



# Biopsy of Skin Rashes and Non-Neoplastic Skin Disorders

## Introduction

Biopsies of inflammatory skin lesions and skin rashes display differing features depending upon the 'age' of the lesion, (some dermatopathologists use the concept of 'lives of lesions' – early, typical established or involuting rashes). For most rashes, the optimal result is obtained by biopsying a typical 'established', representative lesion.

The exceptions include vesiculobullous, ulcerating and pustular lesions. Biopsy of an early lesion in these cases is optimal, prior to secondary degenerative and regenerative changes, scarring or secondary infection. These render recognition of the underlying primary pathologic process either difficult or impossible. Biopsies should be taken from an early blistering lesion and include some apparently normal adjacent skin to allow better analysis of the level of the split. In many, if not all cases, a second biopsy should be taken for immunofluorescence studies.

The diagnostic features of skin rashes may also be modulated by physical factors, (scratching or traumatised lesions), or by therapy, (either topical or systemic). Avoid biopsying traumatised, excoriated areas of skin rashes, preferably selecting areas which the patient could not have reached.

Some skin disorders may be subtle and require comparison with adjacent normal tissue, in which case incisional biopsy including the lesion area and adjacent normal skin is required – these include some connective tissue naevi, anetoderma, atrophoderma and some disorders of pigmentation (e.g. vitiligo). Lesions which are ulcerated, traumatised or old and scarred are unlikely to display specific diagnostic features.

## Summary of Key Points

- Biopsies for inflammatory skin disease should include the subcutaneous fat as relevant histopathologic features may be present in the deep dermis and subcutaneous fat
- Pathologists in assessing biopsies of skin rashes consider the pattern of the inflammation and the tissue reaction pattern
- Request forms must include detailed description of the rash and the clinical differential diagnosis.

For unusual skin rashes, referral to a dermatologist could be considered and in difficult cases, dermatologists may take multiple biopsies of skin rashes. For practitioners in isolated areas teledermatologic consultation is available.

## Tips on Optimising Skin Biopsies

Interpretation of biopsies can be difficult for a number of reasons and wherever possible the factors listed in Table 1 should be avoided and the biopsy site carefully selected.

Punch biopsies should be handled gently and not grasped/ crushed with forceps. Inflammatory cells and some tumour cells are extremely fragile and 'forcep crush artefact' can render specimens undiagnosable. For instance in cases where the differential diagnosis includes a dense dermal reactive infiltrate and lymphoma, crush artefact may preclude final diagnosis.

**Table 1. Potential Pitfalls**

Category	Feature	Comment
Inappropriate site	<ul style="list-style-type: none"> <li>• Biopsy from centre of rash or from longstanding, old lesion</li> <li>• Biopsy includes too much normal skin</li> </ul>	<ul style="list-style-type: none"> <li>• In general, biopsy the advancing edge of the rash, incorporating a little adjacent normal skin. Biopsy clinically typical areas of a disseminated rash</li> <li>• Older lesions may be resolving and not show diagnostic features</li> </ul>
Inappropriate depth	<ul style="list-style-type: none"> <li>• Biopsy does not include deep reticular dermis and subcutaneous fat</li> </ul>	<ul style="list-style-type: none"> <li>• Some skin rashes have deep dermal inflammation</li> <li>• Subcutaneous fat is required to diagnose panniculitis</li> </ul>
Irritated or excoriated rashes	<ul style="list-style-type: none"> <li>• Lichenification</li> <li>• Ulceration</li> <li>• Secondary infection</li> </ul>	<ul style="list-style-type: none"> <li>• Changes secondary to excoriation may completely dominate, rendering accurate diagnosis impossible</li> </ul>
Previous topical therapy	<ul style="list-style-type: none"> <li>• Steroids</li> <li>• Antifungals</li> <li>• Irritants – e.g. Podophyllum</li> <li>• Over the counter and herbal lotions</li> </ul>	<ul style="list-style-type: none"> <li>• Steroids may completely modulate features of a rash, rendering it non diagnosable</li> <li>• Fungi may be absent or difficult to see after antifungal treatment</li> </ul>
Artefacts	<ul style="list-style-type: none"> <li>• Thermal</li> <li>• Crush</li> <li>• Poor fixation</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid cautery or electro-dissection</li> <li>• Avoid biopsy of recently cryotherapied lesions</li> <li>• Biopsies should be handled gently and fixed immediately</li> </ul>



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## Pathologists Approach To Interpretation Of Inflammatory Skin Biopsies

A general understanding of skin pathology and how pathologists approach diagnosis of skin rashes assists in appreciating the necessity for deep and representative biopsies.

