Fungal Diseases of the Hair and Scalp

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A fungus is any member of the group of eukaryotic organisms that are classified as a kingdom separately from plants, animals, protozoa, and chromista. A characteristic that places fungi in a different kingdom is chitin in their cell walls. Fungi, like animals, are heterotrophs. They acquire their food by absorbing dissolved molecules, typically by secreting digestive enzymes into their environment. Fungi do not

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R. M. Trüeb et al. (eds.), *Hair in Infectious Disease*,
https://doi.org/10.1007/978-3-031-30754-6_5

photosynthesize. Growth is their means of mobility, except for spores, which may travel through air or water. Fungi are the principal decomposers in ecological systems. The fungus kingdom encompasses an enormous diversity of taxa with varied ecologies, life cycle strategies, and morphologies. Abundant worldwide, most fungi are inconspicuous because of the small size of their structures and their cryptic lifestyles in soil or on dead matter. Fungi include symbionts of plants, animals, or other fungi and also pathogenic parasites.

Fungal infection is transmittable disease caused by fungi. Fungal infections have a worldwide distribution and are common, affecting more than one billion people every year. The different types are traditionally divided according to the part of the body affected: superficial, subcutaneous, and systemic.

Fungi that cause infections include the dermatophytes, yeasts, molds, and dimorphic fungi that can exist in the form of both mold and yeast. Signs and symptoms range widely.

Superficial fungal infections include common tinea of the skin (ringworm), piedra, and yeast infections such as pityriasis versicolor, candida intertrigo, and oral thrush. Subcutaneous types include eumycetoma and chromoblastomycosis, which affect tissues in and beneath the skin. Systemic fungal infections are more serious and include cryptococcosis, histoplasmosis, pneumocystis pneumonia, aspergillosis, and mucormycosis, with pneumonia-like symptoms or meningitis.

Fungal infections are more likely to occur in people with weak immune systems, such as individuals with HIV/AIDS or on corticosteroids, cancer treatments, or antibiotics, people with diabetes, the very young, and the very old.

During the 2003 SARS outbreak, fungal infections were reported in 14.8–33% of people affected, and it was the cause of death in 25–73.7% of people with SARS [1]. During the COVID-19 pandemic, some fungal infections have been associated with COVID-19. The most common serious fungal infections in people with COVID-19 include aspergillosis and invasive candidiasis [2] COVID-19-associated mucormycosis is generally less common but as of 2021 was noted to be significantly more prevalent in India.

Diagnosis of a fungal infection is based on signs and symptoms, microscopy, or culture and sometimes requires a biopsy.

Treatment is generally with antifungal drugs and depends on the specific infection and its extent, in the form of a cream, by mouth, or injection. Some may require surgically removing the infected tissue.

As a matter of fact, the scalp was the site in which Johann Lukas Schoenlein originally reported in 1839 resp. David Gruby in the early 1840s, where human disease could be caused by fungi, specifically *Trichophyton schoenleinii* in favus resp. *Microsproum audouinii* in scalp ringworm.

The scalp may occasionally also be the site of mycetoma and of systemic fungal infections (dermatomycosis).

5.1 Dermatophytes

Dermatophytosis, tinea, or ringworm is a superficial fungal infection of the skin with dermatophytes. About 40 types of dermatophytes can cause ringworm. They are typically of the *Trichophyton*, *Microsporum*, or *Epidermophyton* species. Globally, approximately 20% of the population may be infected at any given time.

These fungi afflict various parts of the body. Infections of the groin and inner thighs (tinea inguinalis or jock itch) are more common in males, and infections of the lower legs (tinea cruris) are more frequent in women who shave their legs, while infections of the body (tinea corporis), face (tinea faciei), hands (tinea manuum), feet (tinea pedis or athlete's foot), and nails (tinea unguim or onychomycosis) occur equally in both sexes.

Infection of the beard area in men (tinea barbae or barber's itch) is by definition seen only in males and most commonly among agricultural workers, since transmission is more common from animal-to-human than human-to-human, making it a zoonotic disease. Prior to the introduction of modern-day antisepsis, tinea barbae was also transmitted from person to person by contaminated barber's razors or clippers, hence the term barber's itch. Three clinical types of tinea barbae are recognized:

1. Inflammatory or kerion-like (Fig. 5.1a)
2. Superficial or sycosiform type (*Sycosis parasitaria*) (Fig. 5.1b)
3. Circinate, spreading type (Fig. 5.1c)

Infections of the scalp (tinea capitis or scalp ringworm) are particularly common in children, where they can be either transmitted from animal to human or from human to human. The Latin names are for the clinical disease patterns, and not the agents that cause them.

Risk factors include using public showers, contact sports such as wrestling, excessive sweating, contact with animals, obesity, age, and poor immune function. When ringworm spreads from animals to humans, it is termed zoophilic and if between people, anthropophilic. Fungi thrive in moist, warm areas, such as locker rooms, tanning beds, swimming pools, and skin folds; accordingly, those that cause dermatophytosis may be spread by using exercise machines that have not been disinfected after use or by sharing towels, clothing, footwear, or hairbrushes.

Tinea capitis (scalp ringworm) is a dermatophytosis of the scalp and the associated hair. The different organisms causing tineas capitis may present with several different clinical patterns. Clinically, a noninflammatory and an inflammatory type occurs. The existence of an asymptomatic carrier state in tinea capitis has been repeatedly documented with its important epidemiologic implications, since silent sources are more difficult to detect and eradicate.

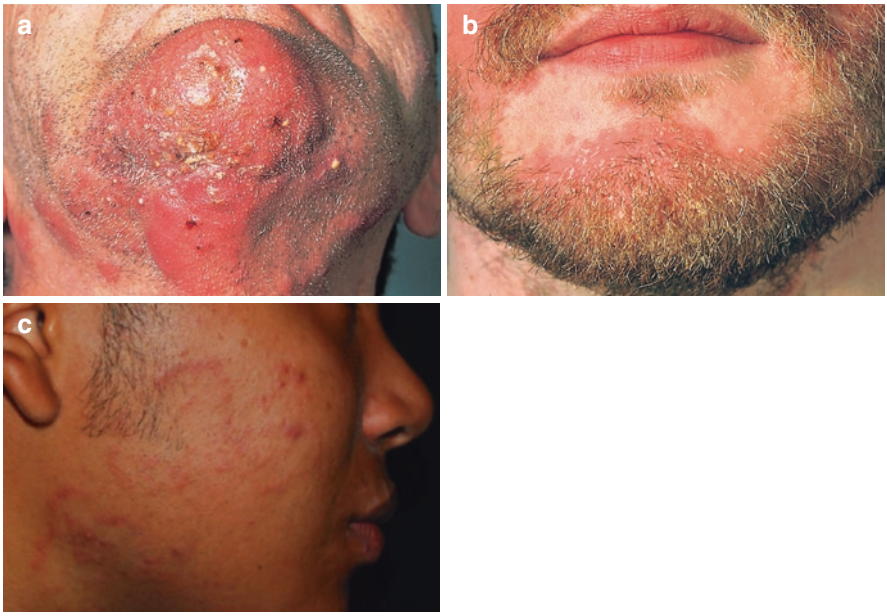


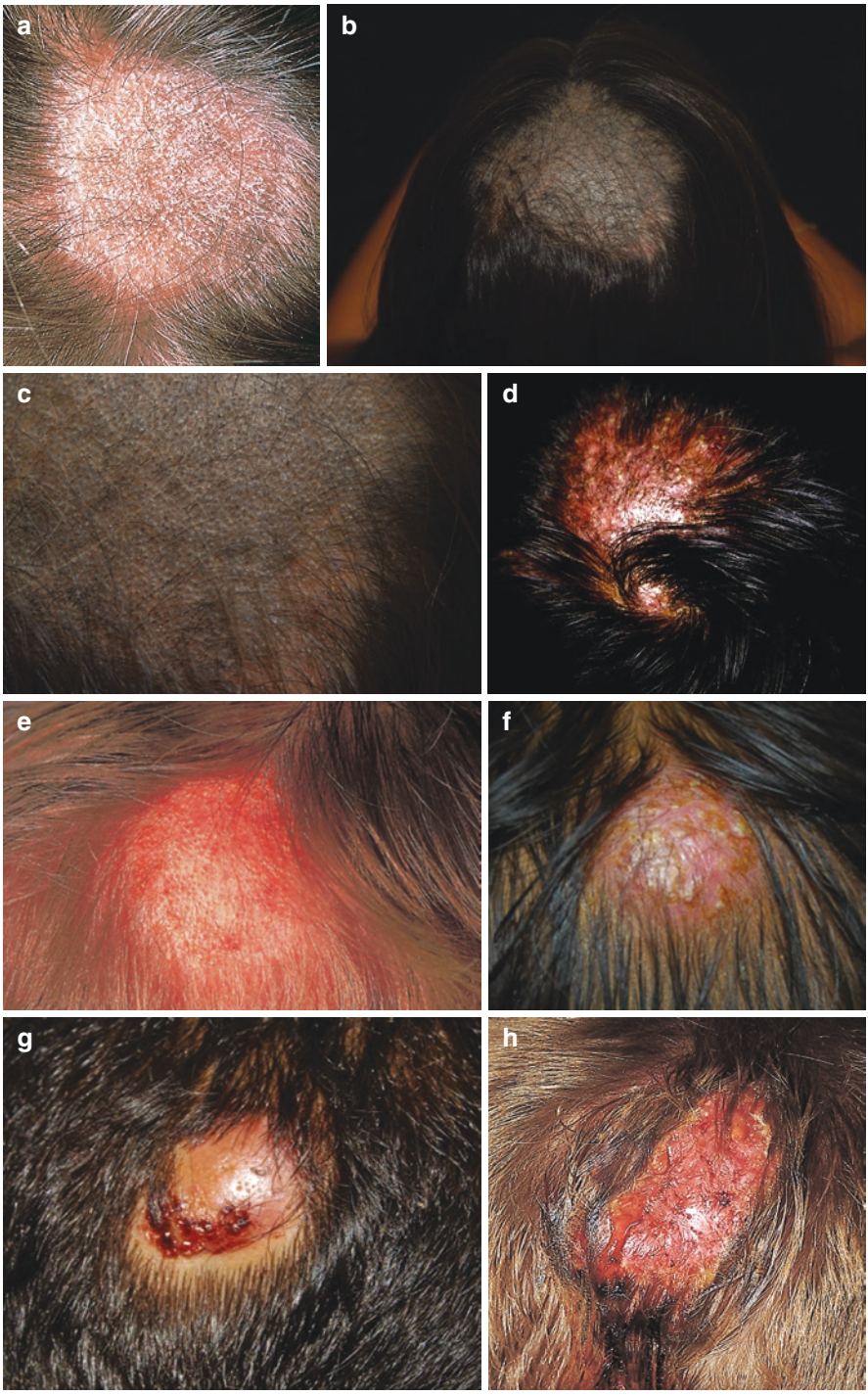
Fig. 5.1 (**a**–**c**) Tinea barbae (barber's itch): (**a**) inflammatory kerion-like, (**b**) superficial sycosiform, (**c**) circinate spreading type (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)

