

Chapter 12

Infections

Keywords Viral infection • Fungal infection • Dermatophyte • Scabies

This chapter discusses a collection of infectious entities that are relatively commonly encountered in dermatopathology specimens. This is an admittedly abbreviated listing of the various cutaneous infections encountered in the skin. It is meant to reflect common or uniquely important entities rather than an encyclopedic text on the subject. For example, certain esoteric infections (e.g., *Strongyloides*) will not be covered because it is beyond the spirit of this text. Some common entities, such as impetigo, will not be discussed because it is so rarely biopsied. As a rule, many of the entities do not neatly fall into a reaction pattern; therefore, they will be described according to the general class of infection. One exception is tinea versicolor, which will be described in Chap. 13.

Viral Infections

Molluscum contagiosum

Clinical Features

Molluscum contagiosum presents as solitary or multiple centrally umbilicated papules. It is most common in children and adolescents, but may present at any age. Lesions are most common on the head and neck, followed by genitalia, the latter is often the result of sexual transmission. Fomite transmission is the major route of infection, accounting for the frequency in young children. Immunosuppressed patients can have widespread lesions.

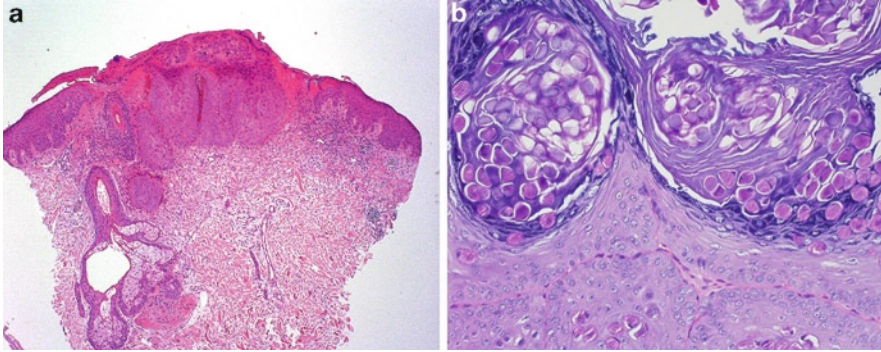


Fig. 12.1 *Molluscum contagiosum*. (a) In *Molluscum contagiosum* there is an endophytic proliferation of epidermis. (b) The infected keratinocytes have large intracytoplasmic eosinophilic viral inclusions

Microscopic Features

The lesions are characterized by an inverted proliferation of squamous epithelium that opens to the epidermal surface in the central portion. Within the cytoplasm of the keratinocytes, there are intracytoplasmic eosinophilic viral inclusions (Fig. 12.1) (Table 12.1). Occasionally, there can be rupture of the invaginated epithelium leading to a brisk inflammatory response mimicking a ruptured folliculitis. In such cases, deeper levels may reveal the characteristic viral inclusions.

Table 12.1 Key microscopic features: *Molluscum contagiosum*

- Endophytic proliferation of epidermis
- Intracytoplasmic eosinophilic viral inclusions

Differential Diagnosis

For typical cases, there is essentially nothing else in the differential diagnosis due to the distinctive appearance of *Molluscum contagiosum*. As noted above, some cases can be confused with a folliculitis (Table 12.2).

Table 12.2 Practical tips: *Molluscum contagiosum*

- If clinically suspected and not seen, get deeper levels on the block
- Can mimic folliculitis in cases where there is rupture; deeper levels usually reveal keratinocytes with viral inclusions

Herpesvirus Infections

Clinical Features

Herpesvirus infections are usually encountered in three settings: oral lesions of Herpes simplex 1 (HSV-1), genital lesions of Herpes simplex 2 (HSV-2), or reactivation of Varicella zoster in the form of herpes zoster (shingles). HSV-1 infection usually

initially presents in childhood and as vesicular crusted lesions around the mouth. Patients can have episodes of reactivation throughout life. HSV-2 is typically acquired in adult life and is generally the result of sexual transmission. Lesions are similar to HSV-1 but are most common on genital or perianal skin. For herpes zoster, there is a linear, painful vesicular eruption that follows a dermatomal distribution. It is more frequent in older adults but may be seen in a wide age range.

Microscopic Features

Essentially, all of these entities have the same histological features. Distinction between subtypes requires culture or other techniques (e.g., direct fluorescent antibody tests). Classically, there is an intraepidermal vesicle with acantholysis and degenerating keratinocytes. The diagnostic feature is the presence of keratinocytes with intranuclear viral inclusions (Fig. 12.2). The intranuclear inclusions have an eosinophilic to steel gray appearance with peripheral margination of the chromatin. Frequently, the affected keratinocytes fuse, resulting in multi-nucleation (Table 12.3). In older lesions, the epidermis may be necrotic and it is vital to look for evidence of viral inclusions in the necrotic epidermis. Follicles should also be examined, as it is sometimes possible to identify virally infected cells that are not recognizable in the necrotic epidermis, or because the epidermal surface is ulcerated. Finally, in some resolving lesions, no viral inclusions are evident and the histological features are a nonspecific granulomatous dermatitis (Fig. 12.3).

Differential Diagnosis

The diagnosis is generally quite straight forward. For more subtle cases, entities such as pemphigus or even acute spongiotic dermatitis can be considered. Neither of these has intranuclear viral inclusions. Once the epidermis is completely ulcerated,

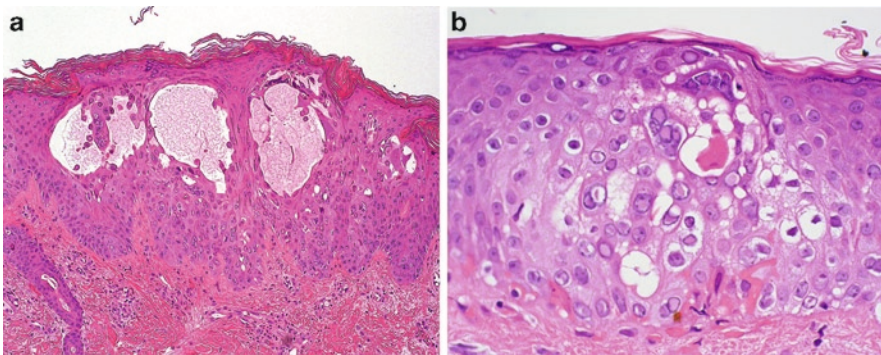


Fig. 12.2 *Herpesvirus*. (a) Intraepidermal vesicles with acantholysis are the classic lesion of herpesvirus infection. (b) The virally infected cells have intranuclear steel gray inclusions with peripheral condensation of the native chromatin. Multinucleation is common

Fig. 12.3 *Post-Zoster granulomatous inflammation.* In some case, after the viral infection has histologically resolved, there is a granulomatous inflammatory infiltrate. This is nonspecific, but suggestive in a clinical setting where zoster is suspected clinically. (Courtesy of Dr. Soon Bahrami)

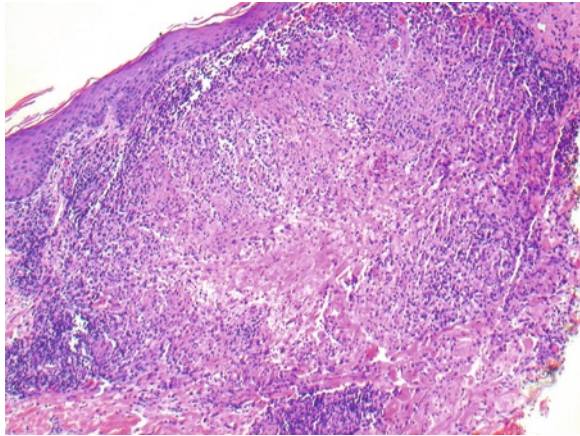


Table 12.3 Key microscopic features: herpesvirus infections

-
- Intraepidermal vesicle with ballooning degeneration, acantholysis
 - Multinucleated keratinocytes
 - Intranuclear viral inclusions with steel gray color and peripheral condensation of chromatin
 - Follicular involvement common
-

it may be more difficult to recognize the presence of the virus. If there is still some necrotic epidermis present, it may be possible to recognize the remnants of viral nuclear inclusions. Failing that, close examination of follicles will often reveal presence of the virus (Table 12.4).

