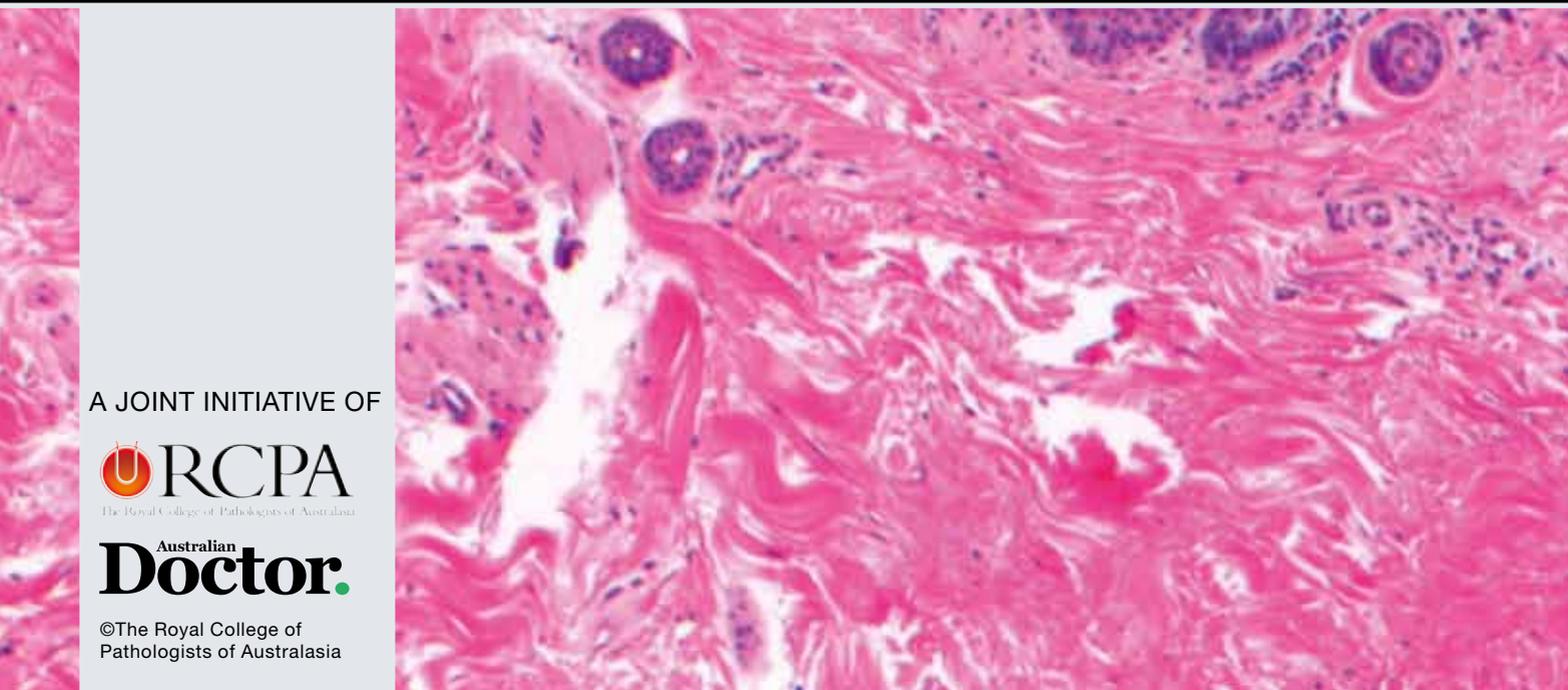


COMMON SENSE PATHOLOGY

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

FEBRUARY 2016

Biopsy diagnosis of inflammatory skin disease



A JOINT INITIATIVE OF

 **RCPA**
The Royal College of Pathologists of Australasia

**Australian
Doctor.**

©The Royal College of
Pathologists of Australasia

This issue of *Common Sense Pathology* is a joint initiative of *Australian Doctor* and the Royal College of Pathologists of Australasia.