The noninflammatory type begins as a small erythematous papule surrounding a hair shaft. Subsequently, the lesion spreads centrifugally, involving the hairs in its path. Typically, there is scaling with minimal inflammation, and the hairs frequently break off just above the level of the scalp, rather than being shed entirely (Fig. 5.2a).

Black dot tinea capitis is due to extremely brittle hair shafts that break at the level of the scalp. The remnants of hair left behind in the infected follicle appear as black dots on clinical examination (Fig. 5.2b, c). There may be diffuse scaling with minimal hair loss and inflammation. When hair loss occurs, the affected areas are characteristically multiple or polygonal in outline with distinct, fingerlike margins. Black dot infections may also be quite inflammatory, ranging from a pustular folliculitis (Fig. 5.2d) to furuncle-like lesions or obvious kerion.

The inflammatory type may either present as superficial inflammatory tinea capitis with a seborrheic dermatitis-like appearance with redness and scaling with or without loss of hairs (Fig. 5.2e) and as such may not be recognized, especially in

Fig. 5.2 (**a**–**h**) Tinea capitis (scalp ringworm): (**a**) superficial non-inflammatory, (**b**, **c**) black dot alopecia (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**d**) with pustular folliculitis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**e**) superficial inflammatory, (**f**) deep inflammatory (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), (**g**, **h**) kerion (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)


a
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adults, or as deep inflammatory tinea capitis with a spectrum of inflammatory changes ranging from a pustular folliculitis (Fig. 5.2f) to a kerion, which presents as an inflammatory, boggy mass, studded with broken hairs, and oozing purulent material from the follicular orifices (Fig. 5.2g, h).

The inflammatory type of tinea capitis is caused most commonly by zoophilic organisms, such as *Microsporum canis* or geophilic dermatophytes, such as *Microsporum gypseum*. The noninflammatory type is produced most commonly by *Microsporum audouinii* or *Microsporum ferrugineum*. Black dot tinea capitis is most often caused by endothrix organisms, such as *Trichophyton tonsurans* or *Trichophyton violaceus*.

Favus or tinea favosa is a chronic mycotic infection of the scalp, glabrous skin, and/or nails that is characterized by the formation of yellowish crusts within the hair follicle (scutula) (Fig. 5.3a, b) and is most commonly caused by *Trichophyton schoenleinii* (Fig. 5.3c, d). In the early stages of infection, the hyphae invade the hair follicle and gradually distend the follicular opening. On microscopic examination, the favus hair shows hyphae coursing lengthwise of the hair shaft and no arthroconidia. The concentrations of hyphae and keratinous debris take root at the opening of the hair follicle, where they gradually expand to form yellowish, cup-shaped structure that may become 1 cm or more in diameter. The center of such a scutulum is often pierced by a single, lusterless, dry hair.

Favus is typically a chronic infection that begins early in life and commonly extends into adulthood. Up until the advent of modern therapies, favus was widespread worldwide. Prior to Schönlein's recognition of it as a fungal disease, it was frequently confused with leprosy, and European sufferers were sometimes confided to leprosaria. Today, due to this species' high susceptibility to the modern antifungals, it has been eliminated from most parts of the world except rural central Asia and scattered rural areas of Africa associated with conditions of poor hygiene, malnutrition, and squalor. It is mainly a disease connected to demographic poverty and isolation but is so readily treatable that it is among the diseases most likely to be completely eliminated by modern medicine.

The variable clinical presentations are in part due to the fungal organism involved with its specific ecology and type of hair involvement. The organisms associated with clinical types of tinea capitis are summarized in Table 5.1.

Diagnosis of tinea capitis requires a high rate of suspicion. At times, tinea capitis may be difficult to distinguish from other scaling skin diseases, such as psoriasis and seborrheic dermatitis. Pustular lesions on the scalp of children are more commonly associated with fungal infections, while in adults, they are more commonly seen with bacterial infection.

The basis for the diagnosis is a positive microscopic examination (Fig. 5.4a) and mycological culture of epilated hairs for evaluation of colony morphology (Fig. 5.4b) and microscopic morphology (Fig. 5.4c) [3]). Using traditional methods to verify the existence of a fungal infection in children with suspected tinea capitis is a cumbersome process. Scraping scale and pulling hairs for culture or microscopic examination can be time-consuming and uncomfortable for the child. For this purpose, the brush method has been proven a reliable, painless, and more expedient way to

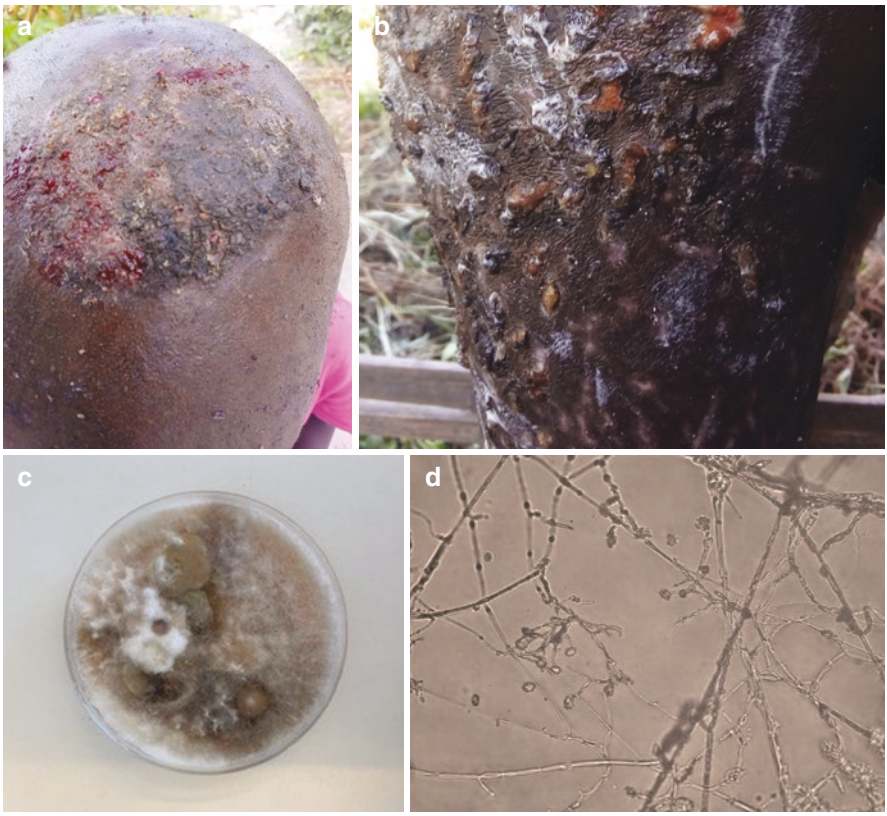


Fig. 5.3 (**a**–**d**) Tinea favosa (favus): (**a**) of the scalp and (**b**) glabrous skin. Yellowish, circular, cup-shaped crusts (scutula) grouped in patches like a honeycomb. These increase in size and become crusted over so that the characteristic lesion eventually can only be seen round the edge of the scab. (**c**) Colony morphology (*Trichophyton schoenleinii*): whitish, waxy, or slightly downy, with a heaped or folded appearance. (**d**) Microscopic morphology (*Trichophyton schoenleinii*): hyphae are septate, highly irregular, and knobby. The subsurface hyphae usually form characteristic antler-like branching structures (favic chandeliers); they have swollen tips that resemble nail heads

Table 5.1 Organisms associated with clinical types of tinea capitis

Inflammatory	Noninflammatory	Black dot	Favus
M. canis *M. gypseum* *T. mentagrophytes* *T. tonsurans* *T. verrucosum* *T. schoenleinii* *M. audouinii* *M. nanum*	*M. audouinii* *T. tonsurans* *M. canis* *M. ferrugineum*	*T. tonsurans* *T. violaceum*	*T. schoenleinii* *T. violaceum* *M. gypseum*

obtain cultures from children with suspected tinea capitis [4]. It can also be used for detection of the carrier status within affected families [5] and in pets, specifically cats [6]. In our experience, the toothbrush sampling technique is most effective for this purpose [7]. Fungal culture samples from the scalp or the haircoat are collected by stroking the respective skin surface with a sterile toothbrush. Specimens are inoculated onto Sabouraud agar and incubated at 25 °C for 21 days. The optimum inoculation technique is to press the toothbrush bristles onto the agar plates to maximize growth of the fungus and minimize introduction of contaminant inoculation [8].