Table 12.4 Practical tips: herpesvirus infections

-
- Look for evidence of viral infection in necrotic keratinocytes
 - Examine follicles when epidermis is ulcerated
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Human Papillomavirus Infections

The most common entities encountered in dermatopathology caused by human papilloma virus (HPV) include verruca vulgaris, verruca plantaris, verruca plana, and condyloma acuminatum.

Clinical Features

Verruca vulgaris, caused by HPV-1, 2, 3, and 4, is the most common HPV related lesion in dermatopathology. They present as papules or plaques with a rough,

hyperkeratotic surface. They are most commonly encountered on the fingers and hands but may be encountered in a variety of locations. Verruca plantaris (and palmaris) is caused by HPV-2 and presents most frequently on the sole of the foot and less commonly on the palm. They are solitary or multiple hyperkeratotic but less elevated lesions. Verruca plana, caused by HPV-3, presents as small skin-colored to brown minimally elevated papules. They are usually multiple and present on the face or extremities. Condyloma acuminatum, caused by HPV-6, 8, 11, 16, and 18, most commonly, are dome-shaped papules presenting on the genitalia, perianal skin or groin.

Microscopic Features

Verruca vulgaris has papillomatosis, hyperkeratosis, and variable parakeratosis. The peripheral edges of the lesion claw toward the center in a buttressed fashion (Fig. 12.4). The koilocytes are most easily seen in the granular layer. They are

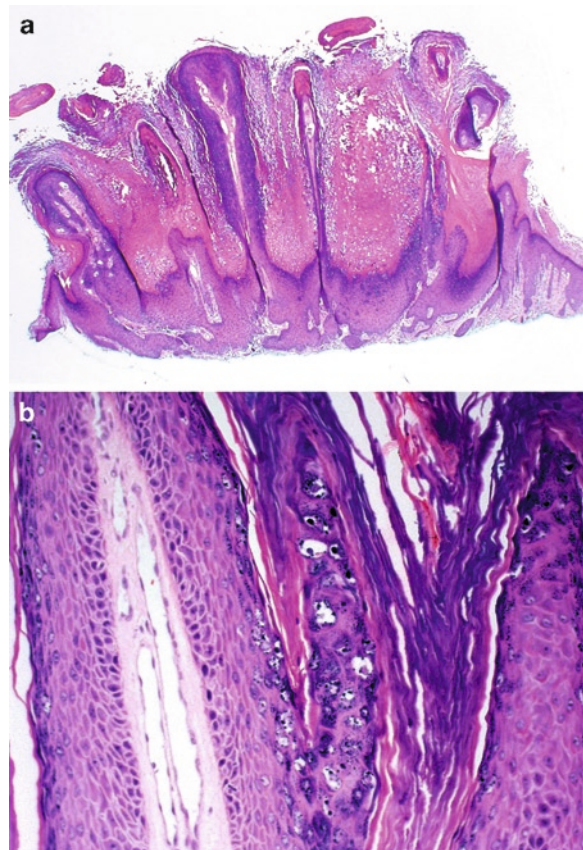


Fig. 12.4 *Verruca vulgaris*. (a) There is a papillomatous surface and the peripheral edges of the lesion claw in toward the center resembling a buttress. (b) The papillary dermal blood vessels are dilated. The koilocytes have irregular nuclei and coarse keratohyaline granules

characterized by vacuolated keratinocytes with coarse keratohyaline granules. The papillary dermal blood vessels in the tips of the papillations are dilated, and there is often hemorrhage in the overlying stratum corneum (Table 12.5).

Verruca plantaris has a thick hyperkeratotic surface. A papillomatous architecture may be less apparent, and the lesion is frequently partly endophytic (Fig. 12.5). Koilocytes are present and may be quite prominent.

Table 12.5 Key microscopic features: human papilloma virus (HPV) infections

-
- Verruca vulgaris
 - Papillomatous surface
 - Hemorrhage in stratum corneum overlying tips of the papillations
 - Dilated blood vessels in tips of papillations
 - Buttressed edges
 - Koilocytes with coarse keratohyaline granules
 - Verruca plantaris
 - Endophytic growth
 - Buttressed edges
 - Koilocytes
 - Verruca plana
 - Less prominent papillomatosis
 - Lacks buttressed edges
 - Koilocytes
 - Condyloma acuminatum
 - Polypoid silhouette
 - Subtle koilocytes
-

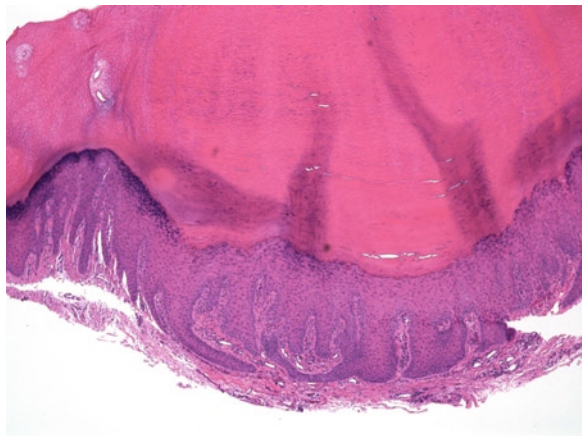


Fig. 12.5 *Verruca plantaris*. Verruca on the sole have an endophytic growth pattern, but otherwise features typical of a verruca

Verruca plana is acanthotic, but lacks pronounced papillomatosis and the buttressed edges (Fig. 12.6). The granular layer is thickened and koilocytes are present, but they may be less prominent than verruca vulgaris or plantaris.

Condyloma acuminatum usually has a polypoid, dome-shaped silhouette, lacking the papillomatous surface (Fig. 12.7). Koilocytes are frequently and maddeningly subtle. In such cases, it may be necessary to pursue extra testing to confirm the presence of HPV. In our experience, chromogenic in situ hybridization is superior to routine immunohistochemical stains.

Fig. 12.6 *Verruca plana*. Flat warts have less pronounced papillomatosis and do not have the prominent peripheral buttressing

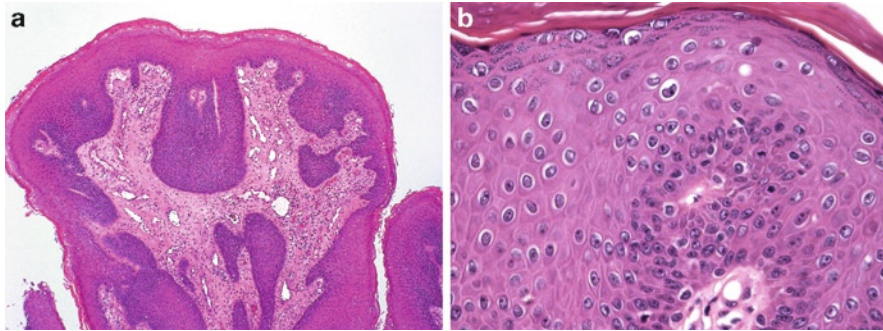
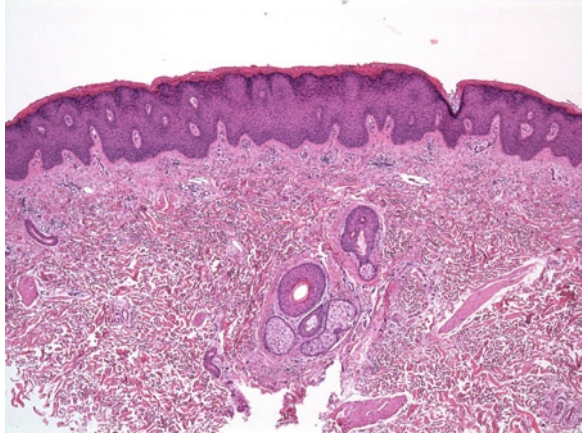


Fig. 12.7 *Condyloma acuminatum*. (a) Condyloma acuminatum frequently has a polypoid growth pattern. (b) Koilocytotic change is often subtle

Differential Diagnosis

For verruca vulgaris, the differential diagnosis is usually not difficult. In irritated or inflamed lesions, koilocytes may not be as evident. This situation can cause

confusion with an irritated seborrheic keratosis, or possibly a squamous cell carcinoma. The papillomatous surface with hemorrhage in the stratum corneum, dilated papillary dermal blood vessels and buttressed edges are keys to the diagnosis. It should be pointed out that the overlap between some cases of verruca vulgaris and irritated seborrheic keratosis can be so significant that it is not always possible to unequivocally distinguish them. Some use the term “verrucal keratosis” in this situation. Some reactive atypia is allowed in irritated or inflamed verruca vulgaris, but prominent pleomorphism or a desmoplastic stroma are clues to the diagnosis of squamous cell carcinoma. It should be remembered that malignancy can arise in cutaneous warts, especially in older patients or organ transplant patients.

