopic dermatitis and the anatomical site affected.

Face and flexures

- Mild to moderate atopic dermatitis – use hydrocortisone 1%, hydrocortisone acetate 1% or desonide 0.05%
- Moderate to severe atopic dermatitis – use methylprednisolone aceponate 0.1% or mometasone furoate 0.1%

Limbs and trunk

- Mild atopic dermatitis – use hydrocortisone 1% or desonide lotion 0.05%
- Moderate atopic dermatitis – use betamethasone valerate 0.02% or triamcinolone acetonide 0.02%
- Severe atopic dermatitis – use betamethasone dipropionate 0.05% or mometasone furoate 0.1%

* Preparations available in Australia.

Parents in this country often believe that medical treatment for atopic dermatitis with TCS is dangerous and that 'natural' therapy is safe and therefore preferable.[7] A questionnaire-based study found that 72.5% of people worried about using TCS on their own or their child's skin.[8] Although skin thinning was the most prevalent fear (34.5%), 9.5% of patients were concerned about systemic absorption resulting in retardation of growth and development. The most commonly used TCS was 1% hydrocortisone, and one-third of the patients using this classified it as being either strong or very strong, or were unsure of its potency. This highlights the need for improved patient education regarding the safety, potency and appropriate use of TCS.

The website of the National Eczema Association in the USA is an excellent resource for patients and/or parents (http://www.nationaleczema.org). One

3. EDUCATING PARENTS IN THE USE OF TOPICAL CORTICOSTEROIDS[7]*

Recommendations from parents of children with atopic dermatitis regarding how medical practitioners can best engage and educate them about the use of topical corticosteroids include:

- understand, respect and validate parental concerns
- do not dismiss the desire to investigate allergy as a cause of atopic dermatitis
- alleviate guilt
- emphasise the positives: outcome, safety, prognosis
- encourage acceptance of 'no cure'
- realise parental trust in the GP is a major factor
- empower parents to withstand negative forces
- provide written and videotaped information that addresses parents' fears
- refer child to dermatologist if response to treatment is suboptimal
- warn parents of the possible confusing information they may receive from pharmacists

* Adapted from Smith SD, et al. *Australas J Dermatol* 2010; 51: 168-174.[7]

of their many brochures, which can all be downloaded, discusses the myths associated with TCS and provides tips for using these preparations (although not all the TCS mentioned are available in Australia).

Impact of complementary and alternative medicine

Complementary and alternative medicine (CAM) therapies are commonly used by parents to treat their children's atopic dermatitis.[30,31] There are many reasons for this, ranging from a desire to find a lasting 'cure' for the illness to a fear of 'unnatural' TCS therapy and 'petrochemical' moisturisers.

Parents often experience guilt, feelings of failure and a sense that they should somehow have prevented the disease. They often find that the media focus on allergy as the primary cause of atopic dermatitis, promote 'natural' products and characterise Western medicine as dangerous. They thus feel under pressure from this and other sources (such as family, friends and school teachers) to avoid 'dangerous and unnecessary' medical treatments. It is not uncommon for parents to preferentially commence treatment with what they believe to be a 'natural' product, the effectiveness of which is based on simplistic theories, and only move to using TCS when the atopic dermatitis is 'very severe'.[7] Furthermore, it is not unusual for parents to seek CAM therapies concurrently with conventional medical opinions. This results in an increased financial burden and conflicting advice, which can lead to treatment failure. Also, the use of 'natural' therapies may result in the withholding of effective treatment.[32]

Parents often find it difficult to accept the concept of 'control rather than cure' in the effective management of atopic dermatitis.[7] The inherent chronic relapsing and remitting nature of atopic dermatitis is frustrating and disappointing for parent and patient, and parents may view TCS as simply masking the underlying condition. However, when TCS are used effectively at the first sign of a flare, ongoing control is less of an issue.

The GP as health educator and dispeller of myths

It is important for GPs to have confidence in using TCS. Unfortunately, a paucity of dermatology teaching time at university level often leaves medical graduates with less information than they require when practising in the community. Understanding the safety of these products if used correctly is vital if GPs are to be able to adequately reassure patients. This involves using TCS of adequate potency matched to the severity of the atopic dermatitis, in amounts that cover all involved areas daily until the skin is a normal colour and texture, and without a specified time limit.[33]

4. INCREASING PARENTAL CONFIDENCE IN TOPICAL CORTICOSTEROID USE[7]*

Suggestions for increasing parental confidence about the use of topical corticosteroids in children with atopic dermatitis include:

- provide safety data on topical corticosteroids
- provide safety data on emollients
- Provide information on relative potencies of prescribed topical corticosteroids
- demonstrate use of topical corticosteroids
- explain the concept of scientific testing
- explain the true role of allergy in atopic dermatitis
- explain how topical corticosteroids work in atopic dermatitis
- outline the possible outcomes of failure to treat
- discuss the importance of improving the child's quality of life

* Adapted from Smith SD, et al. *Australas J Dermatol* 2010; 51: 168-174.[7]

Targeted education of parents of children with atopic dermatitis to increase overall adherence has been shown to improve compliance and discourage the use of restricted diets (in cases where it is believed that allergy is the cause of the condition).[16,17,34] Building a strong patient-clinical relationship, simplifying treatment regimens and increasing the frequency of follow up are also important mitigating strategies to improve treatment compliance in childhood atopic dermatitis.[35]

It has been demonstrated that multidisciplinary teams and support groups set up specifically around education and quality of life are successful in lowering anxiety in parents of children affected by atopic dermatitis and in adult patients.[34,36-38] However, parents have highlighted that it is the importance of the trusted relationship with their medical practitioner that forms the key platform

for patient and parent education at the coal face of daily clinical practice.[7,30,38]

Parents of children with atopic dermatitis have suggested mechanisms by which medical practitioners can engage and educate them about the use of TCS (Box 3).[7] It is important for medical practitioners to be cognisant of the sources of parental concern as well as to acknowledge that corticosteroid 'phobia' is ultimately a fear generated by misinformation. With the correct information, this belief can be positively modified and parental confidence about the use of TCS increased (Box 4).[7]

It is also important that medical practitioners recognise the positive impact of providing appropriate educational support as this helps alleviate parental guilt and fosters understanding of the genetic and chronic nature of atopic dermatitis. It also empowers parents to withstand the many negative influences they encounter daily. Despite the fact that food allergy testing is positive in 35 to 40% of these children,[39] food allergy is often of limited clinical importance in patients with atopic dermatitis. However, a willingness to validate parental hopes by investigating food allergies will be seen as part of the support that parents seek from their child's medical practitioner. Should allergy assessment be sought, consultation with a clinical immunologist is recommended.

Conclusion

Atopic dermatitis is a chronic waxing and waning condition with a largely genetic pathogenesis. It has a substantial effect on the quality of life of affected children and their families. Children and parents often suffer needlessly because of inadequate disease control as a result of poor treatment compliance, particularly with TCS. Fear of treatment, particularly with TCS, is a common reaction to misinformation, which comes from a range of sources, including family, friends, doctors and pharmacists.

Understanding the difficulties faced by parents of children with atopic dermatitis, and their potential fears about TCS, helps GPs provide a framework of strategies to increase parents' confidence in and adherence to treatment with TCS, and ultimately to improve the quality of life of their children. The key strategies are to provide information about the safety of TCS, demonstrate the use of moisturisers and TCS, explain the genetics and chronicity of atopic dermatitis, address allergy concerns and acknowledge the impact on the patient and the family unit. MT

References

1. Staab D, von Rueden U, Kehrt R, et al. Evaluation of a parental training program for the management of childhood atopic dermatitis. Pediatr Allergy Immunol 2002; 113: 84-89.
2. Balkrishnan R, Housman T, Grummer S, et al. The family impact of atopic dermatitis in children: the role of the parent caregiver. Pediatr Dermatol 2003; 20: 5-10.
3. Carroll C, Balkrishnan R, Feldman SR, Fleischer AB Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family and society. Pediatr Dermatol 2005; 22: 192-199.
4. Cork M, Britton J, Butler L, Young S, Murphy R, Keohane SG. Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. Br J Dermatol 2003; 149: 582-589.
5. Ben-Gashir M, Seed P, Hay R. Quality of life and disease severity are correlated in children with atopic dermatitis. Br J Dermatol 2004; 150: 284-290.
6. Chamlin SL. The psychosocial burden of childhood atopic dermatitis. Dermatol Ther 2006; 19: 104-107.
7. Smith SD, Hong E, Fearns S, Blaszczynski A, Fischer G. Corticosteroid phobia and other confounders in management of childhood atopic dermatitis explored using parent focus groups. Australas J Dermatol 2010; 51: 168-174.
8. Charman C, Morris A, Williams H. Topical corticosteroid phobia in patients with atopic eczema. Br J Dermatol 2000; 142: 931-936.
9. Fischer G. Compliance problems in paediatric atopic eczema. Australas J Dermatol 1996; 37: S10-S13.
10. Skoner J, Schaffner T, Schad C, Kwon AY, Skoner DP. Addressing steroid phobia: improving the risk-benefit ration with new agents. Allergy Asthma Proc 2008; 29: 358-364.
11. Brown K, Rehmus W, Kimball A. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. J Am Acad Dermatol 2006; 55: 607-613.
12. Mooney E, Rademaker M, Dailey R, et al. Adverse effects of topical corticosteroids in paediatric eczema: Australasian consensus statement. Australas J Dermatol 2015; 56: 241-251.
13. Bieber T. Atopic dermatitis. N Engl J Med 2008; 358: 1483-1494.
14. Foley P, Zuo Y, Plunkett A, Merlin K, Marks R. The frequency of common skin conditions in preschool-aged children in Australia. Arch Dermatol 2003; 139: 318-322.
15. Stensen L, Thomsen SF, Backer V. Change in prevalence of atopic dermatitis between 1986 and 2001 among children. Allergy Asthma Proc 2008; 29: 392-396.
16. Lam J, Friedlander SF. Atopic dermatitis: a review of recent advances in the field. Pediatr Health 2008; 2: 733-747.
17. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. Arch Dis Child 1997; 76: 159-162.
18. Lewis-Jones S. Measuring the burden of atopic eczema in young children and the family unit. J Invest Dermatol 2005; 125: viii.
19. Smith SD, Fischer G. Childhood atopic dermatitis: exploring the safety, efficacy and potential misinformation around topical corticosteroids. AJP: The Australian Journal of Pharmacy 2016; 97: 83-88.
20. Lewis-Jones S, Mugglestone MA, Guideline Development Group. Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. BMJ 2007; 335: 1263-1264.
21. Hong E, Smith SD, Fischer G. Evaluation of the atrophogenic potential of topical corticosteroids in pediatric dermatology patients. Pediatr Dermatol 2011; 28: 393-396.
22. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol 2006; 155: 145-151.
23. Hon KL, Kam WY, Leung TF, et al. Steroid fears in children with eczema. Acta Paediatr 2006; 95: 1451-1455.
24. Ou HT, Feldman SR, Balkrishnan R. Understanding and improving treatment adherence in pediatric patients. Semin Cutan Med Surg 2010; 29: 137-140.
25. Smith SD, Farrugia LL, Harris V, et al. Evaluation of the influence of family and friends, and the Internet on patient perceptions of long-term topical corticosteroid use. J Dermatolog Treat 2017: 28: 642-646.