Wood's lamp examination will reveal bright green to yellow-green fluorescence of hairs infected by *M. canis*, *M. audouinii*, *M. rivalieri*, and *M. ferrugineum* and a dull green or blue-white color of hairs infected by T. *schoenleinii* [9].

In individuals with *M. canis* infection, scalp dermoscopy will show characteristic small comma hairs [10] (Fig. 5.4d) or corkscrew hairs (Fig. 5.4e).

Histopathology of scalp biopsy shows fungi sparsely distributed in the stratum corneum and hyphae extending down the hair follicle, placed on the surface of the hair shaft. These can be made visible with either the periodic acid-Schiff (PAS) (Fig. 5.4f) or Grocott's methenamine silver stain (GMS) stain. While the former will only stain living fungal organisms magenta, the latter will stain both living and dead fungal organisms brown to black. These findings may be associated with a neutrophilic (within the hair follicle) or granulomatous (perifollicularly) inflammatory tissue reaction.

Due to the risk of permanent scarring alopecia (Fig. 5.5a–c), treatment of tinea capitis should be initiated promptly and, independent of the type of clinical presentation or age of the patient, should always be systemic for successful management (Fig. 5.6a–c). While griseofulvin has been the original systemic antimycotic agent successfully introduced in 1958 for treatment of fungal infections of the scalp and nails, as well as of the skin when antifungal creams have not worked, and the gold standard for the treatment of tinea capitis, today, it has been replaced with the newer antimycotic agents terbinafine and itraconazole for better compliance reasons (griseofulvin must be ingested with a fatty meal and has high rate of adverse effects, such as nausea, diarrhea, headache, trouble sleeping, and feeling tired, and long treatment duration). Terbinafine given for 2 to 4 weeks is at least as effective as griseofulvin given for 6 to 8 weeks for treatment of *Trichophyton* scalp infections (Fig. 5.7: endotrich infection) However, griseofulvin is more effective than terbinafine for treatment of *Microsporum* scalp infections. In the latter case, oral itraconazole is preferred for a duration of 4 to 6 weeks or sometimes longer (up to 12 weeks), depending on clinical and mycological findings [11] (ectotrich infection).

It is known that *T. schoenleinii* can survive for years on epilated hair. For this reason, cleanliness with removal of hairs or other sources of infection is an important factor in controlling the disease [12]. Treatment of tinea capitis (in children) is summarized in Table 5.2.

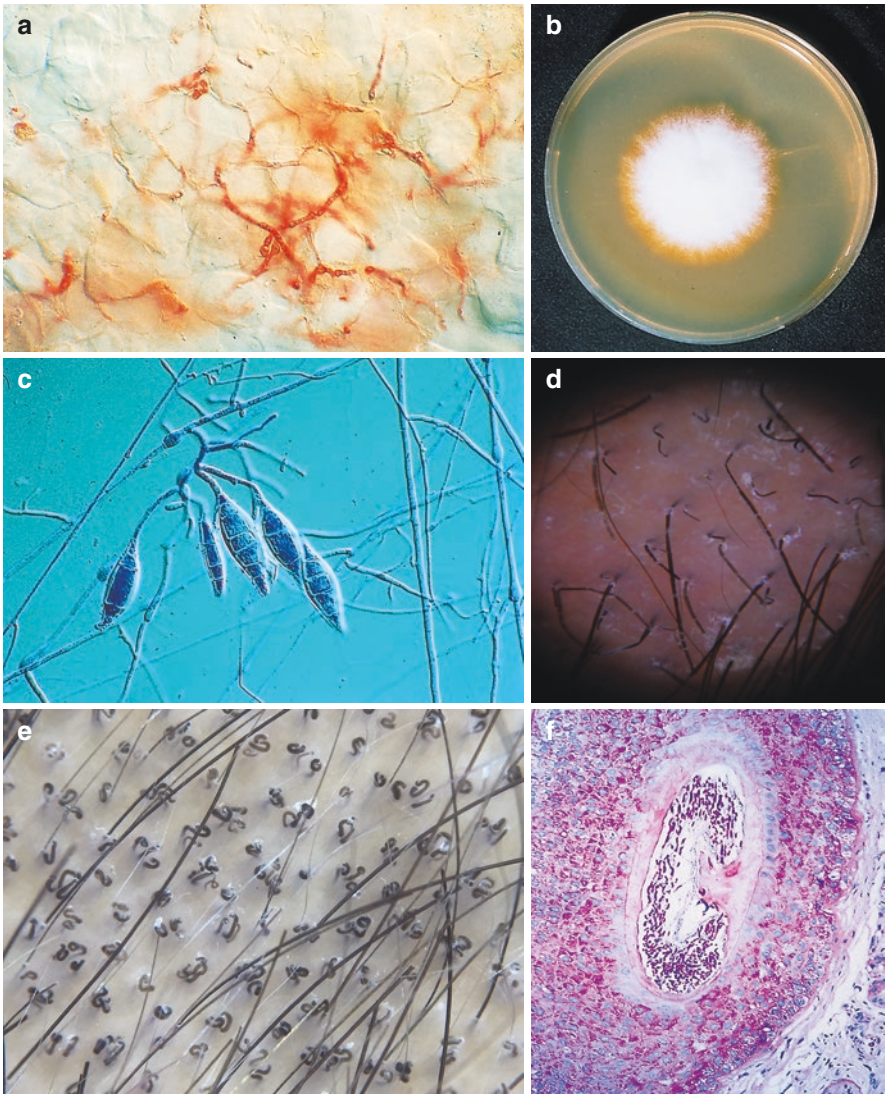


Fig. 5.4 (**a**–**d**) Diagnostic techniques in mycology: (**a**) direct microscopic examination with visualization of fungal hyphae (Congo red), (**b**) mycological culture (Sabouraud agar), (**c**) with direct visualization of microscopic fungal morphology (lactophenol cotton blue), (**d, e**) dermoscopy of scalp: (**d**) comma hairs (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil), and (**e**) corkscrew hairs, (**f**) histopathology with visualization of fungal hyphae in the biopsy (PAS stain)

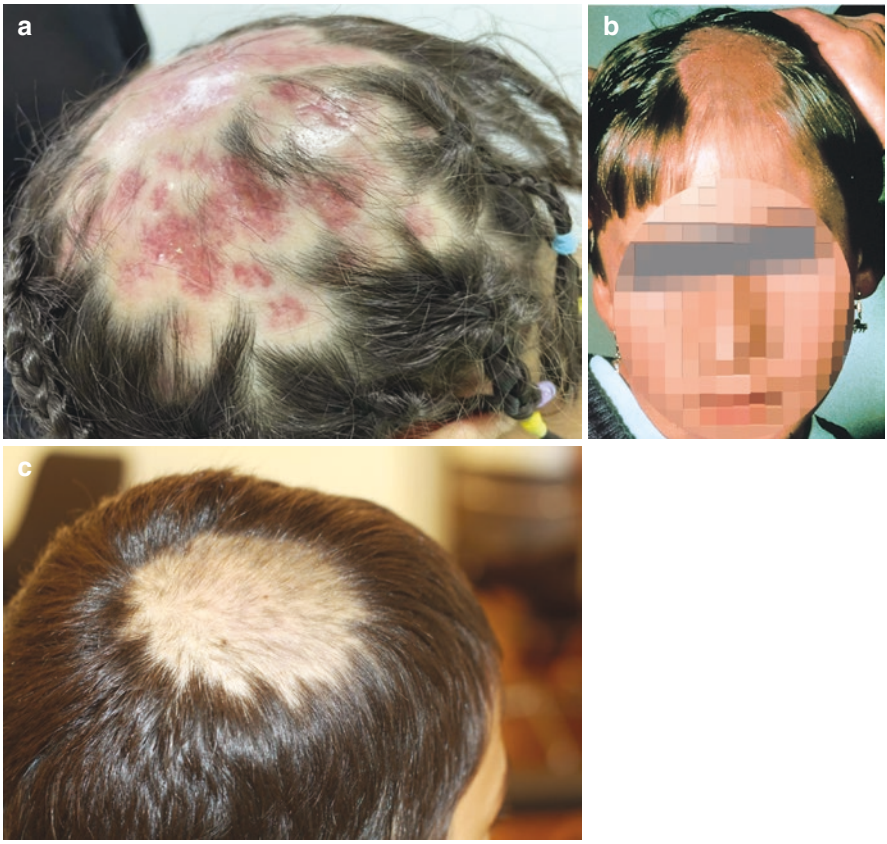


Fig. 5.5 (**a**–**c**) Tinea capitis management: (**a**) due to potential widespread scarring and (**b**) permanent alopecia, treatment should be prompted early and with a systemic antimycotic agent, independent of patient age, clinical presentation type, or fungus species. However, choice of antimycotic agent and duration of treatment will depend on the fungal specie. (**c**) Partial regrowth of hair