Published by Cirrus Media
Tower 2, 475 Victoria Ave, Locked Bag 2999
Chatswood DC NSW 2067.
Ph: (02) 8484 0888 Fax: (02) 8484 8000
E-mail: mail@australiandoctor.com.au
Website: www.australiandoctor.com.au
(Inc. in NSW) ACN 000 146 921
ABN 47 000 146 921 ISSN 1039-7116

© 2016 by the Royal College of Pathologists of Australasia

www.rcpa.edu.au
CEO Dr Debra Graves
Email: debrag@rcpa.edu.au

While the views expressed are those of the authors, modified by expert reviewers, they are not necessarily held by the College.

Common Sense Pathology

Editor: Dr Steve Flecknoe-Brown
Email: sflecknoebrown@gmail.com

Australian Doctor Education

Director: Dr Linda Calabresi
Email: linda.calabresi@cirrusmedia.com.au

Chief Content Producer: Cheree Corbin

Email: cheree.corbin@cirrusmedia.com.au

Graphic designer: Edison Bartolome

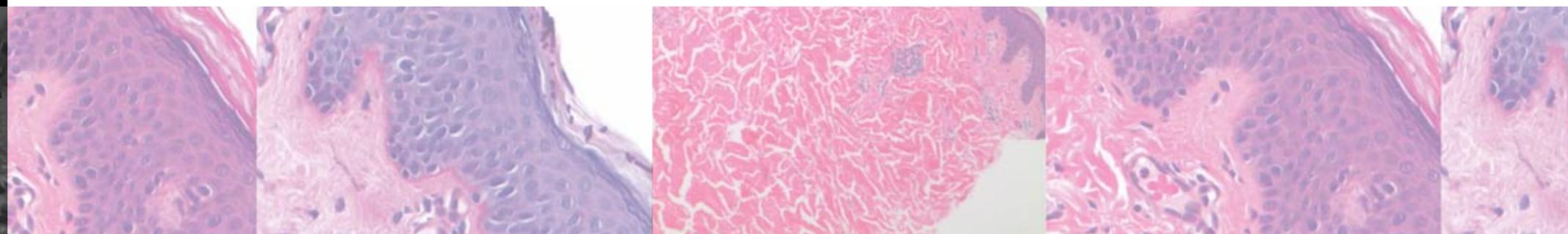
Email: edison.bartolome@cirrusmedia.com.au

Production co-ordinator: Eve Allen

Email: eve.allen@cirrusmedia.com.au

For an electronic version of this and previous articles, you can visit www.australiandoctor.com.au or download an ebook version from www.australiandoctor.com.au/ebooks. You can also visit the Royal College of Pathologists of Australasia's website at www.rcpa.edu.au. Click on Library and Publications, then *Common Sense Pathology*.

This publication is supported by financial assistance from the Australian Federal Department of Health.



AUTHOR



Dr Adrian R Gachia
MB BS FRCPA LLB
(Hons 1) FACLM GAICD
Dermatopathologist
Kossard
Dermatopathologists



Introduction

Australia's high skin cancer rate has encouraged many GPs to become confident and skilled in the biopsy investigation and surgical treatment of skin neoplasms. Biopsy investigation of inflammatory dermatoses has been less enthusiastically embraced.

Reasons for this include the perception that many inflammatory dermatoses do not require biopsy confirmation, dermatoses refractory to first-line treatment require specialist dermatologist referral, biopsy findings are often ambiguous or unhelpful, or that the information obtained does not justify biopsy injury. While these reservations are sometimes valid, skin biopsy carefully performed is an inexpensive, rapid and effective way to assist definitive diagnosis of a patient's rash.

The keys to successful biopsy diagnosis are formulating a clear, clinical differential diagnosis in advance, choosing the correct site and individual lesions to biopsy, choosing correct biopsy type and technique, and having a good relationship with your dermatopathologist.

Clinical examination is essential

Detailed clinical history is essential for accurate diagnosis. Our largest organ is also the organ most amenable to direct inspection. This diagnostic opportunity should never be missed. Patients who present with apparently localised hair, nail or skin disease require whole-body skin inspection to exclude more widespread disease. Lesion distribution is at least as important as the appearance of an individual lesion when formulating an accurate differential diagnosis. Many inflammatory dermatoses involve oral, nasal, ocular and genital mucous membranes. Patients need to be specifically asked about such involvement during the course of clinical examination, followed by direct inspection whenever the differential diagnosis includes a condition that is known to possibly involve the mucous membranes. Once your differential diagnosis has been decided, it is necessary to then decide how biopsy might help to further refine it.