26. Smith SD, Lee A, Blaszczynski A, Fischer G. Attitudes of Australian dermatologists to the use and safety of topical corticosteroids in paediatric atopic dermatitis. Australas J Dermatol 2015; 56: 241-251.
27. Smith SD, Lee A, Blaszczynski A, Fischer G. Pharmacists' knowledge about use of topical corticosteroids in atopic dermatitis: pre and post continuing professional development education. Australas J Dermatol 2016; 57: 199-204.
28. Farrugia LL, Lee A, Fischer G, Blaszczynski A, Carter SR, Smith SD. Evaluation of the influence of pharmacists and GPs on patient perceptions of long-term topical corticosteroid use. J Dermatolog Treat 2017; 28: 112-118.
29. Li AW, Yin ES, Antaya RJ. Topical corticosteroid phobia in atopic dermatitis: a systematic review. JAMA Dermatol 2017; 153: 1036-1042.
30. Hughes R, Ward D, Tobin A, Keegan K, Kirby B. The use of alternative medicine in pediatric patients with atopic dermatitis. Pediatr Dermatol 2007; 24: 118-120.
31. Johnston G, Bilabo RM, Graham-Brown RA. The use of complementary medicine in children with atopic dermatitis in secondary care in Leicester. Br J Dermatol 2003; 149: 566-571.
32. Ruzicka T. Atopic eczema between rationality and irrationality. Arch Dermatol 1998; 134: 1462-1469.
33. Smith SD, Harris V, Lee A, Blaszczynski A, Fischer G. General practitioners knowledge about use of topical corticosteroids in paediatric atopic dermatitis in Australia. Aust Fam Physician 2017; 46: 335-340.
34. Schafer T, Riehle A, Wichmann H, Ring J. Alternative medicine in allergies – prevalence, pattern of use, and costs. Allergy 2002; 57: 694-700.
35. Sokolova A, Smith SD. Factors contributing to poor treatment outcomes in childhood atopic dermatitis. Australas J Dermatol 2015; 56: 252-257.
36. Ricci G, Bendandi B, Aiazzi R, Patrizi A, Masi M. Three years of Italian experience of an education program for parents of young children affected by atopic dermatitis : improving knowledge produces lower anxiety levels in parents of children with atopic dermatitis. Pediatr Dermatol 2009; 26: 1-5.
37. Weber MB, Fontes Neto Pde T, Prati C, et al. Improvement of pruritus and quality of life of children with atopic dermatitis and their families after joining support groups. J Eur Acad Dermatol Venereol 2008; 22: 992-997.
38. Ohya Y, Williams H, Steptoe A, et al. Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. J Invest Dermatol 2001; 117: 852-857.
39. Katerlaris CH, Peake JE. 5. Allergy and the skin: eczema and chronic urticaria. Med J Aust 2006; 185: 517-522.

COMPETING INTERESTS: None.

Hidradenitis suppurativa

Debilitating and challenging to treat

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Hidradenitis suppurativa is a debilitating chronic skin disease of intertriginous areas, which may be misdiagnosed as boils or ingrown hairs in the early stages. Treatment often requires a combination of lifestyle modifications, medications and laser or surgical interventions.

KEY POINTS

- Hidradenitis suppurativa (HS) is a debilitating chronic skin disease characterised by inflammatory nodules, abscesses, sinus tracts, comedones and fibrotic scarring.
- HS lesions are most common in the axillae but can occur in any intertriginous area.
- The cause of HS is not completely understood and is likely to be multifactorial; contributing factors may include obesity, smoking, hormonal fluctuation, inflammation and genetics.
- The main clinical features supporting an HS diagnosis are a history of recurrent painful or suppurating lesions (typically deep-seated inflammatory nodules) in intertriginous areas, with a chronic or relapsing course.
- There is no single efficacious therapy for HS and a combination of lifestyle modifications, medical and laser or surgical interventions is often required.
- Referral to a dermatologist is recommended for patients with moderate to severe HS.

Hidradenitis suppurativa (HS) is a debilitating chronic skin disease. It is characterised by painful nodules that may progress to abscesses and in severe cases can lead to sinus tract formation, fibrotic scarring, dermal contractures and skin induration. HS causes significant morbidity because of its painful remitting and relapsing course. The pathogenesis is not completely understood but primarily involves occlusion of terminal hair follicles and subsequent hyperkeratinisation and inflammation.[1] There are a number of theories to explain these histological changes, which implicate factors such as obesity, tobacco smoking, genetics, inflammation and hormonal variation. There is currently no single effective therapy for this condition, and management often involves a combination of medical and surgical options.

Epidemiology

The estimated prevalence of HS is 1 to 4% of the population.[2] HS tends to occur in the second or third decades of life and is significantly more common in women than in men (female to male ratio of 3 to 1).[3]

MedicineToday Dermatology Collection 2017; 2(2): 23-27
First published MEDICINE TODAY 2016; 17(3): 31-36
Updated November 2017

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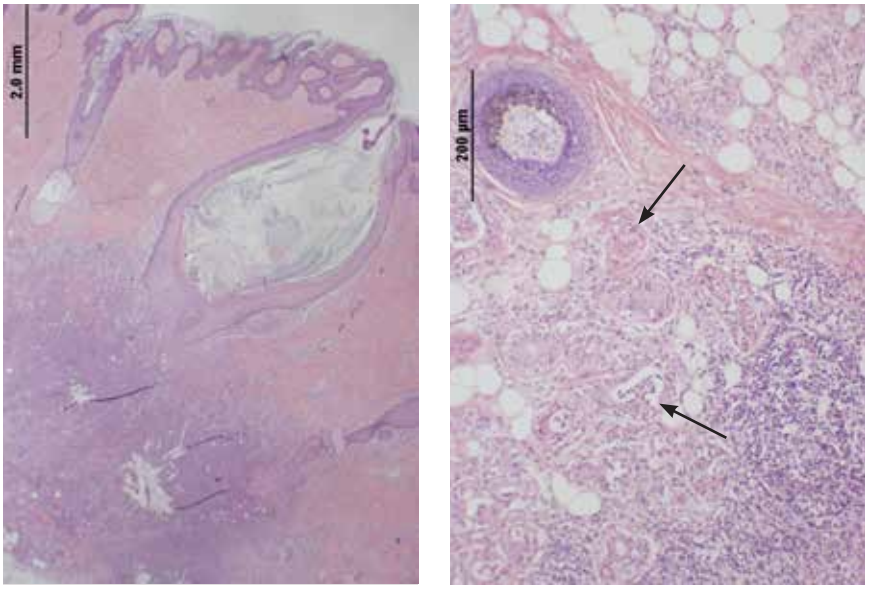


Figures 1a and b. Skin biopsy specimen from a 25-year-old man showing some of the classic features consistent with hidradenitis suppurativa. a (left). Sinus lined with stratified squamous cells and a heavy mixed inflammatory cell infiltrate in the lower half of the dermis. b (right). Inflammation of the apocrine glands (arrows) adjacent to a hair follicle.

Images courtesy of Dr Tricia Saurine and Dr Jessica Reagh, Royal North Shore Hospital, Sydney, NSW.

Presentation

HS is characterised by deep-seated tender subcutaneous inflammatory nodules. The onset of HS is often insidious, with sporadic solitary nodules that persist for several days to months. Episodes of nodules may recur in the same location or general area. Early symptoms of HS include pain, pruritus, heat and hyperhidrosis. Patients often present in general practice with early- stage lesions, which are commonly misdiagnosed as boils (furuncles) or ingrown hairs caused by waxing or shaving. However, HS lesions differ from furuncles as they are deep-seated and round-topped, lacking the typical pointed appearance of furuncles.

An HS nodule may progress to an abscess and rupture at the skin surface, exuding a foul-smelling discharge. Alternatively, HS nodules may regress without rupture or persist deep within the skin, leading to sinus tract formation. As the disease process continues, fibrosis, dermal contractures and induration of the skin can occur. HS commonly causes significant impairment of quality of life.[2]

HS lesions are most common in the axillae but can occur in any intertriginous area, including the inguinal area, inner thigh, mammary and inframammary regions, buttocks, pubic region, scrotum, vulva and chest.

Diagnosis

HS is a clinical diagnosis that can be made through careful history taking and examination, informed by knowledge of the characteristic clinical manifestations. Investigations such as skin swabs or biopsies are not necessarily indicated. Microscopy of swabs of lesions predominantly has negative results, showing either contaminants of normal skin flora or occasionally secondary bacterial infections.[4] Skin biopsy may be warranted (Figures 1a and b) to exclude differential diagnoses such as cutaneous Crohn's disease and ulcerated squamous cell carcinoma (Marjolin's ulcer). Imaging such as ultrasound examination may be of clinical benefit for preoperative planning.

Diagnostic criteria

Primary diagnostic criteria for HS include:

- a history of recurrent painful or suppurating lesions (typically deep-seated inflammatory nodules), with
- at least two episodes over a six-month period.[4]

The signs of HS include:

- nodules, comedones, sinus tracts, abscesses and/or fibrotic scarring, particularly in patients with chronic disease (Figures 2a and b)
- lesions in characteristic locations, such as the inguinal area, inner thigh, mammary and inframammary regions, buttocks, pubic region, scrotum, vulva and chest (Figures 3a and b).

A positive family history is a secondary diagnostic criterion. In addition, a negative swab result or the presence of normal skin microbiota suggests HS.

Clinical staging

The Hurley clinical staging system is frequently used in clinical trials to differentiate patients with HS into three severity groups:[2]

- stage I – abscess formation (single or multiple) without sinus tracts and cicatrisation or scarring
- stage II – recurrent abscesses with sinus tracts and scarring, single or multiple widely separated lesions
- stage III – diffuse or almost diffuse involvement, or multiple interconnected sinus tracts and abscesses across the entire area.

Assessment of disease severity in patients with HS requires a combination of Hurley staging and physician assessment combined with patient perception and experience of disease. This can be objectively assessed using a validated tool such as the Dermatology Life Quality Index.

Differential diagnosis

Other diseases that cause inflamed nodules, recurrent abscesses or sinus tracts and may be mistaken for the different

stages of HS are listed in the Box.

Pathogenesis

The pathogenesis of HS is not fully understood. However, there is now greater understanding of the disease from the explosion of research on the topic over recent years. The histopathology of HS has shown the origin of the pathological process is from follicular occlusion and subsequent inflammation.[1] Essentially, the hair follicles become occluded then rupture and re-epithelialise with an associated immune response. Recent studies have suggested that the interleukin-12 to interleukin-23 pathway and tumour necrosis factor alpha (TNF-α) are involved in the pathogenesis of HS, adding credence to the theory that it is an immune or inflammatory disorder.[5] The cause of the follicular occlusion and subsequent inflammation is thought to be multifactorial and includes obesity, smoking, hormonal fluctuation, genetics and inflammation.