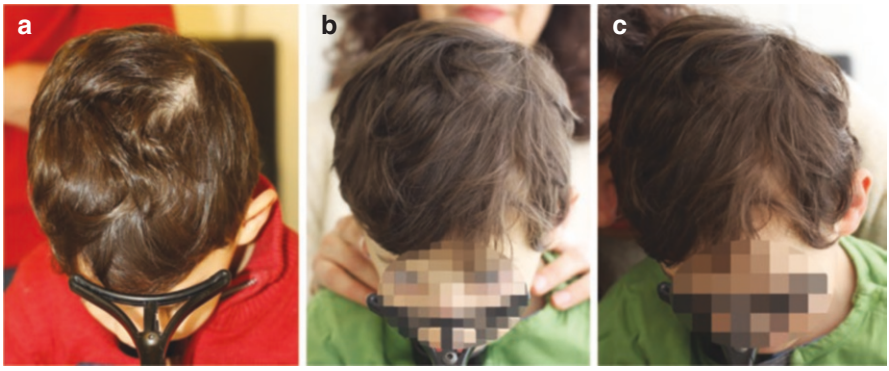


Fig. 5.6 (**a**–**c**) Example of successful treatment of tinea capitis with total regrowth of hair

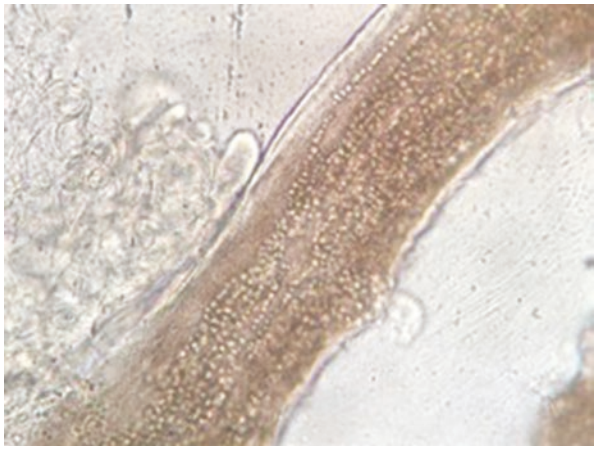


Fig. 5.7 Endotrich infection. Anthrophilic pathogens, such as *T. tonsurans*, mainly grow endotrich (penetrating into the hair), while zoophilic pathogens, such as *M. canis*, grow ectotrich (around the hair) with large spore cuffs. Therefore, zoophilic pathogens are highly contagious and need a longer treatment time

Table 5.2 Treatment of tinea capitis (children)

• Systemic antimycotic treatment: in the case of endotrich infection with *Trichophyton* spp. with oral terbinafine 6 mg/kg body weight per day for 2–4 weeks; in the case of ectotrich infection with *Microsporum* spp. with oral itraconazole 5 mg/kg body weight per day for 4–6 weeks (or sometimes longer depending on clinical and mycological findings), in combination with
• Topical antimycotic treatment, either as shampoo (selenium disulfide, ketoconazole, or povidone iodine) or topical antimycotic agent (ciclopiroxolamine, an imidazole, or terbinafine)
• May combine oral prednisone 1 mg/kg body weight per day for 1–2 weeks in case of deep inflammatory tinea (Kerion)
• Combine with oral antibiotic, preferably an oral macrolide antibiotic, if secondary pathogenic bacterial infection is present.
• Check for carrier status for sanitation of family members or pets, depending on anthropophilic or zoophilic fungal agent resp. detected in mycologic culture

Dermatophytid reactions (*Trichophyton*, *Microsporum*) are fungus-free disseminated skin lesions resulting from induced sensitization in patients with fungal infections. They are usually accompanied by a reactive delayed trichophytin skin test. Clinically, dermatophytid reactions may take several forms, including follicular papules (Fig. 5.8), erythema nodosum, vesicular id reactions of the hands and feet, erysipelas-like, erythema annulare centrifugum, urticaria, and vasculitis. These reactions tend to occur at the height of the dermatophyte infection, or just after initiation of systemic antifungal therapy. The mechanism responsible for the id reaction is believed to involve an immunologic response to systemically absorbed fungal antigen. Disappearance occurs when the dermatophyte infection is successfully treated. In case of especially widespread or inflammatory id reactions, a short course of concomitant corticosteroid therapy in addition to the antifungal agent may be warranted.

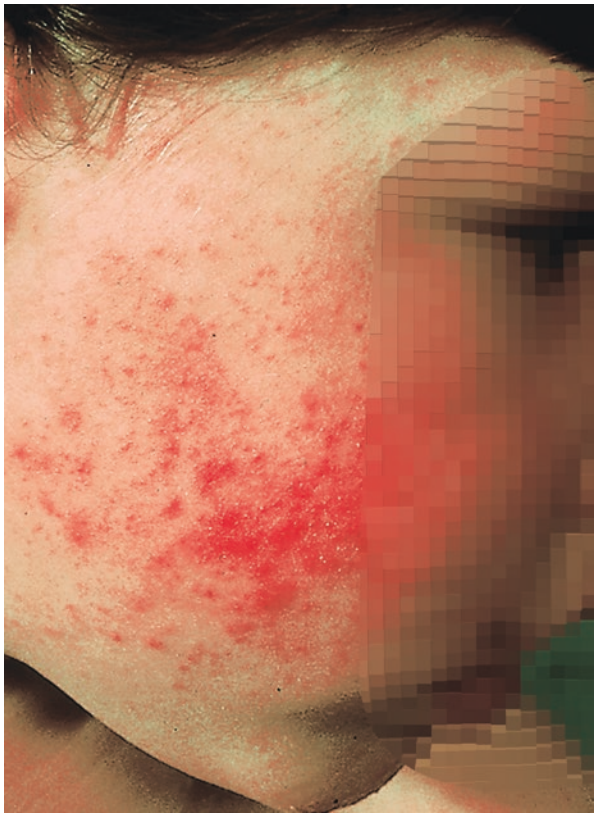


Fig. 5.8 Papular dermatophytid reaction

5.2 Yeasts

Yeasts are eukaryotic, single-celled microorganisms classified as members of the fungus kingdom. The first yeast originated hundreds of millions of years ago, and at least 1500 species are currently recognized. They are estimated to constitute 1% of all described fungal species. Yeasts are unicellular organisms that evolved from multicellular ancestors, with some species having the ability to develop multicellular characteristics by forming strings of connected budding cells known as pseudohyphae or false hyphae.

5.2.1 Candida

Candidiasis is a fungal infection due to any type of *Candida*, a yeast. More than 20 types of *Candida* can cause infection with *Candida albicans* being the most common.

Candida yeasts are generally present in healthy humans, frequently part of the human body's normal oral and intestinal flora, and particularly on the skin. However,

their growth is normally limited by the human immune system and by competition of other microorganisms, such as bacteria occupying the same locations in the human body. *Candida* requires moisture for growth, notably on the skin.

Signs and symptoms of candidiasis vary depending on the anatomical area affected and the immunity of the individual.

In healthy, immunocompetent individuals, candidiasis is usually a localized infection of the skin, fingernails or toenails, or mucosal membranes, including the oral cavity and pharynx (thrush), esophagus, and the genitalia. Signs and symptoms of candidiasis in the skin include itching, irritation, and chafing or broken skin.

In immunocompromised individuals, *Candida* infections in the esophagus occur more frequently than in healthy individuals and have a higher potential of becoming systemic, causing a much more serious condition, a fungemia called candidemia.

Factors that increase the risk of candidiasis include HIV/AIDS, mononucleosis, cancer treatments, steroids, stress, antibiotic usage, diabetes, and nutrient deficiency. Hormone replacement therapy may also be a predisposing factor. Use of inhaled corticosteroids increases risk of *candidiasis* of the mouth. Inhaled corticosteroids with other risk factors such as antibiotics, oral glucocorticoids, not rinsing mouth after use of inhaled corticosteroids, or high dose of inhaled corticosteroids put people at even higher risk. Treatment with antibiotics can lead to eliminating the yeast's natural competitors for resources in the oral and intestinal flora, thereby increasing the severity of the condition. Almost 15% of people with weakened immune systems develop a systemic illness caused by *Candida* species [13]. Diets high in simple carbohydrates have been found to affect rates of oral candidiasis [14]. Among individuals being treated in intensive care units, the mortality rate is about 30–50% when systemic candidiasis develops [15].

Diagnosis of a *Candida* infection is done either via microscopic examination or culturing.

For identification by light microscopy, a scraping or swab of the affected area is placed on a microscope slide. A single drop of 10% potassium hydroxide (KOH) solution is then added to the specimen. KOH dissolves the skin cells but leaves the *Candida* cells intact, permitting visualization of pseudohyphae and budding yeast cells typical of *Candida* spp.

For the culturing method, a sterile swab is rubbed on the infected skin surface. The swab is then streaked on a culture medium. The culture is incubated at 37 °C for several days, to allow development of yeast or bacterial colonies. Characteristics such as morphology and color of the colonies may allow initial diagnosis of the organism causing disease symptoms (Fig. 5.9a, b).