What to biopsy

Having decided to biopsy, which lesion to biopsy? Inflammatory dermatoses typically have prodromal, evolving, established and resolving phases. Understanding this cycle greatly aids optimal biopsy site selection.

Lesions at different sites may be in different phases.

Prolonged rubbing or excoriation of established or resolving lesions may dramatically alter the histopathology, masking the underlying dermatosis which caused the itch. The histopathological changes in a single biopsy may be unexpectedly mild, idiosyncratic or misleading, compared with the overall picture that emerges from multiple samples.

At least two lesions should therefore be biopsied. If lesions appear clinically different from each other, three, four or sometimes more biopsies from different sites in differing phases will be worthwhile.

Occasionally, two or more inflammatory dermatoses coexist. Multiple biopsies provide an opportunity to obtain all, rather than only one, of the correct diagnoses. Multiple biopsies, including the prodromal phase of blistering disorders, may be especially helpful. Secondary changes from blister disruption frequently complicate assessment of fully developed lesions.

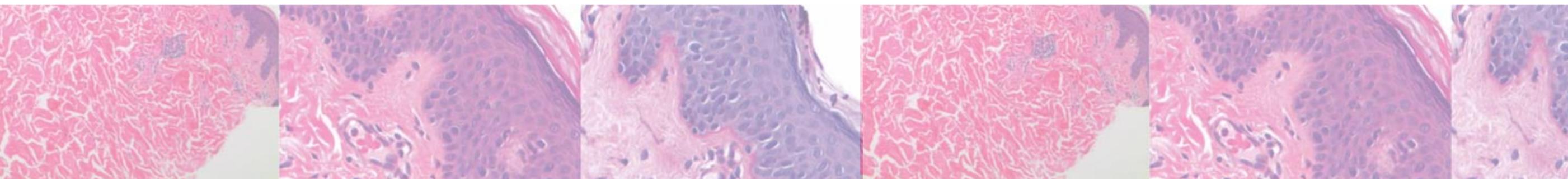
The individual lesions selected for biopsy are also important. A tendency to choose the most dramatic lesion may be misguided, because the drama is commonly due to an underlying incidental lesion, such as seborrhoeic keratosis, insect bite or naevus, or due to secondary injury caused by scratching which masks the underlying dermatosis, rather than a result of the dermatosis itself. If an unusual lesion is selected, at least one other more typical area should also be biopsied.

If a dermatosis involves cosmetically sensitive or tender sites as well as others, biopsying the other sites can be legitimately preferred, provided the other-site lesions appear similar to those on the more sensitive sites. Patients will naturally prefer that choice. Even a suboptimal biopsy is preferable to none if the patient refuses biopsy.

How to biopsy

Options include punch biopsy, shave biopsy, curette, and incisional or excisional surgical biopsy. Generally, for diagnosing inflammatory dermatoses, punch biopsies are preferred.

Punch biopsies are quickly and simply performed. Detailed guides to proper punch biopsy technique



are widely available. Punch biopsies cause minimal trauma. Depending on the site and size, the wound can usually be left open, steri-stripped, or closed with a single suture. The specimen should include epidermis, full-thickness dermis and subcutis. It is vital that the dermatopathologist be able to examine all three layers. Examining only two layers may lead to misdiagnosis. For example, panniculitis cannot be diagnosed from partial superficial punch or superficial shave biopsy. The depth of the dermal inflammation aids the pathological differential diagnosis of many dermatoses. This depth cannot be assessed from superficial samples.

Curettes are generally too superficial or cause too much tissue damage to aid inflammatory dermatosis diagnosis. If a specific dermatosis is being considered where diagnostic changes are confined to the epidermis, but typically patchy — such as in porokeratosis, scabies or tinea — shave biopsy may yield more surface area for examination than punch biopsy. Generally though, this advantage is sufficiently available by collecting two or more punch biopsy samples. Including the suspected diagnosis on the pathology request form allows multiple levels to be cut through the tissue block if diagnostic changes are lacking in initial sections.