Contributing factors

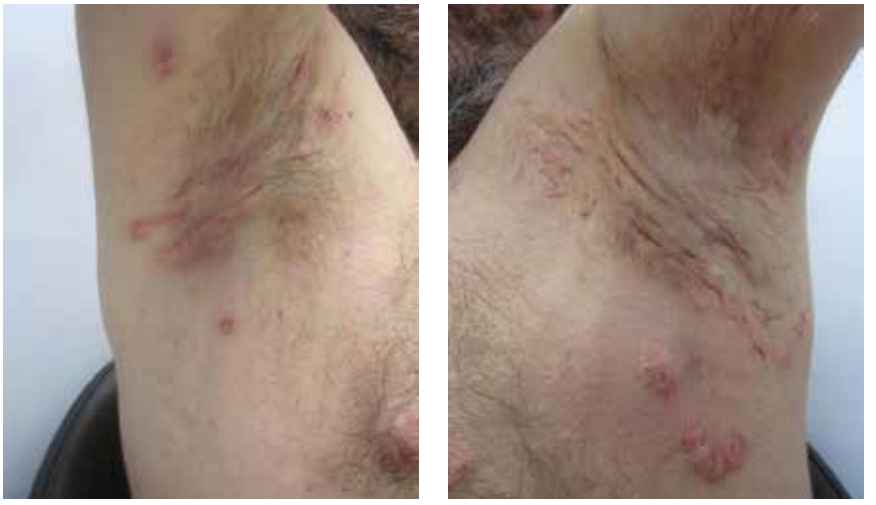
Obesity and metabolic syndrome

An association between obesity and HS has been well established. There is extensive research to suggest that obesity is linked to both the likelihood of developing HS and the severity of disease, and that weight reduction can improve symptoms. A proposed mechanism for this correlation follows the observation that HS typically occurs in intertriginous areas and involves follicular occlusion. With the increased surface area and skin folds in obese patients there is greater shear mechanical stress, pressure and friction on skin that could contribute to follicular occlusion and rupture.[6] Interestingly, there is a growing body of research that identifies an association between metabolic syndrome and HS.[7]

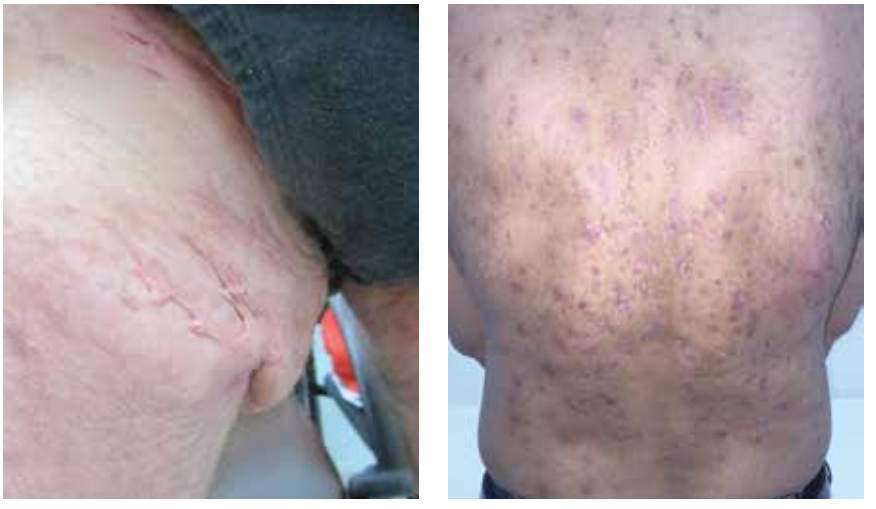
Inflammation

An expanding body of research supports the hypothesis that HS is accompanied by a substantial systemic burden of inflammation. Patients with HS have been found to have higher levels of inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) than patients with psoriasis, suggesting that the inflammatory burden of HS is substantial.[2]

Further, HS has been identified as part of a clinical triad comprising pyoderma gangrenosum, acne and suppurative hidradenitis ('PASH'). PASH represents a new disease entity within the spectrum of autoinflammatory syndromes.[8] It is similar to PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) and aseptic abscess syndrome. All are characterised by recurrent noninfectious inflammatory episodes, the absence of autoantibodies and antigen-specific T cells and the presence of neutrophilic infiltrates.[2] However, PASH is distinguished by its predilection for skin and the lack



Figures 2a and b. Patient with Hurley stage III hidradenitis suppurativa in the axillae, showing inflammatory nodules and hypertrophic scarring.



Figures 3a and b. a (left). Patient with chronic hidradenitis suppurativa in the groin after treatment with biologic therapy, showing hypertrophic scarring from multiple previous lesions. b (right). Patient with Hurley stage II hidradenitis suppurativa after treatment with biologic therapy, showing extensive involvement of the back with inflammatory nodules and scarring.

DIFFERENTIAL DIAGNOSIS OF HIDRADENITIS SUPPURATIVA

Early HS lesions
- Acne
- Cellulitis
- Dermoid cyst
- Folliculitis, furuncles, carbuncles
- Lymphadenopathy
- Perirectal abscess
- Pilonidal cyst

Late HS lesions
- Anal fistula
- Cutaneous Crohn's disease
- Granuloma inguinale
- Ischiorectal abscess
- Ulcerated squamous cell carcinoma (Marjolin's ulcer)

Abbreviation: HS = hidradenitis suppurativa.

of arthritis and visceral involvement. Different mutations within the *PSTPIP1* gene (which encodes a protein involved in T cell regulation, proline-serine-threonine phosphatase-interacting protein 1) have been noted in the three distinct syndromes, suggesting that the location of the mutation within the gene influences the organ predilection.[8]

Smoking

The link between smoking and HS is well established, with most patients with severe disease being smokers. Further, a recent cross-sectional study involving 212 patients over 22 years noted greater remission on cessation of smoking.[9]

Hormonal factors

A role for hormones in the pathogenesis of HS is suggested by the observation that HS affects mainly women, occurs after puberty and is associated with polycystic ovary syndrome.[10] Additionally, it has been noted that HS may decline in postmenopausal women. It has been postulated that androgens play a role in the aetiology of HS, as apocrine glands have androgen receptors with known cyclical premenstrual exacerbations.

Genetics

Genetic susceptibility appears to be an important contributor to HS. A high proportion of patients with HS have a first- or second-degree relative with the disease, and an autosomal dominant mode of inheritance has been identified.[3]

Management

HS is a persistent and debilitating condition. The chronic clinical course, pain, malodorous discharge and deformity are understandably a considerable psychological burden for patients. In a recent study, patients ranked the morbidity of HS above that of alopecia, mild to moderate psoriasis and several other dermatological conditions.[11]

Principles of management

There are currently no formal guidelines for the treatment of HS. Treatment is driven primarily by expert opinion and isolated case reports or series. To achieve effective outcomes, management usually requires a combination of:
- lifestyle changes
- medical therapy
- laser or surgical intervention
- considerable psychological support.

Baseline therapy for HS should include adequate pain management and appropriate dressings (e.g. absorbent nonirritant bandages for suppurative lesions). Lifestyle modifications that can reduce disease severity include advice and support for smoking cessation and weight loss. The disease has a considerable psychosocial impact, and screening for depression and social isolation may be appropriate in some patients.

As there is a spectrum of HS severity, treatment should be based on both the objective severity and impact of the disease on the patient.[4] Early referral to a dermatologist is important for optimum therapeutic management in all patients except those with mild disease, who may be managed by GPs.

Locally recurring lesions can be treated surgically, whereas widespread lesions are more appropriately managed with medical treatment, either as monotherapy or in combination with surgery.

In patients with advanced HS, a multifaceted approach may be adopted, in which surgical therapy is used to remove chronic HS components that are not expected to respond to medical therapy (e.g. scars, fistulas and sinus tracts), and long-term systemic medical therapy is used to treat the acute or subchronic manifestations (e.g. abscesses and inflammatory nodules).

Pharmacological treatments

There are a number of pharmacological treatment options, including topical and systemic antibiotics, corticosteroids, antiandrogen therapy, systemic retinoids and immunosuppressive agents. Successful use of antiandrogens, oral retinoids and immunosuppressants in patients with HS that did not respond to other treatments has been described in case reports and series, but no controlled studies have been conducted with these agents. The use of oral retinoids appears to have limited therapeutic benefit, although one small case series reported isotretinoin to be of some benefit.[12]

Topical or systemic antibiotics

In HS, bacterial colonisation is a secondary event and even potent antibiotic therapy is often futile in the long term. For superficial lesions topical clindamycin may be of some benefit in combination with benzoyl peroxide and other topical nonsoap antibacterial cleansers. In patients with more severe or widely spread lesions, combination therapy with clindamycin and rifampicin to eradicate staphylococci may be effective.[4] Concurrent fungal infections may occur, particularly in the groin area. Microscopy, culture and sensitivity testing of skin swabs can be of benefit to allow targeted antibiotic therapy in the less common cases of secondary bacterial infection of HS lesions.

Intralesional corticosteroids

Intralesional injections of triamcinolone acetonide (5 to 10 mg/mL) have been

advocated to rapidly reduce inflammation associated with acute flares and to manage recalcitrant nodules and sinus tracts.[4] However, this therapy is contraindicated if bacterial infection is suspected clinically.

Antiandrogen therapy – spironolactone

Despite the strong possibility of a hormonal influence in HS, evidence supporting the use of antiandrogen therapy is still lacking. Several small case studies have shown promising results. The potassium-sparing diuretic spironolactone has traditionally been used, because of its known antiandrogen activity. A recent case series showed that spironolactone can be considered as first-line treatment in women with mild to moderate HS.[13]

Immunosuppressants – adalimumab, infliximab

The theory that HS involves an immunological abnormality has prompted investigation into the role of treatment with immunosuppressants, including biologic agents. Adalimumab and infliximab block the effects of TNF-α and have been shown to be useful in patients with severe HS (Figures 2a and b).[12] A recent systematic review of the use of immunosuppressive agents and systemic retinoids in treatment of HS found that infliximab and adalimumab were more effective than other immunosuppressive agents such as colchicine, cyclosporin, dapsone and methotrexate, and systemic retinoids.[14] Use of adalimumab has been approved by the TGA and received a PBS listing in 2017. Access to adalimumab requires an application from a dermatologist.

Laser treatment and surgery

Early definitive surgical intervention has been regarded as one of the most effective treatments for intractable localised disease. For patients with extensive disease, surgical removal of the entire follicular sweat gland apparatus with generous excision margins is currently being advocated as the gold standard treatment.[10] Carbon dioxide laser therapy is another technique used to treat HS by radically removing all keratinocytes in nodules, abscesses and fistulas. However, surgery has been frequently reported to have unsatisfactory outcomes, with results unacceptable to patients. The most common complications are high recurrence rates, scarring and skin graft failure.