Verruca plantaris is not a difficult diagnosis provided there is an adequate specimen. Too often, only the hyperkeratotic surface is biopsied with little or no underlying dermis. In such a situation, it is important to look for evidence of a papillomatous architecture that can be revealed by the pattern of hyperkeratosis and for evidence of hemorrhage in the stratum corneum that can lead the pathologist to suggest the possibility of a verruca (Fig. 12.8). Verruca plana frequently comes submitted with a clinical diagnosis of entities such as actinic keratosis, squamous cell carcinoma, basal cell carcinoma, etc. Recognizing the thickened granular layer with koilocytes is crucial to the diagnosis. Verruca plana does not show significant atypia.

Condyloma acuminatum can be a frustrating diagnosis. It closely resembles seborrheic keratosis. In fact, a clue to the diagnosis is that it resembles a dome-shaped seborrheic keratosis on genital skin. Careful examination usually reveals some koilocytes, though they are not as numerous as in other warts. In cases where there is any doubt, special studies such as chromogenic in situ hybridization should be pursued, as this diagnosis carries important implications. I have heard stories, perhaps apocryphal, about pathologists being successfully sued for over diagnosis of this entity (See sample report for dealing with ambiguous cases) (see Table 12.6).

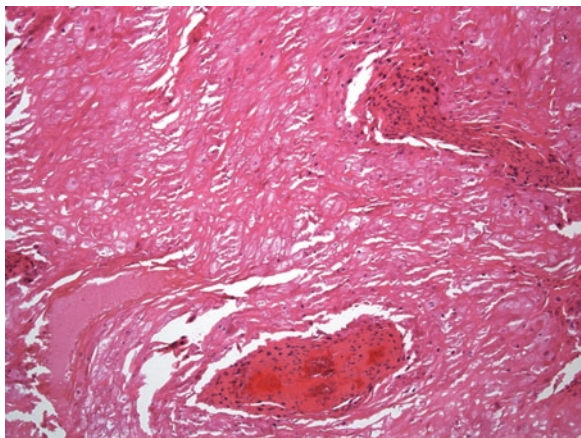


Fig. 12.8 *Superficially sampled verruca plantaris.* Frequently, only the keratotic surface of a verruca plantaris is sampled. The keratotic surface shows remnants of the dermal papillae with parakeratosis and hemorrhage

Table 12.6 Practical tips: HPV infections

-
- Verruca vulgaris
 - Koilocytes in irritated/inflamed warts not always apparent
 - Buttressed edges often a key feature
 - Hemorrhage in stratum corneum and underlying dilated vessels a clue
 - Do not over interpret thickened granular layer as koilocytes in conditions like prurigo nodularis
 - Verruca plantaris
 - Biopsies often superficial due to endophytic growth
 - Multiple levels may be needed
 - May see evidence of papillomatous pattern in stratum corneum
 - Verruca plana
 - Frequently not suspected clinically
 - Look for koilocytes when histologic features do not match clinical diagnosis, especially in lesions from face
 - Condyloma acuminatum
 - Looks like a seborrheic keratosis on low power
 - Koilocytes often subtle
 - Review medical record for evidence of HPV infections (e.g., previous diagnosis of condyloma acuminatum or positive Pap tests)
 - Consider special testing if histology is subtle and the patient has no prior history
-

Fungal Infections

The most common fungal infections encountered are dermatophyte infection, tinea versicolor, and candidiasis. Other important fungal infections to be aware of include blastomycosis, cryptococcosis, sporotrichosis, zygomycosis and aspergillosis. Tinea versicolor is discussed in Chap. 13.

Dermatophyte Infection (Dermatophytosis or Tinea)

Clinical Features

Superficial fungal infections caused by a dermatophyte (species of fungi belonging to the genera *Trichophyton*, *Microsporum*, or *Epidermophyton*) are referred to as “tinea.” These infections are relatively common, and can involve scalp hair and skin of the scalp (tinea capitis), general body surfaces (tinea corporis), feet (tinea pedis) and nail plate (tinea unguium/onychomycosis). Clinical presentation depends on the body site. Features of tinea capitis include localized alopecia, scaling, follicular papules and pustules. Tinea corporis presents as annular, growing crusted areas with central clearing (“ringworm”). Dermatophyte infections of the feet, one of the most common forms of dermatophyte encountered, can present as macerated areas or as vesiculobullous lesions. Onychomycosis, or

tinea unguium, usually presents in older patients and is characterized by yellowish nail discoloration, thickening and separation of the nail plate by the nail bed (onycholysis) and crumbly nails.

Microscopic Features

The quintessential feature of dermatophyte infection is the presence of neutrophils in the stratum corneum (Fig. 12.9). The epidermis shows varying amounts of hyperkeratosis, parakeratosis, spongiosis and acanthosis. In some cases, psoriasiform hyperplasia may be prominent (Fig. 12.10). Within the dermis, there is usually a perivascular mixed inflammatory infiltrate of lymphocytes and eosinophils. The fungal hyphae are often difficult to see on routine H&E stained sections. It is often necessary to perform special stains such as PAS or GMS stains (Fig. 12.11). The

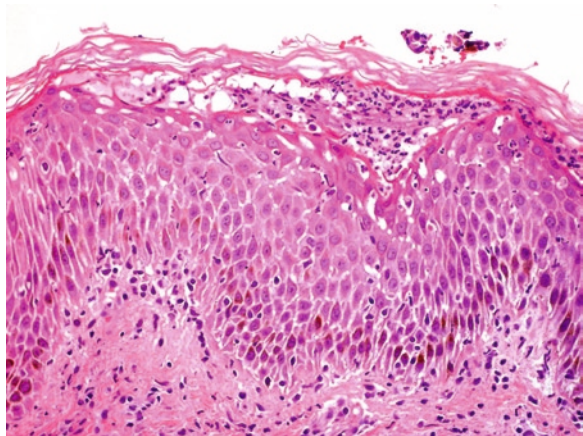


Fig. 12.9 *Dermatophyte infection.* The classic histologic feature of dermatophyte infection seen on routine microscopy is the presence of collections of neutrophils in the stratum corneum

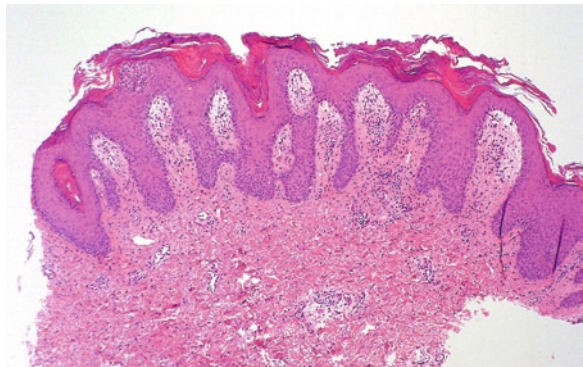


Fig. 12.10 *Dermatophyte infection.* The epidermis may have prominent psoriasiform hyperplasia

hyphae may not be visible in the most heavily inflamed areas of the stratum corneum. Examination of adjacent areas of the stratum corneum usually has a higher yield. Cases may also exhibit the so-called “sandwich sign” in which there is normal stratum corneum overlying an area of parakeratosis/compact hyperkeratosis. The organisms are sandwiched between the normal stratum corneum and altered cornified layer (Fig. 12.12). In tinea capitis, there is frequent involvement of the hair shafts within the follicles (Fig. 12.13); the organism may not be seen in the overlying stratum corneum. The hair shaft may be invaded (endothrix) or surrounded (ectothrix) by the organism, though differentiating between the patterns is not critical. There is an associated acute folliculitis with neutrophils in the follicular epithelium. In tinea capitis, the dermal infiltrate is often more brisk and extends to the mid