In general pathologists assess two patterns:

- The pattern of the inflammation (and inflammatory cell type)
- The reaction pattern to the inflammation

There are four patterns of inflammation and six major reaction patterns which are displayed in Tables 2 and 3.

These two sets of features/patterns are combined to form a variety of complex algorithms for the interpretation of skin rash biopsies. There are seven minor tissue reaction patterns which are rare and these include epidermolytic hyperkeratosis, acantholytic dermatosis, cornoid lamellation, papillomatosis, angiofibromas, eosinophilic cellulitis with flame figures and transepithelial elimination.

**Table 2. Patterns of Inflammation**

• Superficial perivascular inflammation
• Superficial and deep dermal inflammation
• Folliculitis and perifolliculitis
• Panniculitis

**Table 3. Major Tissue Reaction Patterns**

Reaction pattern	Morphologic feature
Lichenoid	Basal cell damage; interface dermatitis
Psoriasiform	Regular epidermal hyperplasia
Spongiotic	Intraepidermal intercellular oedema
Vesiculobullous	Blistering within or beneath the epidermis
Granulomatous	Chronic granulomatous inflammation
Vasculopathic	Pathologic changes in blood vessels

To enable full assessment, biopsies of skin rashes should include the subcutaneous connective tissue. This ensures that the distribution of inflammatory cell infiltrate can be assessed at all anatomical levels.

Inclusion of subcutaneous fat is essential if panniculitis is considered and incisional biopsy is recommended, (since subcutaneous adipose tissue may not be included in punch biopsies). Incisional biopsy enables more accurate assessment of the pattern of the inflammation in the panniculus, (whether the inflammation involves the connective tissue septa within the fat or if the inflammation is predominantly centred within the fat lobules). Rarely, for deep seated inflammatory skin disorders,

deep biopsy incorporating the fascia may be required e.g. to diagnose eosinophilic fasciitis and morphea profunda.

Pathologists, when using their preferred algorithmic approach, end up with a histopathologic differential diagnosis. On the basis of the histopathologic features alone it is not always possible to advance the diagnosis beyond a histopathologic differential diagnosis, stating which diagnosis is preferred. Final diagnosis is often only made with clinico-pathologic correlation, taking into consideration the clinical information and the clinical differential diagnosis. For example a not uncommon scenario is skin rashes with a superficial perivascular infiltrate without spongiosis or other reaction pattern, listed in Table 4.

**Table 4. Superficial Perivascular Dermatitis**

Causes of Superficial Perivascular Dermatitis	
• Drug reactions	• Dermatophytosis
• Viral exanthems	• Chronic urticaria
• Erythrasma	• Superficial annular erythemas
• Resolving dermatoses	• Pigmented dermatoses (Schamberg's and related dermatoses)

A number of skin rashes are spongiotic and Figures 1 and 2 display features of superficial perivascular spongiotic dermatitis with early psoriasiform squamous hyperplasia.

The inflammatory pattern comprises a superficial perivascular infiltrate including lymphocytes, histiocytes and occasional eosinophils. The tissue reaction pattern includes spongiosis and early psoriasiform squamous hyperplasia. A number of skin rashes can display these features, including sub acute allergic contact dermatitis, sub acute nummular dermatitis (discoid eczema), some drug reactions and dermatophytoses.