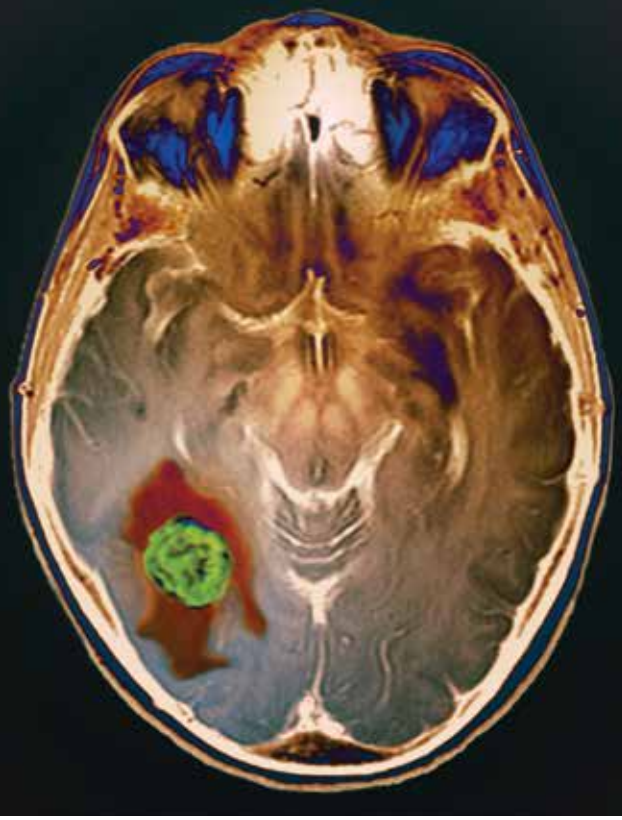
Conclusion

GPs are well positioned to identify patients with HS early in the disease course. Given the high morbidity and psychosocial impact of HS, it is important that clinicians identify the characteristic clinical signs and appreciate the difficulty of treating this disease. Early referral of patients with moderate to severe disease to a dermatologist is important for optimum therapeutic management. Further, with our improved knowledge of the factors that contribute to HS, GPs can have a role in improving the overall health of patients with HS through diagnosing and treating common comorbidities such as metabolic disorders and other inflammatory conditions. MT

References

1. Yu CC, Cook MG. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. Br J Dermatol 1990; 122: 763-769.
2. Pascoe V, Kimball A. Hidradenitis suppurativa current progress and future questions. JAMA Dermatol 2014; 150: 1263-1264.
3. Jemec GB. Hidradenitis suppurativa. N Engl J Med 2012; 366: 158-164.
4. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol 2015; 29: 619-644.
5. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol 2011; 65: 790-798.
6. Kromann CB, Ibler KS, Kristiansen VB, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. Acta Derm Venereol 2014; 94: 553-557.
7. Miller IM, Ellervik C, Vinding GR, et al. Association of metabolic syndrome and hidradenitis suppurativa. JAMA Dermatol 2014; 150: 1273-1280.
8. Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) – a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol 2012; 66: 409-415.
9. Kromann CB, Deckers IE, Esmann S, Boer J, Prens EP, Jemec GB. Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study. Br J Dermatol 2014; 171: 819-824.
10. Barth H, Layton AM, Cunliff WJ. Endocrine factors in pre and post menopausal women with hidradenitis suppurativa. Br J Dermatol 1996; 134: 1057-1059.
11. von der Werth JM, Jemec GB. Morbidity in patients with hidradenitis suppurativa. Br J Dermatol 2001; 140: 809-813.
12. Blok JL, van Hattem S, Jonkman MF, Horvath B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br J Dermatol 2013; 168: 243-252.
13. Lee A, Fischer G. A case series of 20 women with hidradenitis suppurativa treated with spironolactone. Australas J Dermatol 2015; 56: 192-196.
14. Blok JL, van Hattem S, Jonkman MF, Horváth B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br J Dermatol 2013; 168: 243-252.

COMPETING INTERESTS: None.



Advanced melanoma
A new landscape for treatment

ANDREW HAYDON MB BS, PhD, FRACP
MAGGIE MOORE MB BS, FRACP

Recently developed immunotherapies and targeted therapies are now the standard of care for the treatment of advanced melanoma, improving the prognosis for patients diagnosed with this disease. It is important for all members of the healthcare team to be familiar with their role, their therapeutic potential and their unique toxicities.

MedicineToday Dermatology Collection 2017; 2(2): 29-33
First published MEDICINE TODAY 2015; 16(9): 58-61
Updated November 2017

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Over the past 10 years there have been major advances in the systemic therapeutic options for patients with advanced melanoma. Previously, the mainstay of treatment for metastatic disease was chemotherapy, which had low response rates and median survival times of six to nine months. Chemotherapy has now been superseded by intravenous immunotherapy and oral targeted therapy, with more than 50% of patients still alive at two years in the clinical trials of these drugs.[1,2] An understanding of these agents, their unique toxicity profiles and their impact on prognosis will enhance the care of patients with advanced melanoma across the spectrum of their healthcare providers.

Immunotherapies for metastatic melanoma

The importance of the interplay between a patient's immune system and the progression of their melanoma has long been acknowledged. Researchers and clinicians have attempted to exploit this complex interaction for decades with very limited success. Now a new class of drugs, the immune checkpoint inhibitors, has emerged with clear evidence of efficacy and an acceptable, albeit unique, side effect profile. These drugs act by removing an inbuilt 'brake' on the body's immune response against cancer cells. This allows an ongoing antitumour effect from the immune system. The anti-CTLA4 antibody ipilimumab and the anti-PD-1 antibodies pembrolizumab and nivolumab are the furthest advanced of these agents.

Anti-CTLA-4 antibodies (ipilimumab)

Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a key regulator of T cell activity. CTLA-4 on the T cell surface interacts with antigen-presenting cells of the immune system, leading to T cell deactivation and downregulation of the immune response. Ipilimumab blocks this interaction, thus preventing the inhibitory signal and enhancing immune activity against the tumour (Figure 1).

In 2010, the results of the first trial to show a significant overall survival benefit in patients with metastatic melanoma were published.[3] This trial compared ipilimumab with the melanoma glycoprotein 100 vaccine in previously treated patients. It showed an improvement in median survival for patients treated with ipilimumab, from 6.4 months to 10.1 months (hazard ratio [HR] for death, 0.68; $p<0.001$). A second study in previously untreated patients confirmed a survival benefit when ipilimumab was added to chemotherapy,

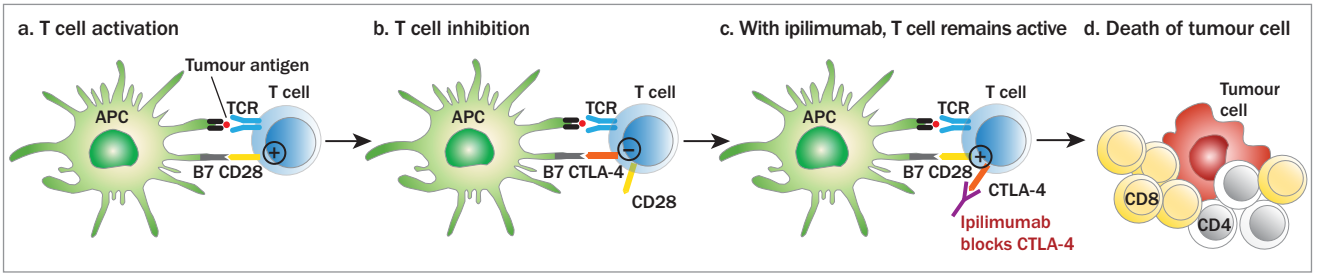


Figure 1. Mode of action of the anti-CTLA-4 antibody ipilimumab. a (far left). Specific antitumour T cells that encounter an antigen-presenting cell (APC) presenting a tumour antigen and expressing B7 costimulatory molecules are activated through T-cell receptor (TCR) and CD28 signalling. b (middle left). The T cell response is then attenuated by upregulation of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), which preferentially binds to B7. c (middle right). Ipilimumab blocks CTLA-4, allowing enhanced T cell stimulation. d (far right). Sustained T cell activation enhances immune activity against the tumour, leading to death of tumour cells.

from 9.1 months with chemotherapy alone to 11.2 months with combination therapy.[4] Although these survival benefits seem modest, and only 10 to 15% of patients have tumour shrinkage with ipilimumab, the initial enthusiasm surrounding this agent related to the durability of the response when it was achieved. It has been reported that almost 20% of patients who were treated with ipilimumab in the early trials are alive more than five years from the time of treatment.[5]

The side effects of ipilimumab are unique and attributable to overactivation of the immune system against nontumour tissue. These autoimmune-type phenomena have been labelled 'immune-related adverse events' (irAEs). Ipilimumab causes irAEs in about 60% of patients, and approximately 20% of these are severe. There have been reports of toxicity in almost every organ system. The most commonly seen side effects with ipilimumab are itch, rash and diarrhoea (Box). Other less common side effects include colitis, autoimmune hepatitis, thyroiditis, hypophysitis, myocarditis, nephritis and neurological toxicity. Moderate to severe irAEs require prompt treatment in a specialist centre with oral or intravenous corticosteroids and occasionally, in refractory cases, more potent immunosuppressive drugs such as infliximab. Ipilimumab is available on the PBS for the treatment of unresectable stage III and IV malignant melanoma.

SIDE EFFECTS OF NEW TREATMENTS FOR ADVANCED MELANOMA

Immunotherapies

- Itch
- Skin rash
- Diarrhoea
- Colitis
- Autoimmune hepatitis
- Thyroiditis
- Hypophysitis
- Guillain–Barré-like syndrome (rare)

Targeted therapies

- Fever
- Fatigue
- Diarrhoea
- Arthralgia
- Liver biochemistry abnormalities
- Skin changes (e.g. rash, hyperkeratosis, papillomas, squamous cell carcinoma)

Anti-PD-1 antibodies (pembrolizumab and nivolumab)

The second class of immune checkpoint inhibitor comprises monoclonal antibodies against the programmed cell death receptor-1 (PD-1). PD-1 is an immune checkpoint receptor that limits T cell activity. Binding of PD-1 to its ligand on tumour cells (PD-L1) leads to deactivation of the T cells. Upregulation of PD-L1 by tumour cells is a mechanism by which immune surveillance of cancers is disrupted. The anti-PD-1 antibodies nivolumab and pembrolizumab bind to PD-1, blocking the interaction with PD-L1 and allowing an enhanced antitumour immune response (Figure 2).[6,7]

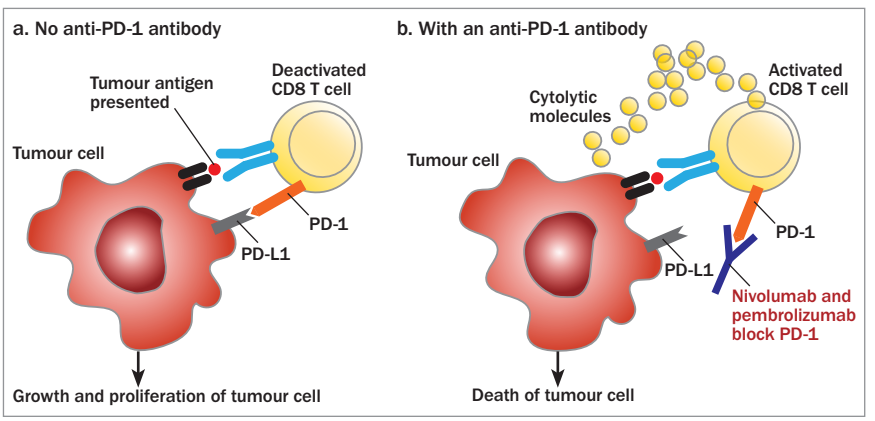


Figure 2. Mode of action of anti-PD-1 antibodies. a (left). T cells are deactivated by binding of programmed cell death receptor-1 (PD-1) to tumour PD-1 ligand (PD-L1), leading to tumour 'immune escape'. b (right). Anti-PD-1 antibodies such as nivolumab and pembrolizumab bind to PD-1, preventing deactivation of the T cell and allowing ongoing immune attack of the tumour cell.