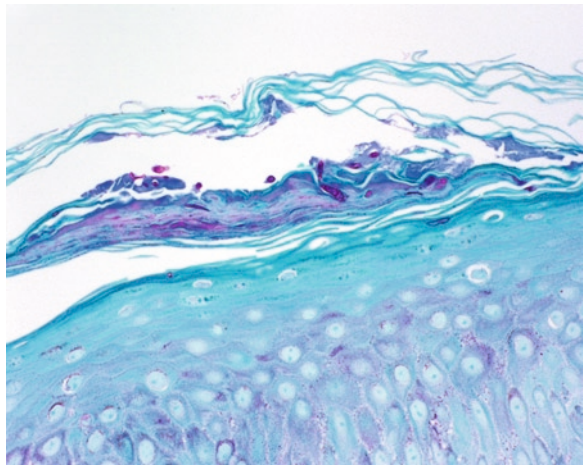


Fig. 12.11 *Dermatophyte infection.* Fungal hyphae in the stratum corneum are highlighted by a PAS stain. The use of a light green counterstain makes visualization of the organisms easier

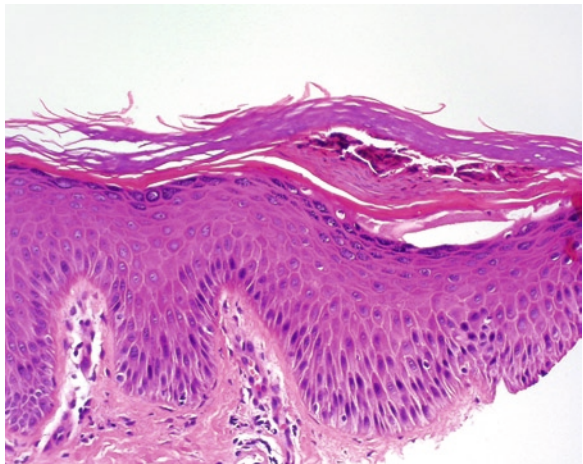


Fig. 12.12 *Dermatophyte sandwich sign.* This is a biopsy from a foot that shows normal stratum corneum overlying a focus of parakeratosis/hyperkeratosis. This pattern, referred to as the sandwich sign is a clue to a possible dermatophyte infection

to deep dermis. Biopsies for the diagnosis of onychomycosis are typically submitted as nail clippings. Therefore, the biopsy only consists of compact nail keratin. Fungal hyphae are usually not evident on routine examination, but require either a PAS or GMS stain (Fig. 12.14). See Table 12.7.

Fig. 12.13 *Tinea capitis*. Numerous fungal organisms are present in the follicle

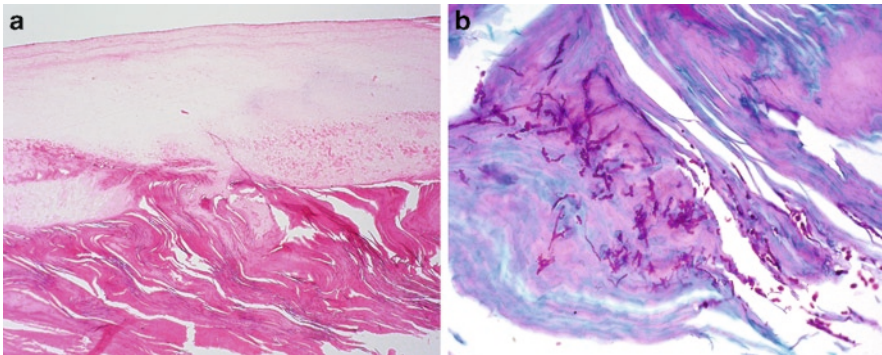
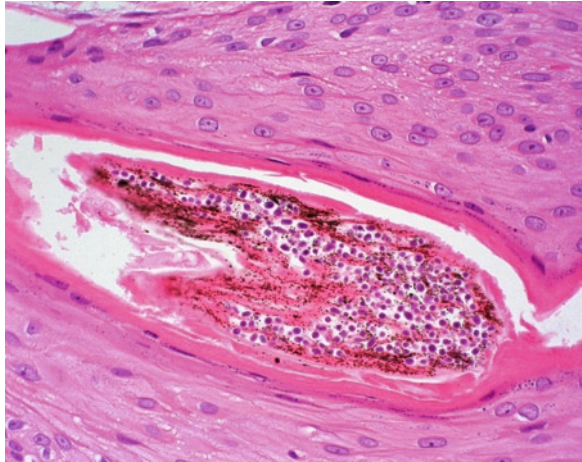


Fig. 12.14 *Onychomycosis*. (a) The hyphae are usually not apparent with routine H&E stains. (b) A PAS stain demonstrates the hyphae in the nail keratin

Table 12.7 Key microscopic features: dermatophyte infection

-
- Neutrophils in stratum corneum
 - Acanthosis, sometimes psoriasiform
 - Superficial perivascular infiltrate usually contains eosinophils
-

Differential Diagnosis

The differential diagnosis of most dermatophyte infections includes spongiotic dermatitis and psoriasis (Chaps. 2 and 3). Requisite for distinction is recognition of the fungus. If neutrophils are present in the stratum corneum of spongiotic dermatitis, it is prudent to consider fungal stains. Similarly, in a biopsy resembling psoriasis, a fungal stain should be considered, especially if the dermal infiltrate contains eosinophils. In many cases, patients may have been treated with topical steroids prior to biopsy. In this situation, some of the typical features, especially epidermal neutrophils, may be absent (Fig. 12.15). It is always important to consider the possibility of dermatophyte infection even when not considered clinically in at least two distinct situations: (1) a rash that has had a poor response to topical steroids and (2) a clinically annular lesion that does not fit another diagnosis (e.g., granuloma annulare, lupus erythematosus). It should be remembered that other annular rashes do occur such as erythema annulare centrifugum.

Candidiasis can be considered in the differential diagnosis. Candidiasis usually presents in intertriginous areas. There are yeast cells as well as pseudohyphae. See below for more details.

In tinea capitis, *Pityrosporum* folliculitis could be considered. Normally, this fungus exists as a normal commensal organism. Occasionally, it will cause a true folliculitis. It can look similar, but there are typically abundant yeast forms in the affected follicle. The yeasts are less intimately associated with the hair shaft. Bacterial folliculitis or other forms of acute folliculitis are in the differential diagnosis as well.

The differential diagnosis of onychomycosis includes other causes of dystrophic nails. If there are collections of neutrophils in the nail keratin and no evidence of fungi, the possibility of psoriasis should be considered. Lichen planus is another cause of dystrophic nail. Often it is not possible to make an unequivocal diagnosis

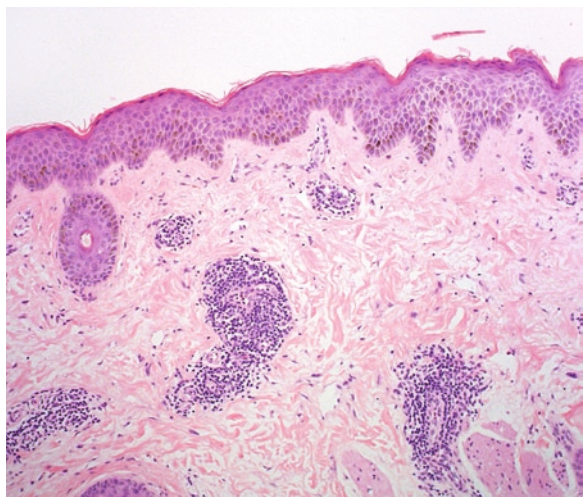


Fig. 12.15 *Dermatophyte infection treated with topical steroids.* Dermatophyte infections treated with topical steroids often lack classic histologic features. Important clues to the diagnosis is history of poor response to steroids or the clinical description of an annular lesion

in the absence of identification of fungal hyphae. The most important role for the pathologist in this setting is to document the absence of fungal hyphae, not to establish a different cause of nail dystrophy. It should be noted that yeast and bacteria are frequently seen in association with nail keratin. Typically, these are commensal organisms, not pathogens, but their presence should be mentioned on the report. Practical tips are summarized in Table 12.8.

Table 12.8 Practical tips: dermatophyte infection

-
- It is important to keep a high index of suspicion for dermatophytosis
 - If neutrophils are in the stratum corneum, consider special stains for fungi
 - If lesion is clinically annular, consider special stains for fungi
 - Always suspect dermatophyte infection when there is a history of a poor response to topical steroids even in the absence of characteristic histologic features
-

Candidiasis

Clinical Features

Candidiasis typically presents as papules and pustules in intertriginous areas and along skin folds. Lesions frequently become confluent and there is often associated erosion.