Size matters. Clinical considerations, including patient age, cosmetic sensitivity of the proposed biopsy site and more general aspects of the doctor–patient relationship, will influence the choice of punch biopsy size. Punch biopsy tools ranging from 1–8mm are widely available. Generally, a 3mm biopsy is the recommended minimum, though 2mm biopsies may be preferred on sensitive sites. If the choice is between 2mm biopsy or nothing, ensure that two or more biopsies are collected. To properly examine a sufficient number of hair follicles in serial horizontal sections when investigating scalp alopecia, 4mm or larger biopsies are preferred.

The ideal biopsy to investigate bullous disorders is sufficiently large to capture an intact blister, without disruption or loss of the blister roof. A 5mm or larger excisional biopsy may be required to achieve this goal.

Biopsy samples must be handled with care. Crush artefact can ruin an otherwise excellent biopsy. Lymphoproliferative disorders are notoriously susceptible

to crush artefact. Crush artefact may mask the diagnosis altogether, or render the specimen unsuitable for the detailed immunophenotyping needed to accurately subclassify the lymphoma. To avoid crush artefact, insert the punch tool deeply and rotate it sufficiently to largely free the tissue core from deeper tissues before attempting to remove the core. Rather than lifting the core with forceps, insert a needle into the dermis to lever the core upwards and facilitate subsequently freeing the deep edge of the core with a sharp scalpel blade. If using forceps to handle tissue, only press lightly.

Standard tissue fixation in 10% neutral buffered formalin is satisfactory in most cases. However, if the differential diagnosis includes a bullous disorder, vasculitis or connective tissue disease, where immunofluorescence studies for immunoglobulins or coagulation cascade products may be helpful, consider taking one or more further biopsies for submission in normal saline (working hours) or transport medium such as Michel's solution (if processing delay is likely to exceed 24 hours). Immunofluorescence studies cannot be performed once the specimen has been placed in formalin.

Always submit biopsies from separate sites in separately identified specimen containers. Your dermatopathologist can then allow for normal regional variations that may otherwise be considered pathological (for example, pathological orthokeratosis versus normally thick keratin on acral sites). This also allows an unexpectedly discovered neoplasm to be traced back to its correct biopsy site for subsequent excision.

When biopsy will help

Your clinical knowledge of inflammatory skin disease and biopsy power will largely determine your decision to biopsy. Determining in advance every instance when biopsy will help resolve your differential diagnosis is difficult. However, provided you have formulated your clinical differential diagnosis carefully, have a clear idea of what you want your dermatopathologist to tell you, and share that with them, the chances are very high that carefully selected and collected biopsies will at least allow



your dermatopathologist to narrow your differential diagnosis for you, if not definitively resolve it.

Engaging with your dermatopathologist

Clinician and dermatopathologist must fully communicate and disclose their information to one another. One peculiar notion is that dermatopathologists should be 'blinded', so as not to 'bias' their diagnosis. This is uncritically derived from general scientific principles and has no place in the biopsy diagnosis of inflammatory dermatoses. Stereotypical and time-dependent histopathological reactions observable and reportable by dermatopathologists are, in isolation, of little use to clinicians. It is the interpretation of those patterns by an experienced dermatopathologist in a known clinical context that yields accurate diagnosis of disease entities. As an initial step, dermatopathologists will often blind themselves to the clinical history by not looking at it before first viewing the slide. Subsequently, all available information is used to synthesise the diagnosis.

The pathology request form is the first, but should not be the only, means for clinicians to convey the

relevant history. At a minimum, information provided should include:

- the number, size, distribution, and macroscopic appearance of lesions;
- their duration;
- whether they have been remitting and relapsing or persistent, and
- the GP's own clinical differential diagnosis.

The patient's age, associated or intercurrent illnesses, drug history, family history, travel and social history are also extremely important. A sure way of including all relevant data is to consider the request form as a written request from one medical colleague to another, seeking a specialist consultation opinion necessary to effectively manage your patient.

As in all professional relationships, knowing your dermatopathologist personally adds tremendous value. If your regular pathologist is not a specialist dermatopathologist, they should at least have ready access to a dermatopathologist colleague from whom to seek specialist opinion as the need arises for your inflammatory dermatosis biopsies. It is difficult for a generalist to master the nuances of all cutaneous inflammatory histopathology.

Language is inevitably individual and idiosyncratic.

Knowing your dermatopathologist and understanding what they mean by their favoured terminology is more rewarding and reliable than any forlorn wish for language to be strictly objective and universal.