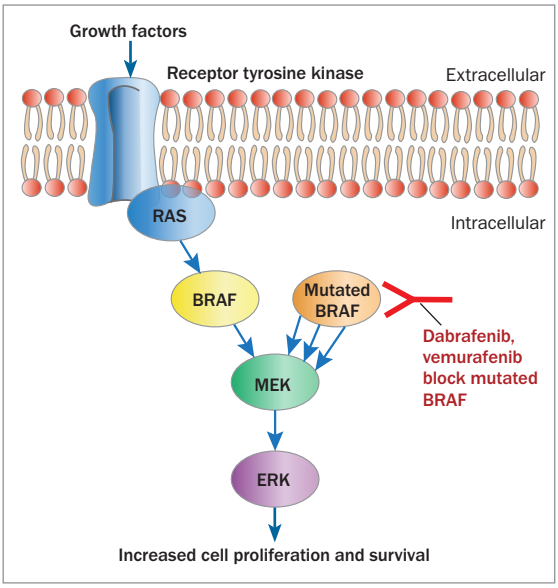


Figure 3. Mode of action of BRAF inhibitors. The mitogen-activated protein kinase pathway is a signalling cascade that is activated when growth factors in the extracellular space interact with receptor tyrosine kinase. Activation leads to enhanced cell growth and survival. Mutated BRAF protein ($BRAF^{V600}$) activates the pathway without the need for upstream signalling from receptor tyrosine kinase, leading to tumour growth. BRAF inhibitors such as dabrafenib and vemurafenib block mutated BRAF activity.

Abbreviations: BRAF = serine-threonine protein kinase; ERK = extracellular signal-regulated kinase; MEK = mitogen-activated protein kinase kinase.

TABLE. FEATURES OF NEW THERAPIES FOR ADVANCED MELANOMA

Drug therapy	Administration
Immunotherapies	
Anti-CTLA4 antibodies	
Ipilimumab	Intravenous infusion every three weeks for four cycles, with an option for re-induction
Anti-PD-1 antibodies	
Pembrolizumab	Intravenous infusion every three weeks, with treatment continued until disease progresses
Nivolumab	Intravenous infusion every two weeks, with treatment continued until disease progresses
Targeted therapies	
BRAF inhibitors	
Dabrafenib	Oral, twice daily on an empty stomach
Vemurafenib	Oral, twice daily on an empty stomach
Combination BRAF and MEK inhibitors	
Dabrafenib plus trametinib	Oral, dabrafenib as above, trametinib once daily on an empty stomach

Abbreviations: BRAF = serine-threonine protein kinase; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; MEK = mitogen-activated protein kinase kinase; PD-1= programmed death receptor-1.

The first randomised trial of an anti-PD-1 antibody in patients with advanced melanoma compared nivolumab with dacarbazine chemotherapy in previously untreated patients.[8] In this study, 73% of patients treated with nivolumab were alive at one year compared with 42% of those treated with dacarbazine (HR for death, 0.42; p<0.001).

A comparison between pembrolizumab and ipilimumab also showed improved outcomes with the use of an anti-PD-1 antibody compared with the anti-CTLA-4 antibody in untreated patients.[2] Pembrolizumab was superior with respect to response rate (33% *vs* 12%), progression-free survival and overall survival (55% *vs* 43% at two years: HR, 0.68; p=0.0008).

The side effect profile of the anti-PD-1 antibodies is the same as ipilimumab; however, severe treatment-related adverse events occur at a lower rate (11 to 21% *vs* 20 to 28%).[8-10]

Combination of anti-PD-1 and anti-CTLA-4 antibodies (nivolumab plus ipilimumab)

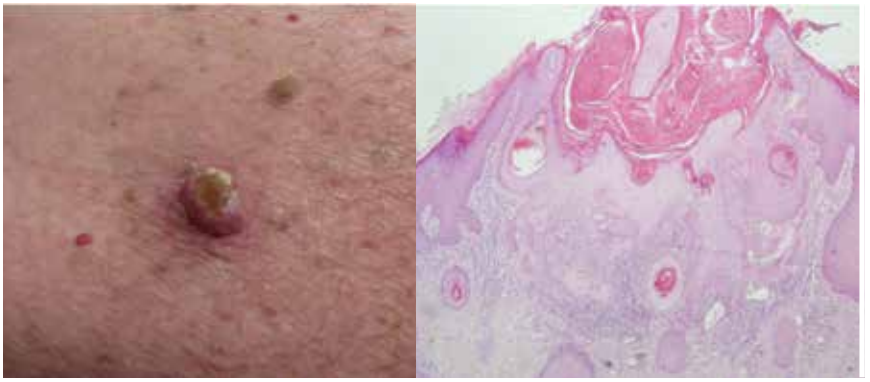
Finally, the combination of nivolumab and ipilimumab has been compared with either ipilimumab or nivolumab alone.[10] The combination therapy led to significantly greater activity (response rate of 58% with combination *vs* 41% and 19% with single agent of nivolumab or ipilimumab, respectively) but a relatively modest overall survival advantage compared with single agent nivolumab of 58% versus 52% at three years. In a descriptive analysis the HR for death with nivolumab plus ipilimumab versus nivolumab was 0.85 (95% confidence interval, 0.68 to 1.07).

The combination regimen carries a much greater risk of high-grade toxicity. In this trial, 59% of patients receiving ipilimumab/nivolumab had a high-grade toxicity compared with 28% in the ipilimumab-alone arm of the trial and 21% in the nivolumab-alone arm.

Pembrolizumab and nivolumab are both listed on the PBS for the treatment of unresectable stage III and IV malignant melanoma. The combination of nivolumab and ipilimumab is not available on the PBS but can be obtained via an access program for well-selected patients.

Targeted therapies in metastatic melanoma

About 40 to 45% of patients with melanoma have a mutation in their tumour cells termed a BRAF mutation. This leads to uncontrolled upregulation of the mitogen-activated protein (MAP) kinase



Figures 4a and b. Squamous cell carcinoma (SCC) in a patient being treated for melanoma, showing a well-differentiated keratoacanthoma-like lesion. SCC is a side effect of single-agent BRAF inhibitor therapy.

pathway, an intracellular signalling pathway with a role in promoting cell growth and division. Uncontrolled upregulation of the pathway leads to increased cell division and tumour growth (Figure 3). Blocking this pathway with oral agents that inhibit both the BRAF protein and a further component of the same pathway, mitogen-activated protein kinase kinase (MEK), leads to rapid tumour shrinkage and improved survival in many patients whose tumours have a BRAF mutation. Conversely these therapies are ineffective in patients whose tumours lack a targetable BRAF mutation.

Features of these therapies and immunotherapies are summarised in the Table.

BRAF inhibitors (dabrafenib and vemurafenib)

Initial phase 3 studies compared BRAF inhibitors with chemotherapy. The BRIM-3 study randomised previously untreated patients with BRAF-mutant metastatic melanoma to receive the BRAF inhibitor vemurafenib or dacarbazine chemotherapy.[11] The vemurafenib group had a significantly higher response rate (48% *vs* 5%), progression-free survival and overall survival (despite crossover). The median survival of patients treated with vemurafenib was 13.6 months versus 9.7 months with chemotherapy (HR, 0.70; p=0.0008). A second study of the BRAF inhibitor dabrafenib compared with chemotherapy had similar findings.[12] Dabrafenib and vemurafenib are now available on the PBS for the first-line treatment of metastatic melanoma.

The most common side effects of BRAF inhibitors are fever, fatigue, diarrhoea, arthralgia, liver biochemistry abnormalities and skin changes (Box). A class effect of single-agent BRAF inhibitors, in addition to rash, hyperkeratosis and papillomas, is the development of squamous cell carcinoma (SCC) of the skin (Figure 4). SCCs occur in about 15% of patients on single-agent BRAF-inhibitor therapy, usually within 10 weeks of commencing treatment. They are managed in the same way as nondrug-induced lesions.

Combination BRAF and MEK inhibition (dabrafenib/trametinib; vemurafenib/cobimetinib)

A mechanism of resistance to single-agent BRAF inhibition is reactivation of the MAP kinase pathway with enhanced signalling through the MEK protein. In an attempt to overcome this, BRAF inhibitors have been tested in combination with MEK inhibition with trametinib or cobimetinib in three randomised trials.[13-15] In each of these studies, the combination of a BRAF inhibitor and a MEK inhibitor was compared with a single-agent BRAF inhibitor as the first-line therapy for BRAF-mutant metastatic melanoma. In all three studies, the combination treatment was superior in terms of response and survival endpoints. Responses were seen in 64 to 68% of patients, median progression-free survival was 11 to 12 months and in recent updates 44 to 45% of patients were still alive at three years.[1,16]

The predominant toxicity seen in patients taking the combination of dabrafenib and trametinib is a drug fever, which occurs in about 70% of patients. The fever may be associated with chills and myalgias and usually resolves quickly with temporary discontinuation of both drugs. Occasionally, the fever is recalcitrant, and corticosteroid therapy may be needed to allow continuation of treatment. The fever syndrome is less common with the vemurafenib/cobimetinib combination where skin toxicities predominate. The hyperkeratotic skin toxicity that often occurs with single-agent BRAF inhibition is rarely seen with combination therapy, however, due to the inhibition of the MEK protein.

The MEK inhibitors trametinib and cobimetinib are both available on the PBS for use in combination with a BRAF inhibitor. The wording of the current PBS listings restricts patients with a BRAF mutation to the use of BRAF/MEK inhibitor therapy as first-line treatment, with immunotherapies only available in subsequent lines of therapy.

Systemic therapy for stage III melanoma

The prognosis of stage III disease, where the melanoma has spread to local lymph nodes, is relatively poor. Five year survival rates are about 60%. Management consists of surgical clearance of the involved lymph node basin followed by observation in most patients. There has been some evidence, in the era before effective therapies for stage IV disease, to support the use of adjuvant interferon.[17] With the improvement in survival being small and the toxicity high, this strategy was never universally accepted or adopted.

The advent of effective therapies for

stage IV disease has led to their assessment for use after complete resection of stage III disease. The first study to assess this approach investigated the use of ipilimumab for three years versus placebo.[18] Administration of ipilimumab resulted in an improvement in overall survival from 54.4% to 65.4% at five years (HR, 0.72; p=0.001). The dose of ipilimumab chosen for use in this study was higher than that used in metastatic disease and resulted in a 54% rate of severe toxicity and a 1.1% rate of toxic death.

A subsequent study randomised patients to ipilimumab versus nivolumab.[19] With a minimum follow up of 18 months, the use of nivolumab was associated with an 11% improvement in recurrence-free survival (66% *vs* 54.5%: HR, 0.65; p<0.001). Nivolumab was significantly better tolerated with high-grade treatment-related toxicity seen in 14.4% of patients on the nivolumab arm compared with 45.9% of those on ipilimumab. A study comparing the use of ipilimumab/nivolumab with nivolumab alone is ongoing.

Finally, the targeted therapies have also been evaluated in this setting. The combination of dabrafenib/trametinib for a year was compared with placebo after resection of stage III disease.[20] At a median follow up of 2.8 years the estimated three-year relapse-free survival was significantly better in the treatment arm at 58% compared with 39% in the placebo arm (HR, 0.47; p<0.001). Toxicity was similar to that seen when these agents are used in metastatic disease.

At present none of these agents are PBS approved for use after resection of stage III disease. The question of whether BRAF inhibition or immunotherapy is the best adjuvant treatment option for resected BRAF mutant stage III melanoma remains unanswered and, in the absence of prospective data addressing this issue, an ongoing challenge for melanoma clinicians.