Microscopic Features

The epidermis has overlying parakeratotic scale that contains the small budding yeast and pseudohyphae (Fig. 12.16). Pseudohyphae are often more numerous than yeast forms. The organisms are usually more apparent on routine sections than dermatophytes, and have a light purple color on H&E stained sections. The epidermis is spongiotic, often with subcorneal pustules (Fig. 12.16). The organism may not be as evident within the pustules. Within the dermis, there is a superficial perivascular mixed infiltrate that usually has eosinophils (Table 12.9). GMS or PAS stains are still useful for highlighting the organisms and may make recognition of yeast forms easier.

Differential Diagnosis

The differential diagnosis includes dermatophyte infection, inverse psoriasis, contact dermatitis, acute generalized exanthematous pustulosis (AGEP), and scabies. Dermatophyte infection usually has a different clinical distribution. Dermatophyte organisms do not have the same light purple color on H&E stained sections and lack yeast. Of course, if you can't distinguish between the two, there is no harm done as both are treated with antifungals.

Fig. 12.16 *Candidiasis*. (a) The yeast and pseudohyphae in the stratum corneum have a light purple color on H&E stained sections. (b) Frequently the epidermis has neutrophilic pustules

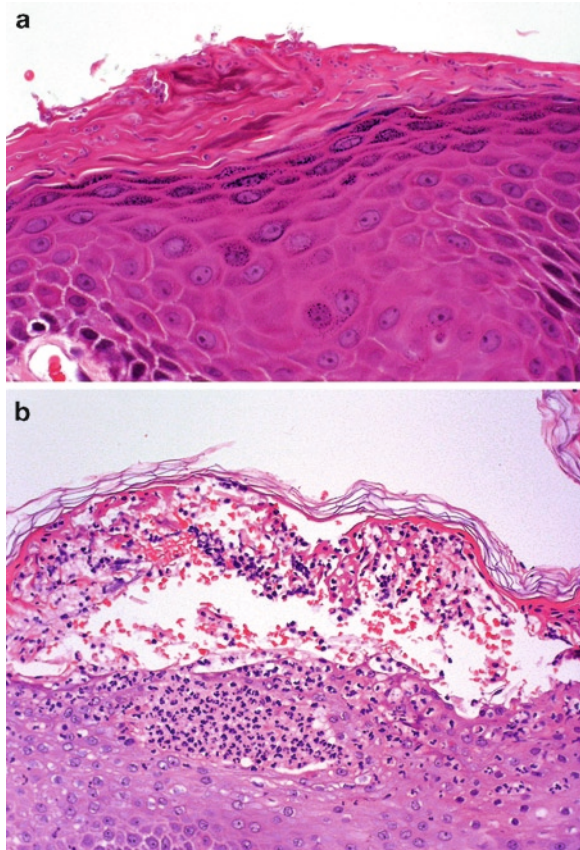


Table 12.9 Key microscopic features: candidiasis

- Neutrophilic pustules
- Spongiosis
- Yeast and pseudohyphae in stratum corneum/
superficial epidermis
- Mixed dermal infiltrate with eosinophils

Inverse psoriasis is a form of psoriasis that present in intertriginous zones and may resemble candidiasis. It lacks yeast or pseudohyphae and does not have eosinophils in the dermal infiltrate.

Contact dermatitis, a form of eczematous dermatitis discussed in Chap. 2, frequently presents in the axillae like candidiasis. In this location, it is usually a reaction to substances

in deodorant. It resembles other forms of spongiotic dermatitis. It lacks fungal organisms and may have Langerhans cell microabscesses in the epidermis.

AGEP is a widespread pustular drug eruption. The histological features may resemble candidiasis, but the distribution is different and again, there are no fungal organisms.

Scabies infestation can clinically present in intertriginous zones, especially the groin. It will be discussed in more detail below. Recognition of the mite and absence of fungal organisms allows for distinction. See Table 12.10.

Table 12.10 Practical tips: candidiasis

-
- Pseudohyphae may greatly outnumber yeast forms
 - Light purple color of organisms on H&E stain is a clue
 - Occurs in skin folds (e.g., groin, axilla)
-

Blastomycosis

Clinical Features

Cutaneous blastomycosis, caused by *Blastomyces dermatitidis*, is usually the result of disseminated systemic infection, but may rarely be the result of direct inoculation of the skin. The cutaneous lesions present as violaceous verrucal plaques. Frequently, a neoplasm such as squamous cell carcinoma is suspected.

Microscopic Features

There is prominent pseudoepitheliomatous hyperplasia of the epidermis in association with a brisk neutrophilic infiltrate (Fig. 12.17). Scattered multinucleated giant cells are present in the dermis. Within the infiltrate and within the multinucleated cells, there are large budding yeasts between 8 and 15 μm in size. The yeasts have thick refractile walls on H&E stained sections (Fig. 12.17). Budding forms have a characteristic broad base. They may be rare, and special stains (PAS, GMS) may help unveil their presence (Table 12.11).

Differential Diagnosis

The most important differential diagnosis is squamous cell carcinoma. The pseudoepitheliomatous proliferation can bear a striking resemblance to malignancy. Given that a neoplasm is often suspected clinically, it is no surprise that cases are misdiagnosed. I have personally reviewed cases of “recurrent squamous cell carcinoma” that were in fact blastomycosis. Obviously, recognition of the organism is the key to diagnosis. Whenever a squamous proliferation is seen in conjunction

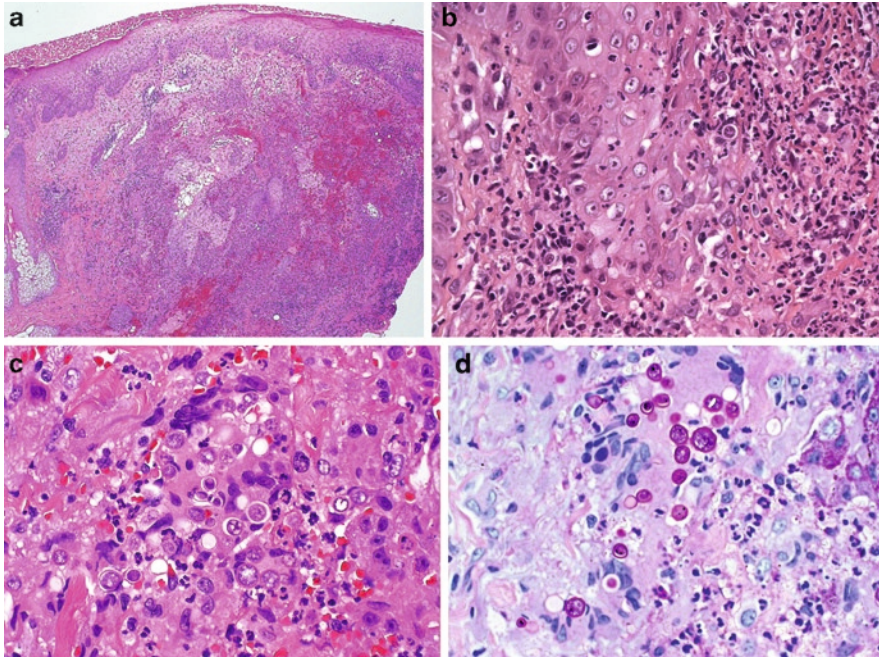


Fig. 12.17 *Blastomycosis*. (a) Pseudoepitheliomatous hyperplasia of the epidermis is common in blastomycosis. (b) In this higher power picture the pseudoepitheliomatous hyperplasia with reactive squamous atypia in association with blastomycosis is appreciated. (c) The yeast of blastomycosis have thick refractile walls. (d) Broad-based budding is characteristic

Table 12.11 Key microscopic features: blastomycosis

- Pseudoepitheliomatous epidermal hyperplasia
- Neutrophil rich infiltrate
- Scattered multinucleated histiocytes
- Large yeast (8–15 μm) with broad-based buds

with a brisk dermal neutrophilic infiltrate, the possibility of blastomycosis should be considered.

The other entity in the differential diagnosis is coccidioidomycosis, caused by *Coccidioides immitis*. Like blastomycosis, it is associated with pseudoepitheliomatous epidermal hyperplasia and a suppurative infiltrate. The organism in the cutaneous lesions is a large thick-walled spherule with numerous endospores. The spherule is much larger than the yeast of blastomycosis (20–80 μm). This disease is endemic in the Southwestern United States and rare to see in patients outside this geographic area. See Table 12.12.