In addition to the pattern of inflammation and major tissue reaction patterns there are a host of “diagnostic clues”, subtle features employed by dermatopathologists to assist with

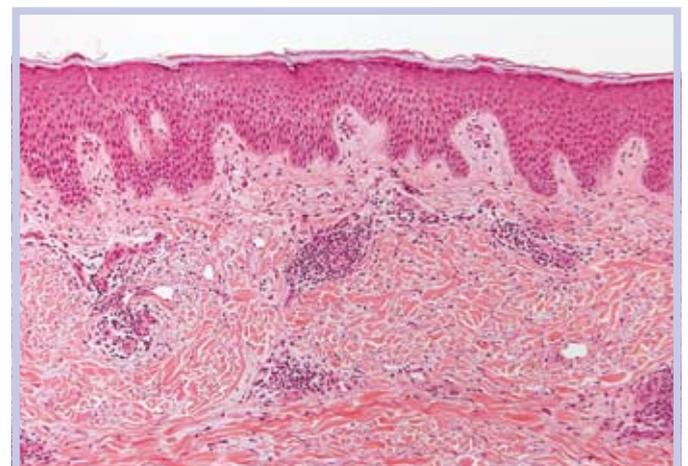


Figure 1. Superficial perivascular spongiotic psoriasiform dermatitis (x10)



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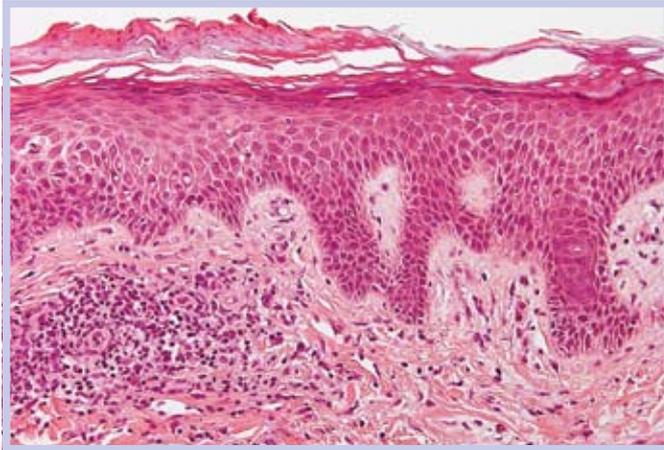


Figure 2. Superficial perivascular spongiotic psoriasiform dermatitis (x20)

fine tuning the differential diagnosis. For instance, relatively common findings in chronic skin rashes with persistent irritation include, compact orthokeratosis, psoriasiform squamous hyperplasia, enlarged follicular infundibular and vertical streaking of collagen in the papillary dermis plus stellate fibroblasts and dendrocytes within the superficial dermis.

## 'Special' Biopsies

### Cutaneous Infections

The sample should be submitted fresh and transported to the laboratory directly for appropriate culture (bacteria, mycobacteria or fungal). For such cases it is suggested that you consult one of our anatomical pathologists prior to biopsying the lesion.

### Direct Immunofluorescence

In addition to routine microscopy, in autoimmune blistering diseases and other autoimmune and inflammatory disorders, direct immunofluorescence can be performed to demonstrate the site of the immunopathology. Transport medium can be obtained from the laboratory on request, (allow sufficient time for delivery of the transport medium), and it is advisable to contact one of our anatomical pathologists prior to taking the biopsy. Alternatively the patient could be referred to a dermatologist or a hospital which deals with these less common skin lesions.

### Alopecia

This is a specialised area and different laboratories have their own biopsy preferences. Many laboratories prefer two specimens; one for traditional sectioning (vertical) and the second for horizontal sectioning (sections taken parallel to the epidermal surface). The punch biopsies should be at least 4mm in diameter to enable hair counts. The punch biopsy should be inserted parallel to the direction of hair growth, and must include the subcutaneous tissue to ensure that the hair bulbs of terminal follicles are included in the sample. In cases of suspected scarring alopecia biopsy, of an erythematous area with residual visible hair shafts should be performed. If the biopsy is taken from an area of complete scarring and total hair loss only non-diagnostic end-stage features will be demonstrated.

A note of caution; be prepared as the scalp is vascular and there may be considerable blood loss.

*References available on request.*

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