Conclusion

There are now two important classes of systemic therapy for advanced melanoma: immunotherapies and targeted therapies. An understanding of these new treatments with regard to their role in patient management, their impact on prognosis and the unique toxicities that may occur is essential to ensure the optimal management of patients with melanoma by all members of their healthcare team. MT

References

1. Long GV, Flaherty KV, Stroyakoviskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017; 28: 1631-1639.
2. Shachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017; 390: 1853-1862.
3. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711-723.
4. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517-2526.
5. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015; 33: 1889-1894.
6. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369: 134-144.
7. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384: 1109-1117.
8. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320-330.
9. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521-2532.
10. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377: 1345-1356.
11. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3):extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15: 323-332.
12. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358-365.
13. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014; 371: 1877-1888.
14. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372: 30-39.
15. Ascierto PA, McArthur GA, Dréno B, et al. coBRIM: a phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAF (V600) mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519). Lancet Oncol 2016; 17: 1248-1260.
16. Flaherty K, Davies M, Grob JJ, et al. Genomic analysis and 3-y efficacy and safety update of COMBI-d: a phase 3 study of dabrafenib (D) + trametinib (T) vs D monotherapy in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma. J Clin Oncol 2016; 34 (Suppl 15): 9502-9502.
17. Mocellin S, Pasqualali S, Rossi CR, et al. Interferon alpha adjuvant therapy in patients with high risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010; 102: 493-501.
18. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 2016; 375: 1845-1855.
19. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected Stage III or IV melanoma. N Engl J Med 2017; 377: 1824-1835.
20. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. N Engl J Med 2017; 377: 1813-1823.

COMPETING INTERESTS: None.

A pigmented macule on the nose

What is your diagnosis?

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The differential diagnosis of pigmented macules on the face can be challenging. Dermoscopy may help, and adding confocal microscopy improves sensitivity and specificity; histopathology, however, remains the gold standard.

Case presentation

A man in his 60s presented for a full skin check. He had heavily sun-damaged skin and a past history of lentigo maligna on the nose that was treated three years ago with cryotherapy and imiquimod. He had noted some new pigmentation arising in that area. On clinical examination, an irregular pigmented macule of two colours was seen (Figure 1). Differential diagnoses included solar lentigo, flat seborrhoeic keratosis, pigmented actinic keratosis and, most importantly, recurrent lentigo maligna.

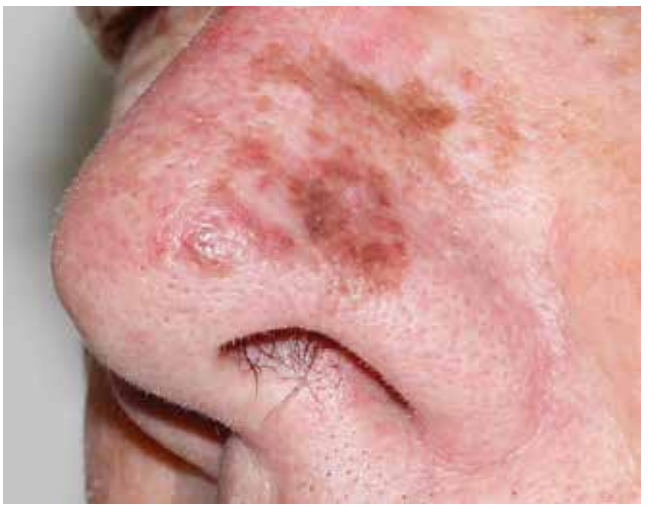

Figure 1. The irregular pigmented macule of two colours on the left side of the patient's nose, diagnosed as lentigo maligna.

Dermoscopic examination showed homogeneous light brown pigmentation, asymmetrical hyperpigmented follicular openings, granular blue-grey pigmentation and rhomboidal structures (Figures 2a to c). As the borders of the lesion were very uneven, in vivo reflectance confocal microscope (RCM) was used to confirm the diagnosis and map the area to treat (Box 1). The RCM image of the epidermis showed multiple atypical large bright round cells (Figure 3), a characteristic feature for pagetoid spread. (Pagetoid cells are cells, melanocytes in this case, that invade the upper epidermis from below. In RCM, they are seen as large bright round cells or as pleomorphic cells with dendritic processes.) A biopsy was performed and the pathology report confirmed the diagnosis of lentigo maligna, ruling out a dermal component.

Discussion

Lentigo maligna is the most frequent type of melanoma on the face. The term 'lentigo maligna' is used when it is confined to the epidermis (in situ) and 'lentigo maligna melanoma' when it invades the dermis.[1]

MedicineToday Dermatology Collection 2017; 2(2): 34-37
First published MEDICINE TODAY 2014; 15(12): 65-68
Updated November 2017

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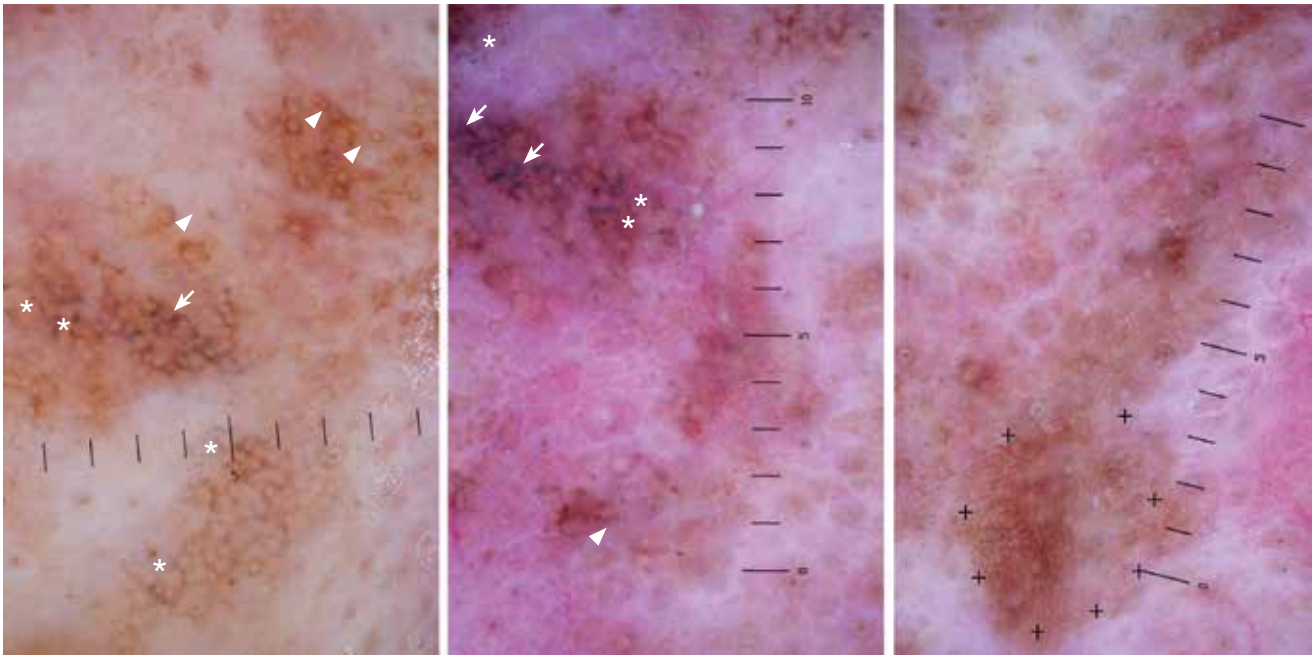

Figures 2a to 2c. Dermoscopic examination of the lentigo maligna in Figure 1. a and b (left and centre). Asymmetrical hyperpigmented follicular openings (triangles), granular blue-grey pigmentation (asterisks) and rhomboidal structures (arrows). c (right). Homogeneous light brown pigmentation (plus signs).

Lentigo maligna tends to occur in chronically sun-exposed areas, mostly on the face and neck. Its incidence is increasing, and has a peak between the ages of 60 and 80 years.

It can be difficult to make the differential diagnosis of pigmented macules of the face with the naked eye, as non-melanocytic lesions and melanocytic lesions have a similar appearance. Dermoscopy helps to make the diagnosis; however, classic melanoma dermoscopy criteria cannot be applied to pigmented lesions on the face. Dermoscopic characteristics of lentigo maligna and lentigo maligna melanoma are summarised in the Table.[1,2]

A progression growth model for lentigo maligna has been described (Figure 4).[3] In the early phase, hyperpigmented asymmetrical follicular openings can be observed, then fine dots and globules appear, forming the annular–granular pattern. When the lentigo maligna becomes invasive, pigmented rhomboidal structures appear and then, as the hyperpigmentation coalesces, follicular openings become obliterated. These features, however, are not all specific for melanoma, as several lesions can simulate the early changes seen in lentigo maligna. Recently, it has been described that the lack of non melanoma features (scales, white follicles, erythema/reticular vessels, reticular and/or curved lines/fingerprints, structureless brown colour, sharp demarcation and classic criteria of seborrhoeic keratosis) in facial lesions has similar sensitivity (88.5% *vs* 94%) and higher specificity (67% *vs* 52%) than the malignant features for the diagnosis of facial melanoma.[4]

Lentigo maligna/lentigo maligna melanoma should be included in the differential diagnoses of melanocytic naevus, flat seborrhoeic keratosis (lentigo senilis), lichen planus-like keratosis and pigmented actinic keratosis. Flat seborrhoeic keratosis usually shows horn pseudocysts, yellow opaque areas, milia-like cysts, fingerprint-like structures, moth-eaten borders and the jelly sign; the lesions may, however, simulate streaks, and thicker lesions can show blue-grey areas and pseudofollicular openings.[5] Lichen planus-like keratosis, a

1. REFLECTANCE CONFOCAL MICROSCOPY

Reflectance confocal microscopy (RCM) allows 'optical' biopsy of the epidermis and superficial dermis (to a maximum of 0.2 mm deep). Compared with dermoscopy, which allows the observation of patterns and features of skin lesions, RCM provides a much sharper image and allows assessment of tissue underlying dermoscopic features at a cellular level, also in the horizontal plane.

Melanin provides a strong contrast in the black and white images of RCM as it backscatters the laser beam, making pigmented cells appear bright. RCM is therefore useful in the assessment of pigmented skin lesions, enabling the size, shape and organisation of the pigmented cells to be readily assessed. RCM is also of use in the evaluation of skin lesions that are not pigmented.

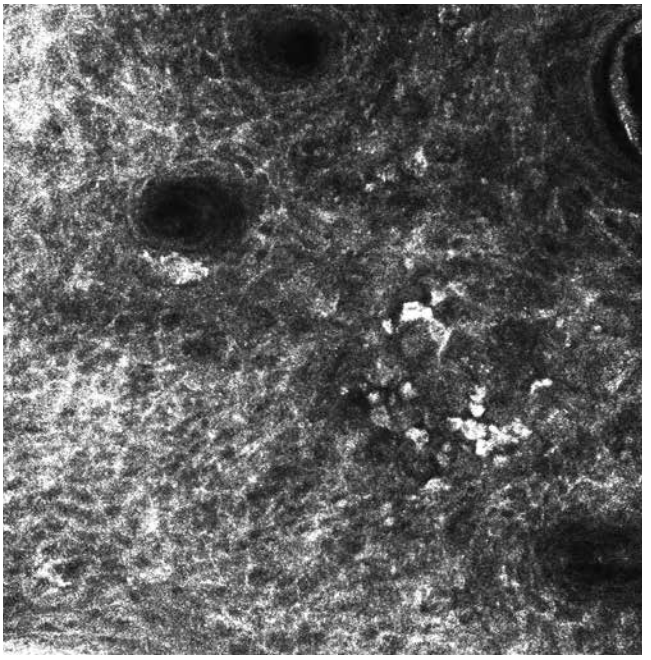

Figure 3. Reflectance confocal microscopy of the lentigo maligna in Figure 1, showing epidermis with multiple atypical large bright pagetoid cells (round and dendritic). (Image 5 µm x 5 µm.)

form of irritated/regressing seborrhoeic keratosis, may have grey dots and globules. Pigmented actinic keratosis may also have grey dots and annular–granular structures but can be differentiated from lentigo maligna by their rough surface, their tendency to be grouped, the usual lack of asymmetrical pigmented follicular openings and the presence of a red pseudo network in a 'strawberry' pattern.[6,7]

The most specific finding that can help differentiate lentigo maligna/lentigo maligna melanoma from other lesions is the presence of asymmetrical hyperpigmented follicular openings.[2] The finding of one or more of the features of lentigo maligna in a melanocytic macule of the face suggests the lesion may be malignant, and a biopsy or at least long-term (six months) digital monitoring should be considered.[8]

Good clinicopathology correlation is necessary as a small sample of a large lesion may not be indicative of the final diagnosis. Large shave biopsy is the preferred mode of diagnosis. If the lesion is growing, a further biopsy specimen should be obtained. Of note, it is very rare to have a new dysplastic naevus on the face of a patient older than 60 years, and the clinician should review the diagnosis with the pathologist in case of discrepancy.