Table 12.12 Practical tips: blastomycosis

- If the biopsy looks like squamous cell carcinoma but there are numerous neutrophils, consider blastomycosis
 - If you practice in the Southwestern United States, this pattern should trigger the search for coccidioidomycosis
- Size matters: the size range of the yeast in blastomycosis is an important clue to avoid confusion with cryptococcosis and coccidioidomycosis

Cryptococcosis

Clinical Features

Cryptococcosis is caused by *Cryptococcus neoformans*. Cutaneous disease is the result of secondary skin involvement by an underlying systemic infection and presents in immunocompromised patients as multiple small ulcerating papules.

Microscopic Features

There are two basic patterns: granulomatous and gelatinous. In the former, there is a granulomatous inflammatory infiltrate in association with the organism. In the latter, there are sheets of the yeast with little inflammatory response (Fig. 12.18). The yeasts are variable in size ranging from 4 to 12 μm and usually have a thick clear capsule (Fig. 12.19). The thick capsule can give the appearance of drops of water within the dermis. Some narrow-based budding may be seen. The organisms can be highlighted by PAS or GMS stains. The capsules can be stained with a mucicarmine stain. A Fontana–Masson stain will also highlight the organism. This is useful in identifying variant organisms lacking capsules (Table 12.13).

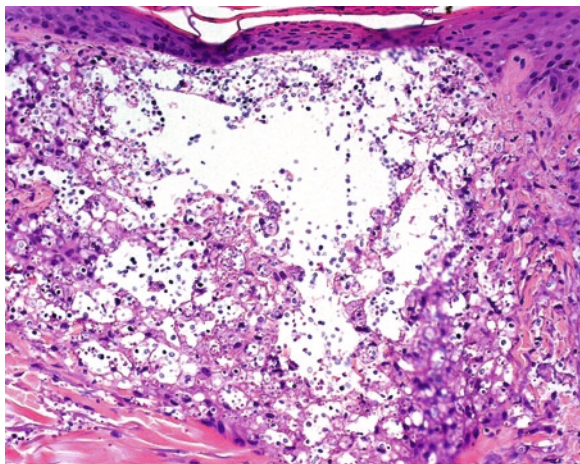


Fig. 12.18 *Cryptococcosis*. The gelatinous pattern is characterized by sheets of organisms in the dermis

Fig. 12.19 *Cryptococcus*.
The yeast have thick capsules
and are quite variable in size

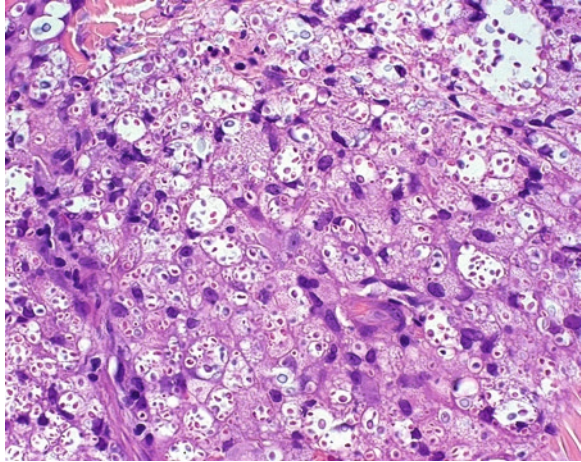


Table 12.13 Key microscopic features: cryptococcosis

- Yeast with thick clear capsule
- Capsule highlighted with mucicarmine stain
- Narrow based budding
- Variable in size: 4–12 μm

Differential Diagnosis

Cryptococcosis can be confused with blastomycosis because of the overlap in size of the organism. *Cryptococcus neoformans* is more variable in size with smaller forms than is seen in blastomycosis. The thick capsule usually allows easy distinction. In selected cases, mucicarmine stains to highlight the capsule or Fontana–Masson stains will allow recognition of cryptococcosis (Table 12.14).

Table 12.14 Practical tips: cryptococcosis

- Size overlap with blastomycosis, but smaller yeast forms too small for blastomycosis
- Water drop appearance on H&E is a clue
- Consider mucicarmine or Fontana–Masson stains

Coccidioidomycosis

Clinical Features

This infection caused by *Coccidioides immitis* is endemic to the Southwestern United States. Cutaneous involvement is rare, occurring in 1% of patients developing

systemic disease. Cutaneous lesion in systemic disease present as verrucal plaques. Interestingly, a subset of patients' with coccidioidomycosis also develop other cutaneous diseases: erythema nodosum and erythema multiforme.

Microscopic Features

The epidermis exhibits pseudoepitheliomatous hyperplasia. Within the dermis, there is suppurative granulomatous inflammation and large spherules containing endospores (Fig. 12.20). The spherules are variable in size, generally ranging from approximately 20 to 80 μm (Table 12.15).

Fig. 12.20 *Coccidioidomycosis*. The characteristic feature is the spherule that contains numerous endospores

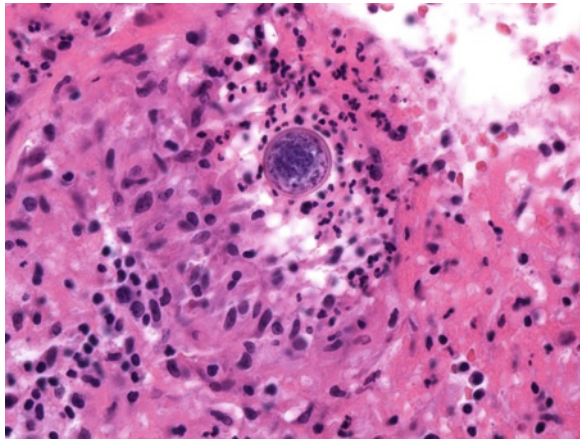


Table 12.15 Key microscopic features: coccidioidomycosis

- Large spherules (20–80 μm) with endospores
- Pseudoepitheliomatous hyperplasia
- Neutrophil-rich granulomatous infiltrate

Differential Diagnosis

The primary differential diagnosis is blastomycosis, which is discussed in detail above (Table 12.16).

Table 12.16 Practical tips: coccidioidomycosis

- Spherules may appear smaller than they truly are depending on plane of section
- Ruptured spherule may be devoid of endospores and appear as empty sacs
- Spherules do not bud; absence of budding helps distinguish from blastomycosis

Sporotrichosis

Clinical Features

Sporotrichosis is caused by *Sporothrix schenckii*. It is a primary cutaneous infection caused by trauma, typically a splinter or rose thorn. It presents an erythematous ulcerated nodule that can progress up the affected extremity following the lymphatics.

Microscopic Features

There is epitheliomatous hyperplasia and suppurative granulomatous inflammation. Small microabscesses are common. Identification of the fungus is often difficult, and special stains (GMS) are almost always required. The organism consists of elongated cigar-shaped budding yeast ranging in size from 2 to 8 μm (Fig. 12.21) (Table 12.17). Rarely asteroid forms, characterized by yeast with numerous radiating spikes, are seen.

Fig. 12.21 *Sporotrichosis*. The GMS stain highlights the yeast of sporotrichosis which are variable in size and often cigar-shaped

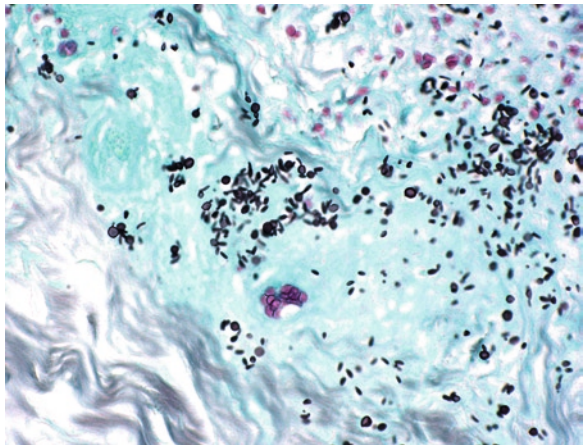


Table 12.17 Key microscopic features: sporotrichosis

- Suppurative granulomatous inflammation with microabscesses
- Cigar-shaped yeast 2–8 μm in size
- Asteroid bodies (rarely seen)

Differential Diagnosis

Because of the clinical presentation of lymphangitic spread, epithelioid sarcoma should be considered because of potential overlapping clinical presentation. Epithelioid

sarcoma can have a pseudogranulomatous pattern, but typically has atypia and a less suppurative appearance. Otherwise other infectious processes should be considered in the differential diagnosis. Diagnosis requires identification of the organism by microscopy or, more frequently, culture (see sample report) (Table 12.18).