Candidiasis may be divided into the following types:

Mucosal candidiasis
- Oral candidiasis (thrush, oropharyngeal candidiasis)
- Pseudomembranous candidiasis
- Erythematous candidiasis
- Hyperplastic candidiasis
- Denture-related stomatitis—*Candida* is involved in about 90% of cases
- Angular cheilitis—*Candida* is responsible for about 20% of cases, mixed infection of *C. albicans* and *Staphylococcus aureus* for about 60% of cases.
- Median rhomboid glossitis
- Candidal vulvovaginitis
- Candidal balanitis—almost exclusively occurring in uncircumcised males
- Esophageal candidiasis (candidal esophagitis)
- Gastrointestinal candidiasis
- Respiratory candidiasis

Cutaneous candidiasis
- Candidal folliculitis
- Candidal intertrigo
- Candidal paronychia
- Perianal candidiasis—may present as pruritus ani
- Candidid
- Chronic mucocutaneous candidiasis (Fig. 5.9b, c)
- Congenital cutaneous candidiasis
- Diaper candidiasis
- Erosio interdigitalis blastomycetica
- Candidal onychomycosis

Systemic candidiasis
- Candidemia, a form of fungemia, which may lead to sepsis
- Invasive candidiasis (disseminated candidiasis)—organ infection by *Candida*
- Chronic systemic candidiasis (hepatosplenic candidiasis)—sometimes arises during recovery from neutropenia
- Antibiotic candidiasis (iatrogenic candidiasis)

Alternative medicine
- A 2005 publication noted that "a large pseudoscientific cult" [16] has developed around the topic of *Candida*, with claims stating that up to one in three people is affected by yeast-related illness, particularly a condition called "candidiasis hypersensitivity" [17]. Some practitioners of alternative medicine have promoted these purported conditions and sold dietary supplements as supposed cures; a number of them have been prosecuted

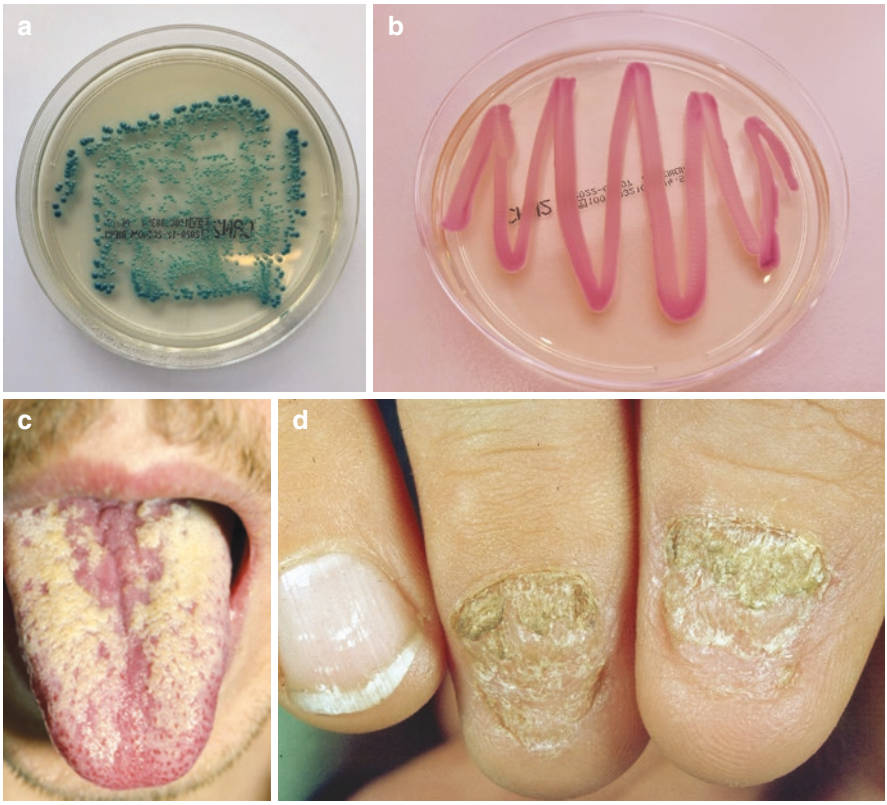


Fig. 5.9 (**a**–**d**) *Candida* spp.: (**a**) *Candida albicans*. Identification in culture on chromogenic *Candida* agar. *C. albicans* can be identified by the blue color of colonies. The concept of developing chromogenic differential media for *Candida* came from the observation that *C. albicans* produces an enzyme N-acetyl-galactosaminidase, which can break down chromogenic hexosaminidase substrates incorporated in a medium. (**b**) *Candida tropicalis*. Identification in culture on chromogenic *Candida* agar by pink color. (**c**, **d**) Chronic mucocutaneous candidiasis: (**c**) involvement of oral cavity and (**d**) nails. Patients may have associated alopecia totalis

Besides bacteria and dermatophytes, *Candida albicans* may rarely cause folliculitis, particularly in the beard area of adult men. Predisposing factors are seborrhea, diabetes, HIV infection, systemic corticosteroids, immunosuppressive treatment, and previous long-term treatment of skin lesions with topical glucocorticosteroid or antibiotics. Occasionally, oral thrush may be the source of infection. Different clinical types of *Candida* folliculitis have been described:

- Similar to impetigo contagiosa with honey yellow crusts
- Folliculitis simplex with small follicular pustules
- Tinea barbae with small nodules covered with crusts
- Perioral dermatitis-like
- Acne conglobate-like with multiple papular pustular lesions
- Disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas

Oral fluconazole is found to be very effective in this condition and should be considered as first-line treatment. It is well absorbed after oral intake and is highly lipophilic, preferentially redistributing in the skin. Its action mechanism is the inhibition of the fungal cytochrome P450-dependent enzymes that block the synthesis of ergosterol [18].

Disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas, such as the beard, seems to represent a distinctive clinical presentation. Originally reported by Collignon and Sorrell in 1983 [19], the condition has been confirmed by several other authors [20–23]. The characteristic clinical picture is widely different from that of classic disseminated candidiasis in immunodeficient patients. Collignon and Sorrell's indicator cases were seven young men who developed similar manifestations of disseminated candidiasis after a single episode of intravenous heroin abuse. Sequential development of lesions of the eye (chorioretinitis), skin (deep-seated scalp nodules and pustulosis), and bone or costal cartilage (vertebrae, costal cartilage, knees, and sacroiliac) was noted within 10 days after injection. Skin lesions were confined to the scalp and other hair-bearing areas. *Candida albicans* was cultured readily from the affected skin. Histological examination of scalp biopsy specimens showed infiltration of hair follicles with chronic inflammatory cells and *C albicans*. Pseudohyphae of *C. albicans* were identified in and around hair shafts. The skin, skeletal, and small eye lesions resolved on systemic treatment with 1 g amphotericin B plus flucytosine. Fortuna et al. report a rare case of scalp infection by *Candida albicans* in an immunocompetent patient and independent of intravenous drug abuse and cautioned dermatologists to not exclude *Candia* infection of the scalp in an immunocompetent patient and perform the respective mycological workup by means of multiple swabs from the affected area. Typically, bacteriological culture is negative. Treatment was successful with oral fluconazole 100 mg bid for 1 month [24].

The autoimmune polyendocrinopathy syndrome with chronic mucocutaneous candidiasis is an autosomal recessive disease caused by mutations in the autoimmune regulator gene and characterized by the clinical triad of chronic mucocutaneous candidiasis (Fig. 5.9c, d), hypoparathyroidism, and adrenal insufficiency.

Additional features may be insulin-dependent diabetes mellitus, chronic atrophic gastritis with pernicious anemia, hypogonadism, alopecia areata, and vitiligo. Onset is in childhood, candidiasis is usually the first symptom, and manifestations continue to appear until the fifth decade, including alopecia. The acquired adult form of chronic mucocutaneous candidiasis may be associated with a thymoma [25].

5.2.2 Pityrosporum

Pityrosporum or *Malassezia* is a genus of fungi that are naturally found on skin surfaces of many animals and humans.

Malassezia was originally identified by the French anatomist and histologist Louis-Charles Malassez (1842–1909) in the late nineteenth century.

French dermatologist Raymond Sabouraud (1864–1938) identified a dandruff-causing organism in 1904 and named it *Pityrosporum malassezia*, in honor of Malassez, but at the species level as opposed to the genus level. When it was determined that the organisms were the same, the term *Malassezia* was judged to possess priority.

Due to progressive changes in their nomenclature, some confusion exists about the naming and classification of *Pityrosporum* yeast species.

In the mid-twentieth century, it was reclassified into *Pityrosporum* (*Malassezia*) *ovale*, which is lipid-dependent and found only on humans. *P. ovale* was later divided into two species, *P. ovale* and *P. orbiculare*, but current sources consider these terms to refer to a single species of fungus, with *M. furfur* the preferred name. *Pityrosporum* (*Malassezia*) *pachydermatis* is found on the skin of most animals. *Malassezia pachydermatis* is a species that is associated with otitis externa in dogs.

As the fungus requires fat to grow [26], it is most common in areas with many sebaceous glands, such as the scalp, face, and upper part of the body.

In the mid-1990s, scientists at the Pasteur Institute in Paris, France, discovered additional species. As of April 2021, Species Fungorum accepts 22 species of *Malassezia*. Work on these yeasts has been complicated because they require specific growth media and grow very slowly in laboratory culture [27]. Identification of *Malassezia* on skin has been aided by the application of molecular or DNA-based techniques.

Malassezia is among the many mycobiota undergoing laboratory research to investigate whether it is associated with types of disease. These investigations show that the *Malassezia* species causing most skin disease in humans, including the most common cause of dandruff and seborrheic dermatitis, is *M. globosa*, though *M. restricta* is also involved [28]. The hypopigmentation or hyperpigmentation on the trunk of tinea versicolor (pityriasis versicolor) is also due to infection by this fungus. Allergy tests for these fungi are also available.

Dandruff is a skin condition that mainly affects the scalp, with flaking that is sometimes associated with mild itchiness. The dandruff scale is a cluster of corneocytes, which have retained a large degree of cohesion with one another and detach as such from the surface of the stratum corneum. The size and abundance of scales are heterogeneous from one site to another and over time. Parakeratotic cells often make up part of dandruff (Fig. 5.10a). Their numbers are related to the severity of the clinical manifestations, which may also be influenced by seborrhea (Fig. 5.10b).