In vivo confocal microscopy features for lentigo maligna/lentigo maligna melanoma have been described, and this technique has been proposed to add sensitivity and specificity to the diagnosis made on dermoscopy, to help target biopsy at the worst

TABLE. DERMOSCOPIC CHARACTERISTICS OF LENTIGO MALIGNA AND LENTIGO MALIGNA MELANOMA[1,2]

Criteria	Description
Classic Stolz criteria (ordered by progression)[2]	
Asymmetrical hyperpigmented follicular opening*	Pigmentation around the follicular openings, often irregularly distributed Histologically corresponds to lentigo maligna invasion of hair shaft
Annular–granular pattern	Fine grey dots and globules around the follicles Mainly caused by melanin and macrophages, not by melanoma cells
Pigmented rhomboidal structures*	Pigmentation around the follicular openings is more dense, forming a rhomboidal shape Associated with invasion
Obliterated hair follicles	Pigmentation coalesces and obliterates the follicular openings Associated with invasion
New criteria proposed by Pralong[1]	
Darkening on dermoscopic examination	The lesion appears darker when observed with dermoscopy compared with the naked eye
Target-like pattern	Dark dot in the centre of the dark circle of a hyperpigmented hair follicle
Increased density of the vascular network	Vascular network of higher density within the lesion
Red rhomboidal structures	Vessels distributed around the hair follicles in rhomboidal shape Associated with invasion
Other criteria	
Regression-associated features	Peppering – grouping of fine grey dots and globules White scar-like areas (advanced melanoma)
Vertical growth-associated features	Ulceration Black structureless areas Blue papular areas
Classic features of extrafacial melanoma	Multiple colours, atypical honeycomb-like pigment network, irregularly distributed globules, dots and streaks

* Asymmetrical hyperpigmented follicular openings and pigmented rhomboidal structures are the most specific features for lentigo maligna and lentigo maligna melanoma.

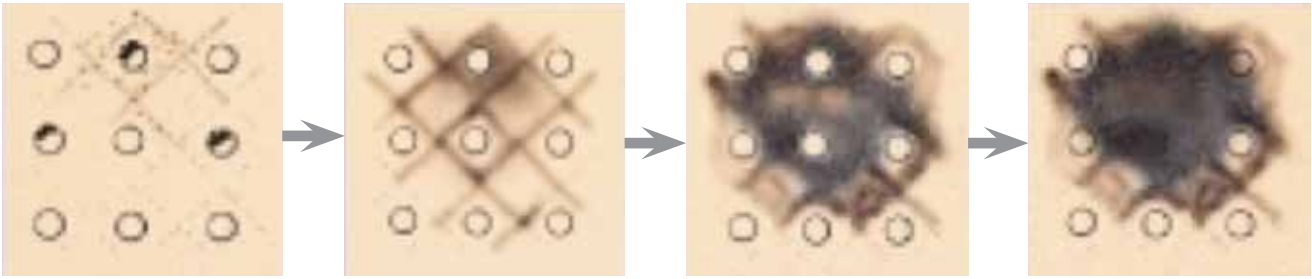

Figure 4. Progression growth model for lentigo maligna described by Schiffner.[3] From left to right: hyperpigmented asymmetrical follicular openings; fine dots and globules (annular–granular pattern); pigmented rhomboidal structures; hyperpigmentation coalesces and follicular openings become obliterated.

Reprinted from Schiffner R, Schiffner-Rohe J, Vogt T, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. J Am Acad Dermatol 2000; 42: 25-32, with permission from Elsevier.

2. KEY POINTS

- The differential diagnosis of pigmented macules on the face can be challenging.
- Dermoscopy may help with the diagnosis, but it is still far from an exact science as some benign lesions have similar features to lentigo maligna
- Confocal microscopy combined with dermoscopy adds sensitivity and specificity to the diagnosis.
- Histopathology remains the gold standard for diagnosis.

area and to map extensive or recurrent lesions, particularly in cosmetically challenging cases.[9-13]

The first line of management for lentigo maligna is complete excision with at least 5 mm margins, which is sometimes difficult to achieve. Second-line treatments are radiotherapy and imiquimod, and these should be discussed in a specialist environment.

Key points about diagnosing a pigmented macule on the nose are given in Box 2.

Conclusion

Dermoscopy has demonstrated its use in assessing pigmented lesions on the face. These lesions, however, do not show the classic melanoma criteria seen elsewhere on the body and the sensitivity of lentigo maligna criteria is not very high. In vivo confocal microscopy has been proposed for difficult cases, although this technology is only available in a few specialised institutions in Australia. Patients in whom diagnosis or management are challenging should be referred to these centres. MT

References

1. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. Br J Dermatol 2012; 167: 280-287.
2. Stolz W, Shiffner R, Burgdorf W. Dermatoscopy for facial pigmented skin lesions. Clin Dermatol 2002; 20: 276-278.
3. Schiffner R, Schiffner-Rohe J, Vogt T, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. J Am Acad Dermatol 2000; 42: 25-32.
4. Tschandl P, Gambardella A, Boespflug A, et al. Seven non-melanoma features to rule out facial melanoma. Acta Derm Venereol 2017; 97: doi: 10.2340/00015555-2759 [Epub ahead of print].
5. Tanaka M, Sawada M, Kobayashi K. Key points in dermoscopic differentiation between lentigo maligna and solar lentigo. J Dermatol 2011; 38: 53-58.
6. Akay BN, Kocyigit P, Heper AO, Erdem C. Dermatoscopy of flat pigmented facial lesions: diagnostic challenge between pigmented actinic keratosis and lentigo maligna. Br J Dermatol 2010; 163: 1212-1217.
7. Zalaudek I, Ferrara G, Leinweber B, Mercogliano A, D'Ambrosio A, Argenziano G. Pitfalls in the clinical and dermoscopic diagnosis of pigmented actinic keratosis. J Am Acad Dermatol 2005; 53: 1071-1074.
8. Altamura D, Avramidis M, Menzies SW. Assessment of the optimal interval for and sensitivity of short-term sequential digital dermoscopy monitoring for the diagnosis of melanoma. Arch Dermatol 2008; 144: 502-506.
9. Guitera P, Pellacani G, Crotty KA, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. J Inv Dermatol 2010; 130: 2080-2091.
10. Guitera P, Moloney FJ, Menzies SW, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. JAMA Dermatol 2013; 149: 692-698.
11. Alarcon I, Carrera C, Alos L, Palou J, Malvehy J, Puig S. In vivo reflectance confocal microscopy to monitor the response of lentigo maligna to imiquimod. J Am Acad Dermatol 2014; 71: 49-55.
12. Guitera P, Haydu LE, Menzies SW, et al. Surveillance for treatment failure of lentigo maligna with dermoscopy and in vivo confocal microscopy: new descriptors. Br J Dermatol 2014; 170: 1305-1312.
13. Guitera P, Pellacani G, Longo C, Seidenari S, Avramidis M, Menzies SW. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. J Invest Dermatol 2009; 129: 131-138.

COMPETING INTERESTS: None.

A case of xanthelasma palpebrarum

BRUCE TATE PhD, FACD

Occurring most often on the medial aspect of the upper eyelids, xanthelasma palpebrarum are of cosmetic concern to patients, but are a significant marker for atherosclerotic disease risk independent of other risk factors.

Case presentation

A 67-year-old woman presented with an 18-month history of gradually enlarging, light yellow plaques on her medial upper eyelids (Figure). The plaques were asymptomatic and mainly of cosmetic concern to her.

The patient had moderate hypertension, which was being treated with amlodipine, but she was otherwise well, taking no other medications and having no known allergies.

Diagnosis

The diagnosis of this condition was xanthelasma palpebrarum.

Differential diagnoses

Favre-Racouchot syndrome

Favre-Racouchot syndrome is the presence of multiple, often grouped, macrocomedones (large blackheads), occurring in the setting of solar elastosis and other features of chronic sun damage. The solar elastosis causes a yellowish discolouration of the skin, and destruction of perifollicular elastin allows the follicular keratin to accumulate and cause the macrocomedones. This syndrome often affects thin skin sites on the face, particularly the temples, malar and periorbital areas. It is mainly seen in the elderly.

MedicineToday Dermatology Collection 2017; 2(2): 38-40
First published MEDICINE TODAY 2010; 11(7): 65-68
Updated November 2017

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Figure. Yellowish plaques on the medial upper eyelids of a 67-year-old woman.

Syringomas

Syringomas are benign tumours of eccrine sweat duct origin. They form small flesh-coloured papules and most often occur on and under the eyelids but sometimes elsewhere on the face or occasionally on the neck or trunk. Usually they are sporadic, but occasionally there is a family history. They are of cosmetic concern only.

Sarcoidosis

Sarcoidosis has many cutaneous manifestations. On the face it tends to involve papules or plaques of various sizes; less often it involves nodules. The lesions are usually red or red–brown but may have a yellowish hue, which can be seen as tiny yellow dots when placed under pressure with a glass slide or dermatoscope. They may form on the nose ('lupus pernio', which should not to be confused with chilblain lupus). The plaques may have prominent blood vessels ('angiolupoid sarcoidosis'). Sarcoidosis may also involve the eyelids, although location only at this site is unusual. Occasionally, sarcoidosis localises to scar sites. Cutaneous sarcoidosis occurs with or without systemic features. Systemic sarcoidosis has many potential manifestations but particularly affects the eyes, lymph nodes and lungs. Diagnosis is made on biopsy because it can imitate various other skin conditions.

Adult orbital xanthogranulomatous disease

There are four recognised variants of adult orbital xanthogranulomatous disease, all rarely reported in the literature. Each are classified as class II non-Langerhans histiocytic proliferations. Histopathological examination shows xanthomatous infiltration of macrophages and Touton giant cells.

- **Adult-onset xanthogranuloma:** These typically present as solitary yellowish dermal or deeper diffuse nodules anywhere on the body including the eyelid. It may be a version of the much more common juvenile xanthogranuloma, which present as solitary or few small dermal nodules anywhere on the body. These can affect the eye too.
- **Adult-onset asthma and periocular xanthogranuloma:** Bilateral yellow swelling of the upper and lower eyelids that often affects the fat of the orbits but also the lungs and lymph

nodes is known as periocular xanthogranuloma. Asthma develops within a few years and often also rhinosinusitis. There may be a strong link to immunoglobulin (Ig) G4-secreting plasma cell infiltration of these areas.