Table 12.18 Practical tips: sporotrichosis

- Organisms are rare; multiple levels often necessary
- Clinical history important
- Don't miss epithelioid sarcoma

Mucormycosis

Clinical Features

Mucormycosis is caused by *Rhizopus*, *Mucor* and *Absidia* fungi. Identifying the specific organism requires cultures. This infection is seen in immunocompromised patients, diabetics, and patients with an underlying hematologic malignancy. Cutaneous lesions are usually the result of disseminated spread, but primary skin infections can be seen as the result of infected burns or trauma. The lesions present as dusky, necrotic plaques. This is a serious infection with a high rate of mortality.

Microscopic Features

The fungi are characterized by broad, ribbon-like relatively non-septate hyphae that branch at right angles (Fig. 12.22). The fungi are frequently angioinvasive and may result in ischemic necrosis in surrounding tissue. The inflammatory infiltrate may be quite mild in nature, owing to the underlying immunosuppression (Table 12.19). The fungi are often more evident with PAS or GMS stains.

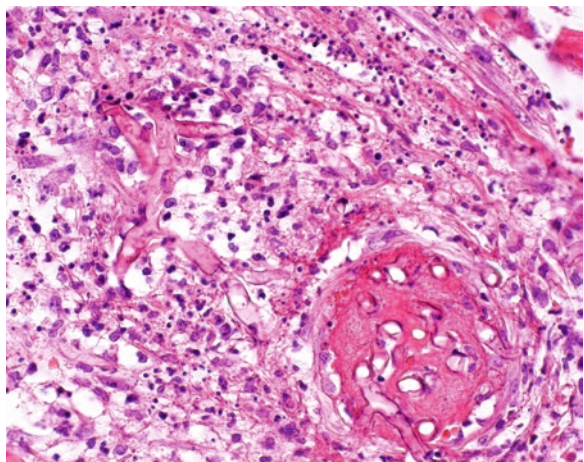


Fig. 12.22 *Mucormycosis*. The hyphae are broad and ribbon-like and relatively nonseptate. Angioinvasion is commonly seen

Table 12.19 Key microscopic features: mucormycosis

-
- Broad relatively nonseptate, ribbon-like hyphae with right angle branches
 - Angioinvasion common
 - Inflammatory infiltrate can be sparse
-

Differential Diagnosis

As a result of the vaso-occlusive nature of the angioinvasion, mucormycosis can be confused with thrombotic disease or vasculitis on low power examination. Higher power examination reveals the presence of fungal hyphae and special stains can be helpful. Other forms of angioinvasive fungal infections, notably aspergillosis, are in the differential diagnosis. *Aspergillus* organisms have narrower hyphae, more regular septations and acute angle branching. As a practical matter, distinction can be difficult as it may be difficult to see the hyphae in the proper orientation in tissue sections or due to degenerative features that can be present in the fungal hyphae (Table 12.20). Correlation with culture results is recommended. In cases where the type of fungal infection is uncertain, a descriptive diagnosis can be useful (see sample reports).

Table 12.20 Practical tips: mucormycosis

-
- Immunocompromised and diabetic patients
 - Some septae often present; their presence does not rule out the diagnosis
 - Broad hyphae helps distinguish from aspergillosis
 - If biopsy resembles vaso-occlusive disease on low power in an immunocompromised patient, consider an angioinvasive fungal infection
 - Degenerative changes in hyphae may preclude definitive diagnosis
 - Consider descriptive diagnosis if necessary (see sample reports)
-

Aspergillosis

Clinical Features

Aspergillosis is caused by *Aspergillus* species. It occurs in the same patient population as mucormycosis and lesions are clinically similar.

Microscopic Features

Classically, the hyphae of *Aspergillus* are regular with septation and acute angle branching, but fine detail may not be apparent in tissue sections. There may be a

Fig. 12.23 *Aspergillosis*. (a) This case of aspergillosis mimicked vasculitis. (b) The PAS stain highlights the fungal hyphae

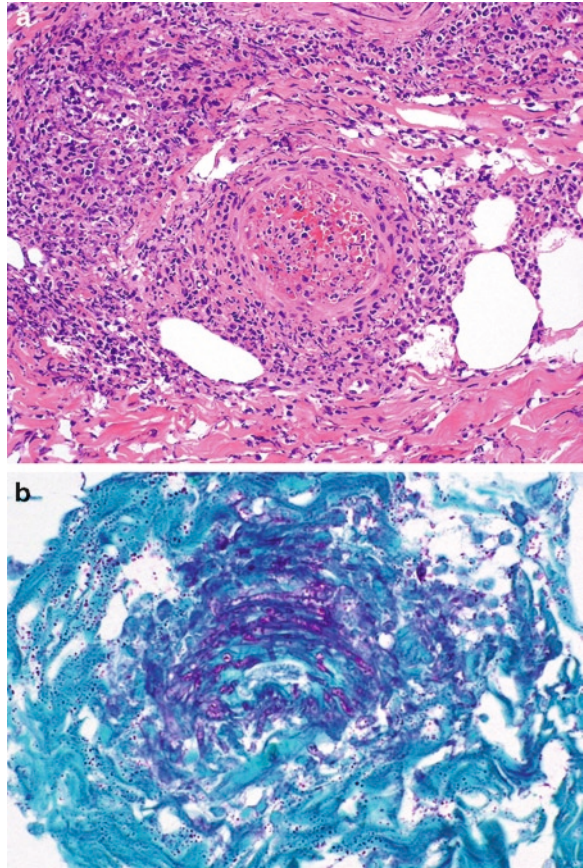


Table 12.21 Key microscopic features: aspergillosis

- Regular septate hyphae with acute angle branching
- Angioinvasion
- Inflammatory infiltrate can be sparse

granulomatous response or there may be little inflammation as result of immunosuppression. Angioinvasion and vascular occlusion is common (Fig. 12.23) (Table 12.21), and there is frequent tissue ischemic necrosis.

Differential Diagnosis

The differential diagnosis includes mucormycosis, which is discussed in detail in the preceding section. *Fusarium* infection can have a similar appearance, but the

hyphae of *Fusarium* branch at right angles and pinch in at branch points (Fig. 12.24). Distinction can be very difficult on tissue sections and correlation with culture results is always recommended. Like mucormycosis, confusion with a thrombotic process or vasculitis is possible on cursory examination. Definitive diagnosis of fungal type is often dependent on culture (see sample reports) (Table 12.22).

Fig. 12.24 *Fusariosis*. The vessel is occluded by fungal hyphae. There is subtle pinching of the hyphae at septations typical of *Fusarium*

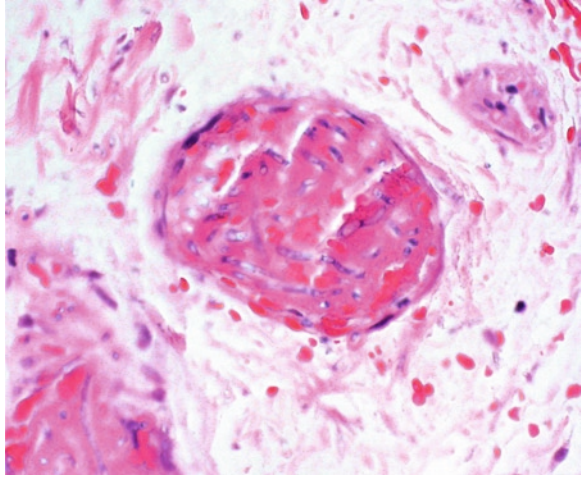


Table 12.22 Practical tips: aspergillosis

-
- Immunocompromised patients
 - If biopsy resembles vaso-occlusive disease on low power in an immunocompromised patient, consider an angioinvasive fungal infection
 - Degenerative changes in hyphae may preclude definitive diagnosis
 - Consider descriptive diagnosis if necessary (see sample reports)
 - Regular pattern of septation favors aspergillosis over mucormycosis
 - Correlation with culture results essential
-

Leishmaniasis

Clinical Features

Leishmaniasis is caused by the parasite *Leishmania*. There has been a resurgence of this diagnosis in the United States and is seen in military personnel and others returning from the Middle East where this disease is endemic. It has a variety of colloquial names including Baghdad boil. Infection is acquired via sandfly bites. Acute lesions present as single pruritic papules that eventuate into ulcerated nodules. Mucocutaneous forms involve mucous membranes as well as the skin and can

cause significant disfigurement as a result of mucous membrane involvement. Chronic forms present as multiple persistent plaques.