The characteristics of the epidermal turnover time, detachment and clusters of corneocytes, and scalp condition in the normal scalp, dry scalp, dandruff, seborrheic dermatitis, and scalp psoriasis are summarized as follows:

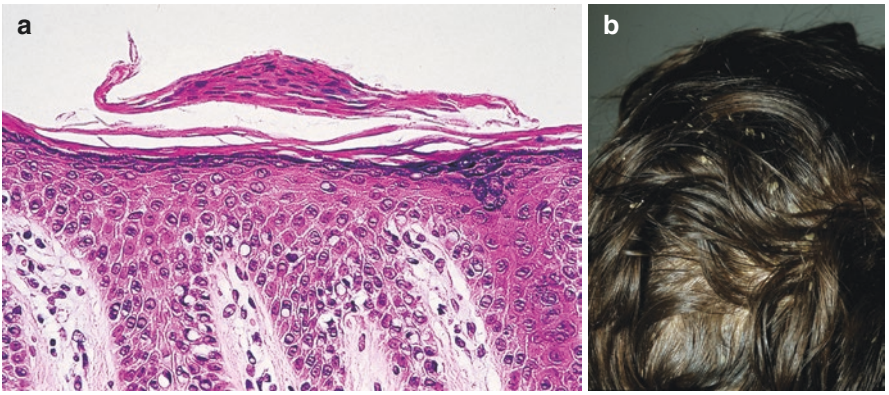


Fig. 5.10 (**a**–**d**) Dandruff: (**a**) histopathology: cluster of parakeratotic corneocytes, (**b**) seborrhea with dandruff, (**c**) scheme of events underlying the pathogenesis of dandruff, and (**d**) targets for management

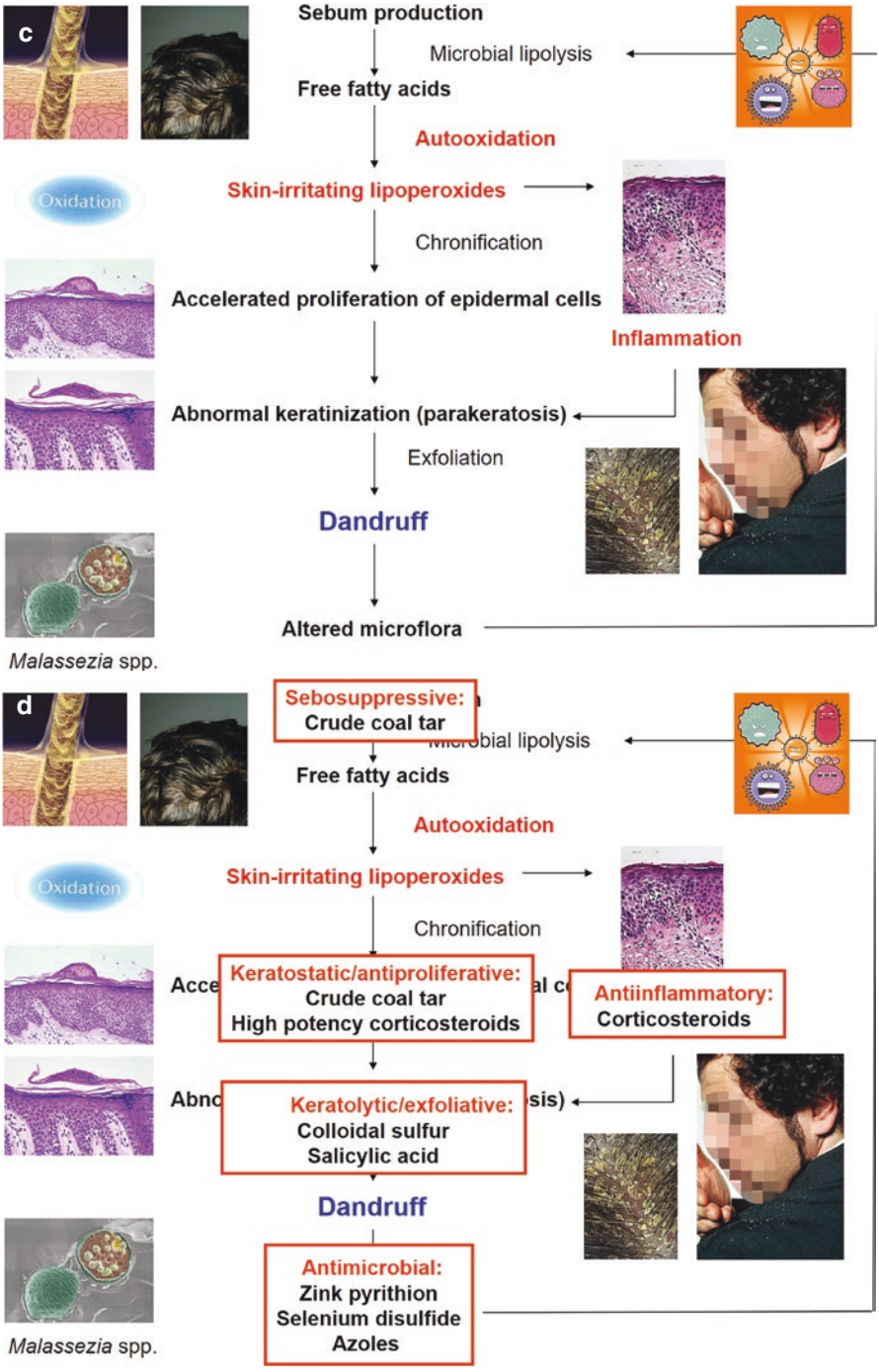
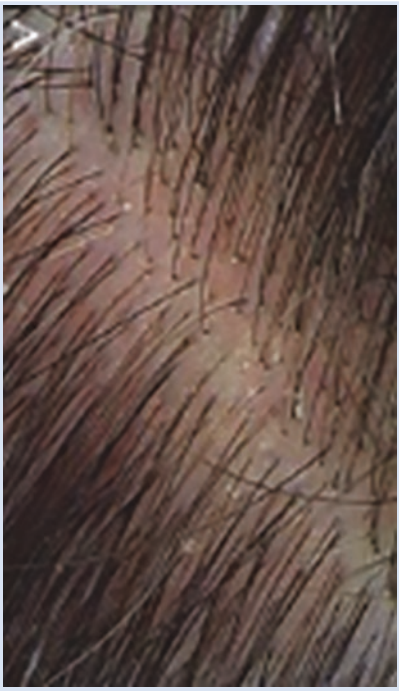
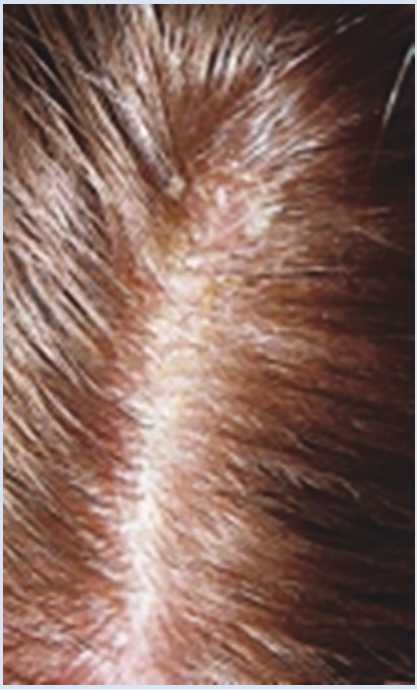
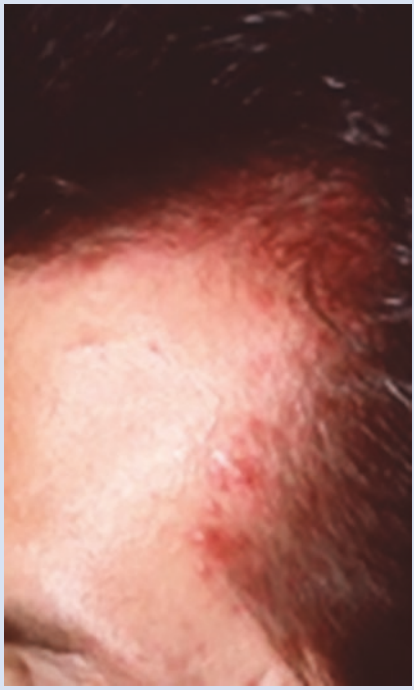


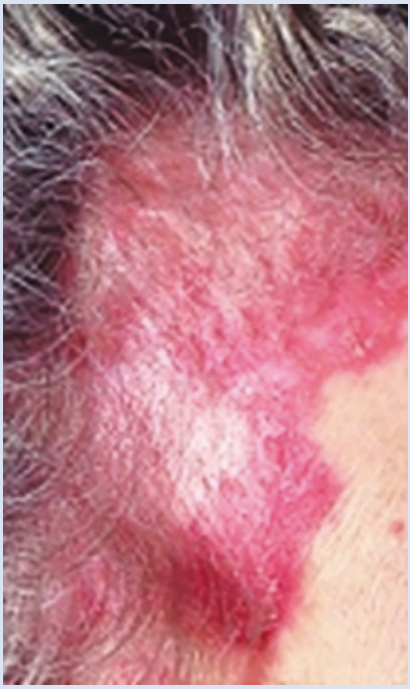
Fig. 5.10 (continued)

	*Normal scalp* Epidermal turnover time: 28–40 days Corneocytes detach as single cells Scalp condition: inconspicuous
	*Dry scalp* Epidermal turnover time: 28–40 days Corneocytes detach in clusters of 10–25 cells Scalp condition: sebostatic

Dandruff
Epidermal turnover time: 7–21 days
Corneocytes detach in clusters of 100–1000 cells
Scalp condition: seborrheic



Seborrheic dermatitis
Epidermal turnover time: 7–21 days
Corneocytes detach in clusters of 100–1000 cells
Scalp condition: seborrheic and erythematous



Scalp psoriasis
Epidermal turnover time: <7 days
Corneocytes detach in clusters of >1000 cells
Scalp condition: erythematous and infiltrated, often reaches 1 cm beyond the hairline

It is now recognized that dandruff in the hair is caused by *Malassezia* yeasts, which break down the sebum fats to produce a new substance, oleic acid, which acts as an irritant in many people. The scheme of events leading to dandruff are summarized in Fig. 5.10c.