Your dermatopathologist should be easy to contact, via a landline, mobile phone or email address displayed prominently on each report. Nothing is less conducive to clinicopathological discussion than advance fear of frustrated attempts to secure contact via secretarial or telephonist intermediaries, insulated via interminable automated telephone selection menus or on-hold muzak. If you have forgotten to include an important fact with the original request form, please ring. If your dermatopathologist dislikes contact, consider acquiring a different dermatopathologist.

A picture paints a thousand words. One invaluable accompaniment to any dermatopathology request is a clinical photograph or two. Technology now makes it simple to capture a few, high-quality images on a smartphone and transmit them via a secure text message or email, assuming this mode of communication is agreed to by both parties. Patient consent should be obtained. Confidentiality should be maintained by including a unique code word in the transmission, which is separately written on the pathology request form for the pathologist to correlate, rather than any patient-identifying data.

CASE STUDY 1

History: A 29-year-old man presented with a six-week history of a fine, scaly, erythematous and focally hypopigmented rash over his back. **Provisional diagnosis** included eczema or a dermatophyte infection. Two 2mm punch biopsies were taken.

Biopsy diagnosis: Tinea (pityriasis) versicolour. Low power (A) shows only trivial superficial dermal inflammation (↑). At higher power (B), many basophilic fungal spores and pseudohyphae lie intertwined within the stratum corneum (↓). The fungi are strongly positive with the PAS stain (C)(↑). The ‘spaghetti and meatballs’ appearance,

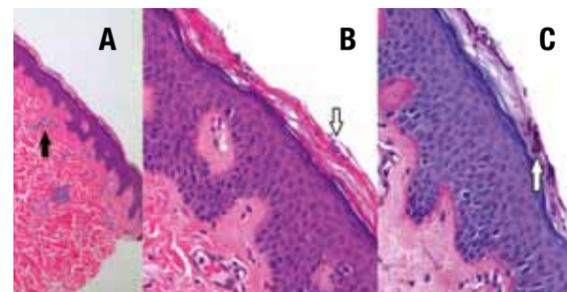
Routinely taking clinical photos also improves the medical record and is invaluable should you later wish to later publish cases together, an activity that in turn builds rapport and the power of the professional relationship. Once the opportunity to take a clinical photograph at first presentation is lost, it may never return.

A strong relationship is one where both clinician and dermatopathologist are confident to express doubt regarding one another’s provisional or initial diagnosis. Healthy scepticism can rescue both sides from error, prompting your dermatopathologist to cut deeper levels or perform other ancillary investigations to discover what the GP is confident should have been evident on the slide.

Finally, knowing when to refer a patient for specialist intervention is essential. If all the recommendations above have been followed and the diagnosis remains uncertain or treatment ineffective, consider specialist referral. Dermatologists will welcome the accompanying biopsy reports, even if the subsequent clinical course warrants repeat biopsies.

Case studies

The following five cases provide examples where biopsy definitively determined the clinical differential diagnosis.

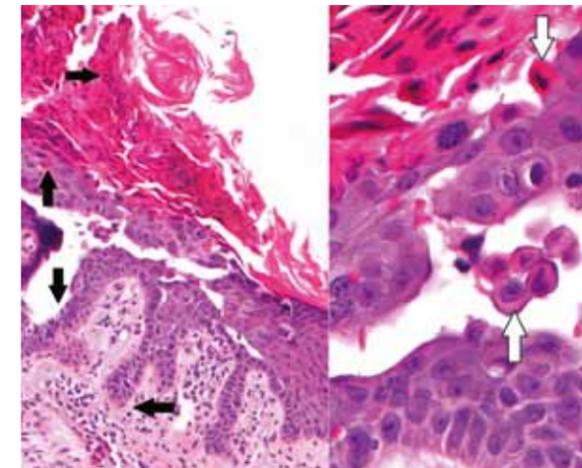


basophilic fungal hue and minimal inflammatory response are characteristic of this *Malassezia globosa* infection in its mycelial phase. This differs from the less conspicuous short eosinophilic hyphae and greater inflammatory reaction of dermatophyte infection. Topical antifungal treatment led to rapid resolution.