Microscopic Features

There is a brisk dermal infiltrate of histiocytes admixed with lymphocytes, plasma cells, neutrophils and eosinophils. The organisms are seen in the cytoplasm of the histiocytes, typically at the periphery of the cell. They are small (3 μm) with a basophilic nucleus on one side and a kinetoplast on the other imparting a safety pin appearance (Table 12.23). The organisms may be better visualized with Giemsa stains (Fig. 12.25).

Table 12.23 Key microscopic features: leishmaniasis

- Mixed infiltrate with histiocytes
- Intracellular organisms in histiocytes
- Organisms have nucleus on one end and kinetoplast on other

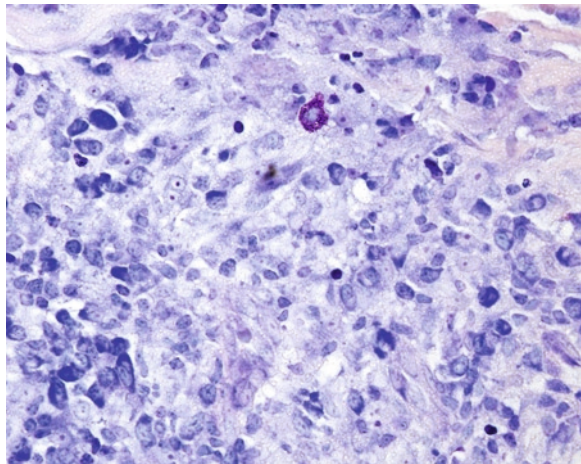


Fig. 12.25 *Leishmaniasis*. Giemsa stain highlighting intracellular organisms

Differential Diagnosis

The organisms are difficult to see because of their small size. They may be overlooked and the infiltrate can be considered a form of granulomatous dermatitis (I have made this painful mistake only to realize the diagnosis on a repeat biopsy). The size of the organism and intracellular location can cause confusion with histoplasmosis. GMS stains and the lack of kinetoplasts can help recognize histoplasmosis (Table 12.24).

Table 12.24 Practical tips: leishmaniasis

- High index of suspicion in patients who are in the military
- Careful examination of histiocytes at high power
- Giemsa stain can help identify organisms

Scabies

Clinical Features

Scabies is caused by cutaneous infestation with the mite *Sarcoptes scabiei*. It is highly contagious and is transmitted by prolonged close contact. The classic clinical lesion is the burrow tract that presents as fine, wavy brown lines between the fingers. Lesions may also be papular, nodular vesicular or eczematous in appearance. Other common locations include the palms, wrists, nipples, inframammary folds, waist, and penis. Immunosuppressed patients may develop widespread, crusted lesions with numerous mites. This is also referred to as Norwegian scabies.

Microscopic Features

The diagnostic finding is the presence of the mite, mite feces, or eggs in the stratum corneum (Fig. 12.26). Findings can be focal and many levels may be necessary. In cases where the mite itself is not seen, egg case remnants described as having the appearance of “pigtailed” may be a clue to the diagnosis (Fig. 12.27). Within, the dermis there is a mixed infiltrate with numerous eosinophils (Table 12.25).

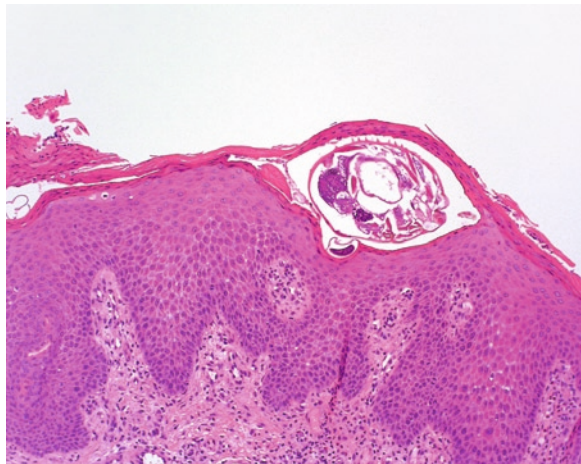


Fig. 12.26 *Scabies*. The sections demonstrates a scabietic mite in the stratum corneum

Fig. 12.27 *Scabies*. In this section only remnants of egg casings are seen. Their appearance has been likened to pigtails

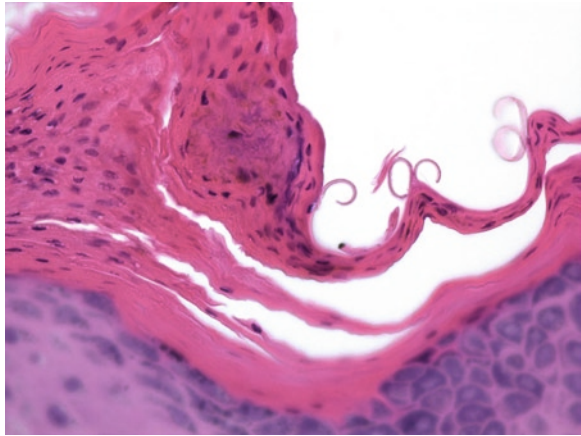


Table 12.25 Key microscopic features: scabies

- Evidence of mites in stratum corneum
- Mixed dermal infiltrate with numerous eosinophils

Differential Diagnosis

If the mite is seen, there is really nothing else in the differential diagnosis. The dermal infiltrate can be confused with dermal hypersensitivity reactions such as urticaria or drug eruptions if there is no histological evidence of scabies infestation. See Table 12.26 for practical tips.

Table 12.26 Practical tips: scabies

- Obtain multiple deeper levels if initial slides are negative
- Evidence of infestation may be subtle: look for “pink pigtailed”

Sample Reports

Since some of the entities in this chapter are so distinctive, sample reports will not be provided for each entity. The sample reports that follow will concentrate on entities that can be ambiguous.

Sample Report: Verruca Plantaris

In this case the lesion is superficially sampled.

Clinical history: Rule out verruca plantaris.

Diagnosis: Hyperkeratosis and parakeratosis consistent with surface of verruca, see comment.

Comment: There is compact hyperkeratosis and parakeratosis with evidence of hemorrhage. Only a limited amount of epidermis is present and it is superficially sampled. There are focal koilocytes present. The findings are consistent with the surface of a verruca. If there is a clinical suspicion of a possible malignancy, a repeat, deeper biopsy would be recommended. Clinicopathologic correlation is recommended.

Sample Report: Condyloma Acuminatum

In this case, unequivocal koilocytotic change is not evident.

Clinical history: Condyloma vs. other.

Diagnosis: Benign keratosis, see comment.

Comment: Sections demonstrate a benign squamous proliferation with a polypoid silhouette. The growth pattern is reminiscent of a condyloma acuminatum, but unequivocal koilocytotic change is not seen. In the appropriate clinical context, the histologic features would be consistent with that diagnosis. Additional testing for HPV can be performed on request. Clinicopathologic correlation is recommended. (Note to reader: if your laboratory has the capacity for assaying for HPV in ambiguous cases, I recommend pursuing additional tests in difficult cases.)

Sample Report: Sporotrichosis

In this case, organisms were not identified.

Clinical history: Rule out sporotrichosis.

Diagnosis: Granulomatous dermatitis, see comment.

Comment: Within the dermis, there is a prominent granulomatous infiltrate with focal microabscess formation. Special stains for fungi (GMS) are negative. The possibility of sporotrichosis cannot be excluded despite negative stains. Identification of the fungal organism is relatively uncommon on histologic examination. Correlation with cultures is recommended.

Sample Report: Mucormycosis

Clinical history: Ulcerated nodule, rule out infection.

Diagnosis: Angioinvasive fungal infection consistent with mucormycosis, see comment.

Comment: Within the dermis, there are numerous fungal hyphae with angioinvasion and vascular occlusion. In order to visualize the hyphae better, a PAS stain was performed. The hyphae are broad and ribbon-like with infrequent septae. The histologic features are most consistent with mucormycosis, but correlation with culture results is recommended.

Sample Report: Aspergillosis

Clinical history: Bone marrow transplant patient, rule out infection.

Diagnosis: Angioinvasive fungal infection suspicious for aspergillosis, see comment.

Comment: Within the dermis, there is an angioinvasive fungal infection with vascular occlusion by numerous fungal hyphae. A PAS stain demonstrates that the hyphae are relatively uniform with frequent septation. Acute angle branching is seen. The histological features are highly suspicious for aspergillosis, but correlation with culture results is essential.

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