Accordingly, management of dandruff aims at targeting the critical steps in its pathogenesis (Fig. 5.10d): sebosuppressive with crude coal tar; keratostatic and antiproliferative with crude coal tar and high-potency glucocorticosteroids; keratolytic and exfoliative with salicylic acid and colloidal sulfur; antimicrobial with selen disulfide, zink pyrithione, ciclopiroxolamin, piroction olamine, ketaconazole, econazole, miconazole, or bifonazole; and anti-inflammatory with low-, medium-, or high-potency glucocorticosteroids depending on the severity.

Seborrheic dermatitis is considered a more severe form of the condition, which includes inflammation of the skin. It represents a chronic recurrent condition characterized by scaling and poorly defined erythematous patches with a predilection for areas rich in sebaceous glands. The scalp is almost invariably affected (Fig. 5.11a); other areas of the skin involved in order of frequency are the face (Fig. 5.11b), chest, and intertriginous areas. Thin arborizing vessels, atypical vessel, and yellowish interfollicular scaling are mainly observed (Fig. 5.11c). Histopathology is characterized in acute lesions by focal, usually mild, spongiosis (Fig. 5.11d), with overlying scale crust containing a few neutrophils (Fig. 5.11e); the crust is often centered on a follicle; the papillary dermis is mildly edematous, blood vessels in superficial vascular plexus are dilated, and there is mild superficial perivascular infiltrate of lymphocytes, histiocytes, and occasional neutrophils, with some

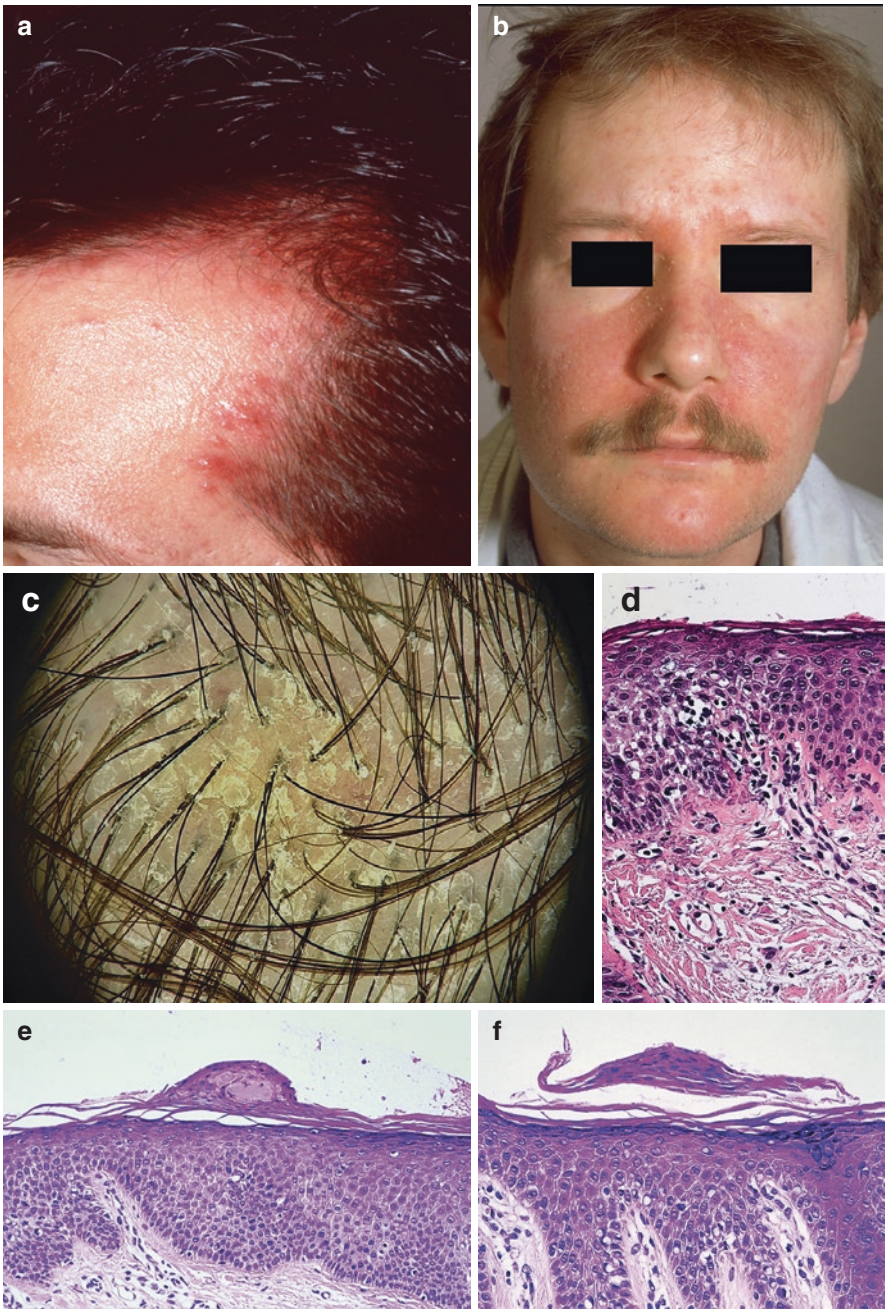


Fig. 5.11 (**a**–**f**) Seborrheic dermatitis (**a**) of the scalp and (**b**) of the face, (**c**) dermoscopy, and (**d**–**f**) histopathology: (**d**) spongiosis with mild exocytosis, (**e**) overlying scale containing neutrophils, (**f**) psoriasiform hyperplasia

exocytosis of inflammatory cells. In subacute lesions, there is also psoriasiform hyperplasia (Fig. 5.11f), initially slight, with mild spongiosis and the other changes already mentioned; numerous yeast-like organisms can usually be found in the surface keratin. Chronic lesions show more pronounced psoriasiform hyperplasia and only minimal spongiosis; sometimes, the differentiation from psoriasis can be difficult, but the presence of scale crusts in a folliculocentric distribution favors seborrheic dermatitis.

The cause of seborrheic dermatitis is understood to involve fungi of the genus *Malassezia*. The inflammatory process is believed to be mediated by fungal metabolites, specifically free fatty acids released from sebaceous triglycerides.

Accordingly, antifungal agents are the mainstay of treatment of seborrheic dermatitis, with a number of well-performed studies proving superiority of ketoconazole and ciclopirox olamine shampoo over placebo for treatment. With respect to the use of topical corticosteroids either as lotion, cream, or foam, there is a consensus that they are useful in the short term, mainly to control erythema and itching, but no data are available regarding whether the combination of topical antifungal agents with topical corticosteroid results in a greater benefit than single-agent therapy.

A typically successful therapy for seborrheic dermatitis of the scalp would be using a 2% ketoconazole or a 1.5% ciclopirox olamine shampoo every other day during the first 2 weeks and thereafter twice weekly, depending on severity, either as monotherapy or in the more severe cases in combination with systemic itraconazole 200 mg daily during the first 7 days of treatment (and thereafter 200 mg every second week), and topical clobetasol propionate 0.05% foam as needed.

Malassezia folliculitis or *Pityrosporum* folliculitis is yet another skin condition caused by *Malassezia* (formerly *Pityrosporum*) yeast. The skin of the upper trunk area including the back, chest, arms, and sometimes the neck is often affected, and this condition is more commonly seen in young to middle-aged adults. Its diagnosis is based on the pruritic papulopustules found in a follicular pattern in these regions (Fig. 5.12a, b) caused by an overgrowth of *Malassezia furfur*, which plugs the follicles. *M. furfur* is lipophilic, requiring fatty acids with carbon chain lengths C11 to C24, like what is present in oily skin to proliferate. The microorganism is part of the normal skin flora but overgrows in certain conditions, particularly in association

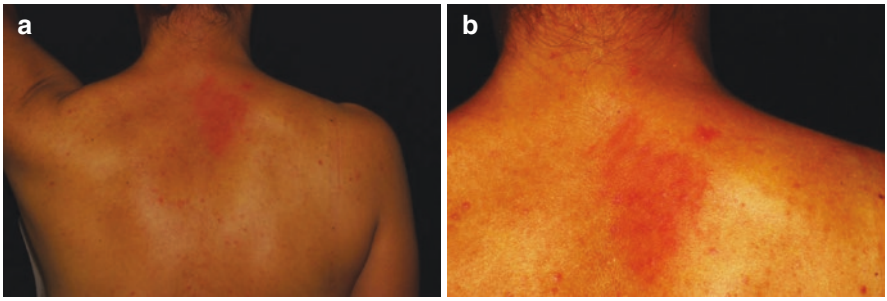


Fig. 5.12 (**a**, **b**) *Malassezia* folliculitis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil)

with oily skin, humidity, or other preexisting dermatologic conditions such as seborrheic dermatitis.

Atopic dermatitis, also known as atopic eczema, is a common, again chronic, relapsing, inflammatory skin disorder that may affect the scalp in a significant manner. The pathogenesis of atopic dermatitis is complex and involves genetics, environmental factors, disrupted permeability of the skin, and immunologic mechanisms.

In infantile eczema (Fig. 5.13), much of the body may be affected, while the typical scalp manifestation is cradle cap. As the children get older, the flector aspects of the extremities are most commonly affected. In adults, the hands and feet are often affected, and a subset of patients suffer of head and neck dermatitis.