CASE STUDY 2

History: A 69-year-old man presented with multiple small, intensely itchy, reddish papules with some scale over his chest, of several months duration. Some had spontaneously resolved. **Provisional diagnosis** included papular eczema or infestation. Two 2mm punch biopsies were taken.

Biopsy diagnosis: Grover’s disease (transient acantholytic dyskeratosis). The biopsy shows epidermal acantholysis (↓), dyskeratosis (↑), elongation and fronding of rete pegs (←), parakeratosis (→), and a mixed inflammatory infiltrate in associated upper dermis including some eosinophils. ‘Corps ronds’ (acantholytic cell balls) (↑↑) and ‘grains’ (large parakeratotic cells) (↓↓) are characteristic. The histopathology resembles the genodermatosis, Darier’s disease and solitary warty dyskeratoma, but

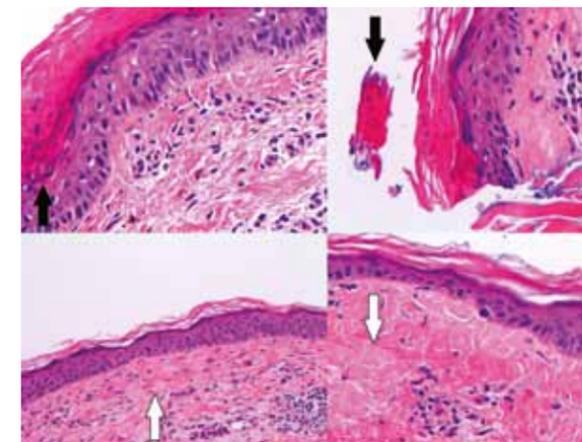


the combination of the clinical history (particularly age, lesion size, multiplicity of lesions, site and spontaneous remission) and histopathology permit specific diagnosis.

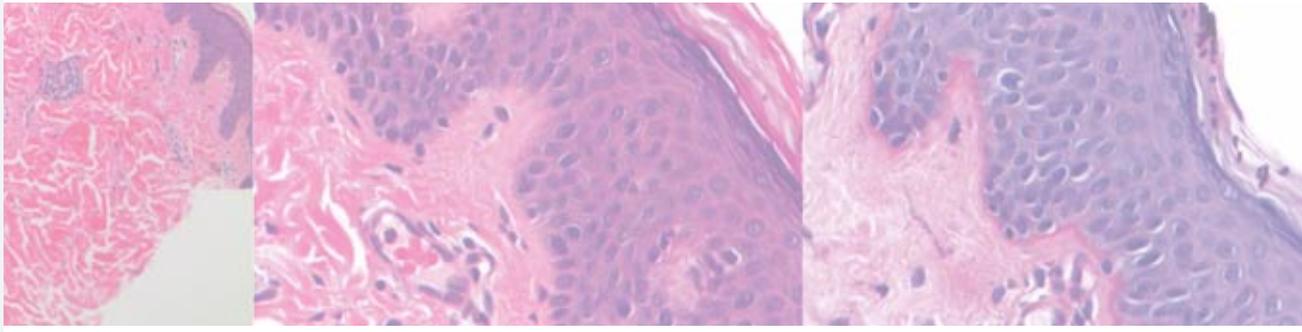
CASE STUDY 3

History: A 73-year-old woman presented with a scaly annular lesion on her upper back. The suggested diagnosis was a BCC. A single 3mm punch biopsy was taken.

Biopsy diagnosis: Porokeratosis. Porokeratosis is a protean genodermatosis with many different clinical presentations. Various clinical forms are not reliably distinguishable on histopathological grounds alone. Clinicopathological correlation is essential. The diagnosis is often unsuspected clinically, and a single biopsy taken. The histological changes are very focal and, unless specifically sought, can be easily missed in a single biopsy. At the annular lesion edge, there is focal loss of the granular layer with single cell dyskeratosis in the spinous layer (↑) and overlying thin vertical column of parakeratin or ‘cornoid lamella’. However, this column may become detached (↓) or flattened. Between these foci, the epidermis shows variable atrophy or hyperkeratosis and lichenoid reaction, with upper dermal angioplasia,