- **Necrobiotic xanthogranuloma:** This is a progressive disease that features destructive skin lesions, multisystem extracutaneous manifestations and a close association with paraproteinaemia. Skin lesions are red–orange to yellow in colour with some atrophy, telangiectatic vessels and sometimes scars and ulcers. The disease mainly affects the face (particularly the periorbital area) and neck, but it may occur on the trunk or proximal limbs. It can affect the heart, skeletal muscle, lungs, kidneys, liver, spleen, intestines and central nervous system. Monoclonal gammopathy is present in 80% of cases, and 10% of such patients develop or have multiple myeloma or occasionally other lymphoproliferative disorders. Affected patients are also prone to cryoglobulinaemia.
- **Erdheim–Chester disease:** This is a lymphohistiocytic infiltration in the orbit and internal organs (including bones, lungs, heart and retroperitoneum).

Systemic amyloidosis

Systemic amyloidosis occurs rarely. There are different forms but the most relevant here is systemic amyloidosis due to amyloid from immunoglobulin light chains whose sources include multiple myeloma. The amyloid protein accumulates around and weakens small blood vessels causing itch and haemorrhage (petechiae or ecchymoses). Larger accumulations of amyloid from immunoglobulin light chains lead to yellowish papules and plaques. The head and neck are particularly affected with the eyelids being a favoured site.

Comment

Xanthelasma are small- to medium-sized, light to mid-yellow coloured plaques seen almost exclusively on or close to the eyelids. They usually occur on the medial aspect of the upper eyelids, and less frequently occur on the lower eyelids. They vary from soft to firm in consistency. Starting quite small as solitary patches or in a small group, on one or both eyelids, they slowly enlarge and tend to merge to form a larger patch. Papules and plaques often form. They usually do not itch. Although uncommon, xanthelasma are considerably more common in women, and the prevalence is higher in middle-age and older.[1]

Xanthelasma are due to accumulation of mainly cholesterol and related lipids in macrophages in the upper dermis. It is not clear why they occur on the eyelids, but factors may include the leakage of small amounts of serum from capillaries as a result of eye rubbing or minor torsional friction from opening and closing the eyes. Normally, low-density lipoproteins (LDL) are slowly catabolised in cells after uptake by apoB/E LDL receptors. The cholesterol released inhibits synthesis of these receptors, forming a negative feedback loop. Oxidised forms of LDL are preferentially endocytosed by macrophages bearing various scavenger receptors where the negative feedback loop does not occur, leading to intracellular accumulation of lipid in macrophages.[2] Some studies show about 50% of all patients with xanthelasma have raised serum cholesterol levels but others show no difference to control groups.[3,4] Those with elevated levels usually have a Fredrickson type IIa pattern of hyperlipidaemia; less often they have a type IIb or III pattern. Occasionally people with xanthelasma also have a corneal arcus or tendinous xanthomas.

A large prospective Danish population study showed that xanthelasma, but not arcus corneae, is a significant and independent risk factor for atherosclerotic disease.[3] This risk held for people with normal lipid levels, and similar findings were seen in a smaller prospective study of Italian adult men.[5] In the Lipid Research Clinics Program Prevalence Study, xanthelasma and corneal arcus were associated with elevated plasma cholesterol and LDL-cholesterol levels, especially in young men.[6] In addition, the odds ratios of ischaemic heart disease were also slightly raised in most groups who had both xanthelasma and corneal arcus.[6] Xanthelasma can also be a marker of other conditions associated with dyslipidaemias, such as nephrotic syndrome, hypothyroidism and liver cirrhosis. It is thus advisable that patients with xanthelasma have a thorough review and receive appropriate management for all atherosclerotic risk factors.

Treatment

Treatment of xanthelasma is only carried out for cosmetic purposes. No cream is available to clear the lesions and some treatments may result in only partial resolution. Once cleared, it is common for the lesions to eventually reappear. The therapeutic options are listed below.

Concealing the lesions

The use of colour-matched cosmetics is the simplest way to conceal the lesions. However, the yellow colour of the lesions can be difficult to hide and, because they are usually plaques, a contour change is usually visible even if the colour is hidden.

Physical destruction

Any method of physical destruction can leave marks, especially decreased or increased pigmentation but sometimes true scars. Pigment changes are particularly an issue in people with darker skin types. The available methods are as follows.

- **Trichloroacetic acid (typically 50% to 70%).** This cheap and readily available weak acid can be used as a chemical peeling agent. It is applied using a cotton bud to the affected areas and rapidly causes moderately painful stinging and a frosty white superficial burn. Some practitioners later neutralise the acid by applying bicarbonate of soda solution. The pain settles in a day or so, then the skin superficially

peels. The healing seems to stimulate clearance of some of the cholesterol-laden macrophages. Repeated applications every one to two months slowly fade the xanthelasma. Sometimes partial fading is all that is achieved. There is also a risk of pigment change (darkening or lightening), which may be temporary or persistent. In a series of 24 patients treated with 70% trichloroacetic acid, 11 had an excellent result, eight a good result and five a satisfactory result. Six had a recurrence of the xanthelasma within six months of treatment.[7]

- **Laser ablation.** Several lasers have been used to ablate the affected skin, some with excellent results.[8] Many operators now favour fractionated carbon dioxide lasers. Resurfacing type carbon dioxide or erbium-yttrium aluminum garnet lasers are also often successful, but pulsed dye, argon, neodymium-doped:yttrium aluminum garnet and potassium titanyl phosphate laser ablation have also been used successfully.[7,9,10] The advantage of laser ablation is that it can be done more accurately, but some modalities are more prone to cause scarring or pigment change (darkening or lightening). The numbers studied are often small and there are no good comparison studies of the main modalities in the one study.
- **Diathermy or radiofrequency ablation.** These methods are less commonly used for xanthelasma. Diathermy is the more crude method of the two that leaves a char that heals with a scar. Both methods are more likely to cause pigment change (darkening or lightening).
- **Liquid nitrogen.** Light freezing with liquid nitrogen has been reported as a successful therapy for xanthelasma,[11] but it is an unreliable treatment and in theory more prone to cause pigment marks, especially loss of colour (more so in people with darker skin).

Surgical excision

Various surgical excision methods have been used to remove xanthelasma.[12-15] It is better suited for xanthelasma of the upper eyelids. Simple fusiform excision is an option, but the scar from this method can be unsightly and is prone to causing noticeable puckering of the skin at the tips of the excised areas. Ectropion or retraction of the eyelids is a limiting factor in the extent of possible surgery. More elegant techniques with better cosmetic outcomes can be performed by ocular or plastic surgeons, usually using classic or modified blepharoplasty incisions. Patients must be warned that the xanthelasma often recurs after surgery. A 40% recurrence rate after primary excision and a 60% rate after a further excision have been reported.[16] Recurrence was most likely in the first year (in 26% of cases).[16]

Other

Treatment of elevated cholesterol is not a primary treatment for xanthelasma, although there has been one report of clearance in a patient taking simvastatin for 10 years.[17] Statin therapy has been found to be effective in some patients in a prominent author's unpublished experience.[18]

Intralesional injection treatment of xanthelasma with pingyangmycin (an antitumour glycopeptide related to bleomycin) was effective in a small series of patients in China.[19] MT

References

1. Bergman R. The pathogenesis and clinical significance of xanthelasma palpebrarum. J Am Acad Dermatol 1994; 30: 236-242.
2. Zak A, Zeman M, Slaby A, Vecka M. Xanthomas: clinical and pathophysiological relations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2014; 158: 181-188.
3. Christoffersen M, Frikke-Schmidt R, Schnohr P, Jensen GB, Nordestgaard BG, Tybjærg-Hansen A. Xanthelasmata, arcus corneae, and ischaemic vascular disease and death in general population: prospective cohort study. BMJ 2011; 343: d5497.
4. Kavoussi H, Ebrahimi A, Rezaei M, Ramezani M, Najafi B, Kavoussi R. Serum lipid profile and clinical characteristics of patients with xanthelasma palpebrarum. An Bras Dermatol 2016; 91: 468-471.
5. Menotti A, Lanti M, Maiani G, Kromhout D. Determinants of longevity and all-cause mortality among middle-aged men. Role of 48 personal characteristics in a 40-year follow-up of Italian Rural Areas in the Seven Countries Study. Aging Clin Exp Res 2006; 18: 394-406.
6. Segal P, Insull W Jr, Chambless LE, et al. The association of dyslipoproteinemia with corneal arcus and xanthelasma. The Lipid Research Clinics Program Prevalence Study. Circulation 1986; 73: 108-118.
7. Nahas TR, Marques JC, Nicoletti A, Cunha M, Nishiwaki-Dantas MC, Filho JV. Treatment of eyelid xanthelasma with 70% trichloroacetic acid. Ophthal Plast Reconstr Surg 2009; 25: 280-283.
8. Nguyen AH, Vaudreuil AM, Huerter CJ. Systematic review of laser therapy in xanthelasma palpebrarum. Int J Dermatol 2017; 56: e47-e55.
9. Balevi A, Ustuner P, Ozdemir M. Erbium:yttrium aluminum garnet laser versus Q-switched neodymium:yttrium aluminum garnet laser for the treatment of xanthelasma palpebrarum. J Cosmet Laser Ther 2017; 19: 100-105.
10. Greijmans E, Luiting-Welkenhuyzen H, Luijks H, Bovenschen HJ. Continuous wave potassium titanyl phosphate laser treatment is safe and effective for xanthelasma palpebrarum. Dermatol Surg 2016; 42: 860-866.
11. Hawk JL. Cryotherapy may be effective for eyelid xanthelasma. Clin Exp Derm 2000; 25: 349-354.
12. Rohrich RJ, Janis JE, Pownell PH. Xanthelasma palpebrarum: a review and current management principles. Plast Reconstr Surgery 2002; 110: 1310-1314.
13. Elabjer BK, Busic M, Sekelj S, Krstonijevic EK. Operative treatment of large periocular xanthelasma. Orbit 2009; 28: 16-19.
14. Then SY, Malhotra R. Superiorly hinged blepharoplasty flap for reconstruction of medial upper eyelid defects following excision of xanthelasma palpebrum. Clin Exp Ophthalmol 2008; 36: 410-414.
15. Levy JL, Trelles MA. New operative technique for treatment of xanthelasma palpebrarum: laser-inverted resurfacing: preliminary report. Ann Plast Surg 2003; 50: 339-343.
16. Mendelson BC, Masson JK. Xanthelasma: follow-up on results after surgical excision. Plast Reconstr Surg 1976; 58: 535.
17. Shields CL, Mashayekhi A, Shields JA, Racciato P. Disappearance of eyelid xanthelasma following oral simvastatin (Zocor). Br J Ophthalmol 2005; 89: 639-640.
18. Flynn PD. Nutritional disorders affecting the skin. In: Griffiths C, Barker T, Bleiker T, Chalmers R, Creamer D, eds. Rook's textbook of dermatology, 9th ed. Chichester, West Sussex, Hoboken, NJ; John Wiley & Sons Inc: 2016.
19. Wang H, Shi Y, Guan H, et al. Treatment of xanthelasma palpebrarum with intralesional pingyangmycin. Dermatol Surg 2016; 42: 368-376.

COMPETING INTERESTS: None.