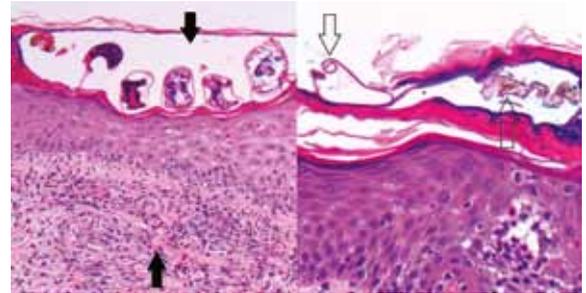
fibrosis and post-inflammatory pigment incontinence (↑↑). These ‘poikilodermatous’ features are not specific, and potentially misleading if the cornoid lamella is missed. Amyloid may be present, as in this case (↓↓). The dermatopathologist’s diagnosis of porokeratosis requires clinical re-evaluation to subclassify the process. Further discussion between clinician and dermatopathologist may be required. Treatment is often difficult.



CASE STUDY 4

History: An 85-year-old nursing home resident with dementia on multiple drugs including oral steroids presented with multiple, intensely pruritic, papules and excoriations on the trunk, upper arms and hands, extending to groin and upper legs. Fellow residents were also itchy. The GP suspected scabies. Three 2mm punch biopsies taken, from chest, wrist and hand.

Biopsy diagnosis: Scabies. Although history alone strongly suggests the diagnosis, two of three biopsies were confirmative. The third biopsy showed excoriation only. The *Sarcoptes scabiei* mite (↓) burrows subcorneally, leaving brown faecal residue (scybala) in its wake. Multiple levels through the tissue block may be required

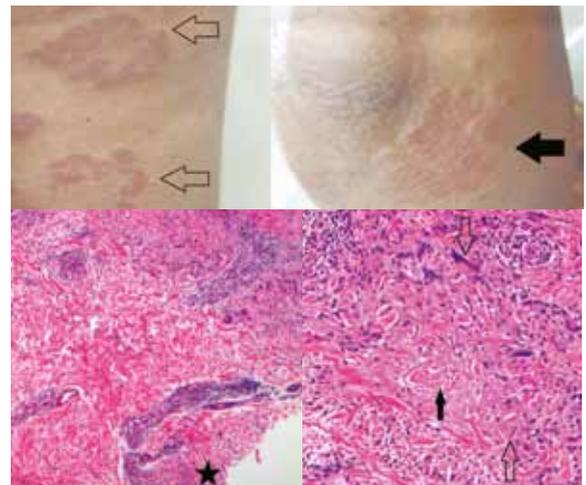


to find the mite body. However, the scybala (↑) and curvilinear pink fragments of eggs or egg casings ('curlicues' or 'pigtales') (↓) may permit definitive diagnosis, even if the mite remains elusive. The associated intraepidermal and dermal inflammation is typically eosinophil-rich (↑) and extends into deeper dermis. Rapid diagnosis allows prompt control of outbreaks in crowded environments.

CASE STUDY 5

History: A 55-year-old woman with a family history of diabetes presented with a 12 month history of an asymptomatic rash, comprising dusky annular and confluent plaques on her chest, thighs (⇐) and arms. The suggested differential diagnosis included necrobiosis lipoidica and sarcoidosis. One 3mm punch biopsy taken from the left elbow (⇐).

Biopsy diagnosis: Granuloma annulare. Granuloma annulare is a usually self-limited dermatosis of unknown cause. It is characterised by 'necrobiotic' (collagenolytic) dermal or subcutaneous papules, often forming grouped annular plaques. Almost any site and age beyond young children may be affected, but the female:male ratio is 2:1. Lesion numbers range from one to multitudes. Known triggers include insect bites, drugs, trauma, sunlight and herpes. More widespread forms such as the present case may be linked to diabetes. Foci of dermal necrobiosis (↑) surrounded by an ill-defined palisade of pale epithelioid histiocytes (↑) and scattered multinucleate giant cells (↓) are typical. Although only one biopsy was taken in this case, it is generously sized and sufficiently deep (★) to confirm the characteristic transdermal involvement.



The epidermis is typically spared, though some cases may perforate. The absence of plasma or foam cells and well-formed epithelioid granulomas, combined with the characteristic necrobiosis, allow necrobiosis lipoidica and sarcoidosis to be confidently excluded.

References available on request

Acknowledgment

Case 5 clinical photographs kindly provided courtesy of Dr Marcia Llewellyn.