The diagnosis of atopic dermatitis is based primarily on the clinical presentation, while skin prick tests, serologic testing, and the atopy patch tests may serve as diagnostic tools. Skin prick tests involve the identification of immediate-type allergic reactions (within 15 min) and serologic testing the detection of allergen-specific IgE. The atopy patch test aims at reproducing delayed-type allergic skin reactions (after 24 to 72 h) to immediate-type allergens, in an effort to determine whether a

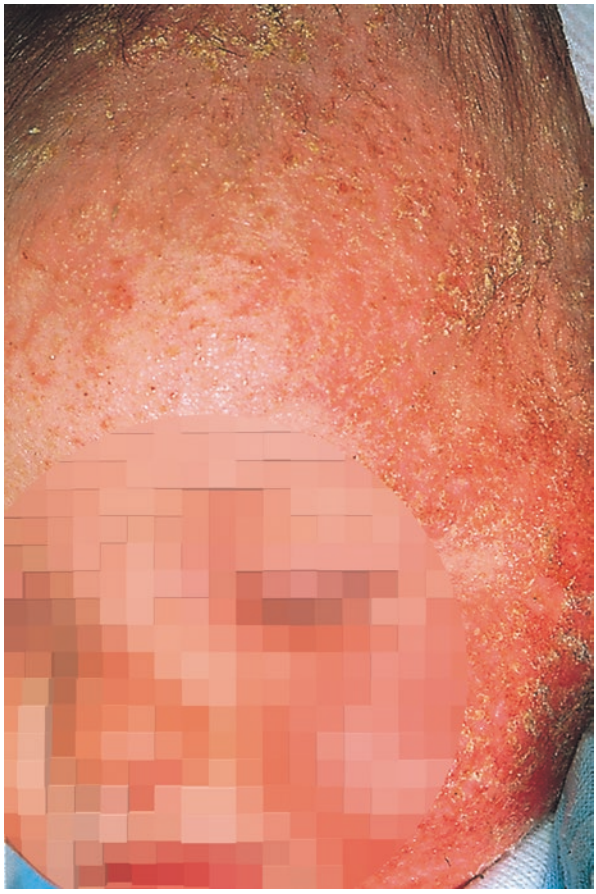


Fig. 5.13 Infantile eczema

specific IgE-mediated allergen is causing the symptoms of the eczematous skin reaction.

A subset of patients with head and neck dermatitis may have a reaction to resident *Malassezia* flora, fueling their condition [29–32]. This reaction is likely related to both humoral- and cell-mediated immunity. Even in the absence of differences in *Malassezia* spp. colonization, patients with head and neck atopic dermatitis are more likely to have positive skin prick test results [33] and *Malassezia*-specific IgE [34, 35], compared to healthy control subjects and to patients with atopy without head and neck dermatitis. However, no clear relationship with atopy patch testing has been found. *Malassezia* allergy may be suspected in patients with atopic disease and:

- Eczema involving the head and neck region
- Exacerbations during adolescence or early adulthood
- Lesions recalcitrant to conventional therapy
- Positive skin prick tests for *Pityrosporum ovale*
- Malassezia-specific IgE

There is literature to suggest that these patients may benefit from a 1- to 2-month course of daily oral itraconazole (200 mg) followed by long-term weekly treatment in combination with regular use of 2% ketoconazole shampoo and 1% ciclopiroxolamine cream [36–40].

Finally, there is ample evidence from data involving collections and characterization of hair samples from various unhealthy scalp conditions to help establish a link between scalp health and hair growth and quality. Most of the published data are epidemiological in nature comparing hair obtained from individuals with dandruff or seborrheic dermatitis, atopic dermatitis, and psoriasis with that from a control group of healthy scalp individuals [41].

The most common manifestation on hair emerging from an unhealthy scalp is an altered cuticle with evidence of surface pitting, roughness, cuticle rigidity, or breakage. In some cases, the impact is manifested as shine reduction. In addition to the physical changes, there are biochemical alterations observed in hair emerging from an unhealthy scalp, with both protein and lipid components affected, most commonly by oxidative damage.

Moreover, a number of observations have found that premature hair loss may be caused by the poor scalp health associated with either dandruff (Fig. 5.14) or seborrheic dermatitis [42–45], indicating that the effect on the preemergent hair fiber may alter the anchoring force of the fiber within the follicle, as evidenced by an increased proportion both of catagen and telogen and of dysplastic anagen hairs (anagen hairs devoid of hair root sheaths) in the trichogram (hair pluck) [46].

Originally, Piérard et al. [47] hypothesized on a microbial-driven inflammatory reaction abutting on the hair follicles and performed a pilot study with 20 males using 0.25% Octopirox leave-on product and demonstrated that the product improved the semi-quantitative self-assessment of hair loss over a 1.5-year

Fig. 5.14 Shedding of tufts of hair within clusters of dandruff

treatment period. Subsequently, Piérard-Franchimont et al. [48] conducted a study to compare the effect of 2% ketoconazole shampoo to that of an unmedicated shampoo used in combination with or without 2% minoxidil therapy for male androgenetic alopecia and found that hair density and size and proportion of anagen follicles were improved almost similarly by both ketoconazole and minoxidil regimens, even in the absence of dandruff. The authors concluded that there may be a significant action of ketoconazole upon the course of androgenetic alopecia and that *Malassezia* spp. play a role in the inflammatory reaction.

Following the original investigations of Piérard et al. and Piérard-Franchimont et al., Berger et al. performed a 6-month, randomized, investigator-blinded, parallel-group clinical study to assess the hair growth benefits of a 1% zinc pyrithione-based shampoo in males between the ages of 18 and 49 years exhibiting Hamilton-Norwood type III vertex or type IV baldness. The efficacy of the 1% zinc pyrithione-based shampoo used daily was compared with that of 5% minoxidil topical solution applied twice daily, a placebo shampoo, and a combination of the 1% zinc pyrithione-based shampoo and the 5% minoxidil topical solution. Hair count results showed a

significant net increase in total visible hair counts for the 1% zinc pyrithione shampoo, the 5% minoxidil topical solution, and the combination treatment groups relative to the placebo shampoo after 9 weeks of treatment [49].

5.3 Molds

A mold is a fungus that grows in the form of multicellular filaments called hyphae in contrast to the yeast that adopt a single-celled growth habit. Molds are a large and taxonomically diverse number of fungal species in which the growth of hyphae results in discoloration and a fuzzy appearance. The network of these tubular branching hyphae, called a mycelium, is considered a single organism. The hyphae are generally transparent, so the mycelium appears like very fine, fluffy white threads. The dusty texture of many molds is caused by profuse production of asexual spores (conidia) formed by differentiation at the ends of hyphae. The mode of formation and shape of these spores are traditionally used to classify molds. Many of these spores are colored, making the fungus much more obvious to the human eye at this stage in its life cycle.

Molds cause biodegradation of natural materials. Some diseases of animals and humans can be caused by certain molds: disease may result from growth of pathogenic molds within the body, the effects of ingested or inhaled toxic compounds (mycotoxins) produced by molds, or allergic sensitivity to mold spores.

Common genera of molds with relevance to human health and disease include *Alternaria*, *Aspergillus*, *Cladosporium*, *Fusarium*, *Mucor*, *Penicillium*, and *Rhizopus.*

Primary cutaneous mold infections are especially caused by *Aspergillus*, *Fusarium*, *Mucor*, and *Rhizopus* spp. These infections may invade deeper tissues and cause disseminated fungal infections in the neutropenic host.

Mold infections involving the scalp have been reported with *Penicillium*, *Aspergillus*, *Mucor*, and *Rhizopus*.

5.3.1 *Penicillium* spp.

Penicillium is a genus of ascomycetous fungi that is part of the mycobiome of many species and is of major importance in the natural environment, in food spoilage, and in food and drug products (penicillin).

Species of *Penicillium* are ubiquitous soil fungi preferring cool and moderate climates, commonly present wherever organic material is available. Saprophytic species of *Penicillium* live mainly on organic biodegradable substances. *Penicillium* species are present in air and dust of indoor environments, such as homes and public buildings.

Penicillin, a drug produced by *P. chrysogenum* (formerly *P. notatum*), was accidentally discovered by Alexander Fleming in 1929 and found to inhibit the growth of Gram-positive bacteria. Returning from holiday on September 3, 1928, Fleming began to sort through petri dishes containing colonies of *Staphylococcus*. He noticed

something unusual on one dish. It was dotted with colonies, except for one area where a blob of mold was growing. The zone immediately around the mold, later identified as *Penicillium notatum*, was clear, as if the mold had secreted something that inhibited bacterial growth. Its potential as an antibiotic was realized in the late 1930s, and Howard Florey and Ernst Chain purified and concentrated the compound. The drug's success in saving soldiers in World War II who had been dying from infected wounds resulted in Fleming, Florey, and Chain jointly winning the Nobel Prize in Medicine in 1945 [50].

Penicillium is rarely reported as an infectious agent in man. This mold is ubiquitous in nature, and its frequent isolation in cultures is routinely ascribed to contamination. Person and Ossi reported a case of possible *Penicillium* tinea capitis in a 3-year-old boy with a 1-month history of patchy occipitoparietal hair loss with loss of luster in the remaining hair and scattered "black dots" and light brown crusts on the scalp. Results of potassium hydroxide examination of epilated hairs were normal; the brownish crusts showed brown, double-walled spores, some of which were clumped. A culture grown on dermatophyte test medium showed *Penicillium* species [51]. Disseminated disease has been reported in severely immunocompromised patients.

Growth of *Penicillium* spp. in culture is rapid. The colony surface at first is white and then becomes very powdery and bluish green with a white border (Fig. 5.15a). Reverse is usually white but may be red or brown.

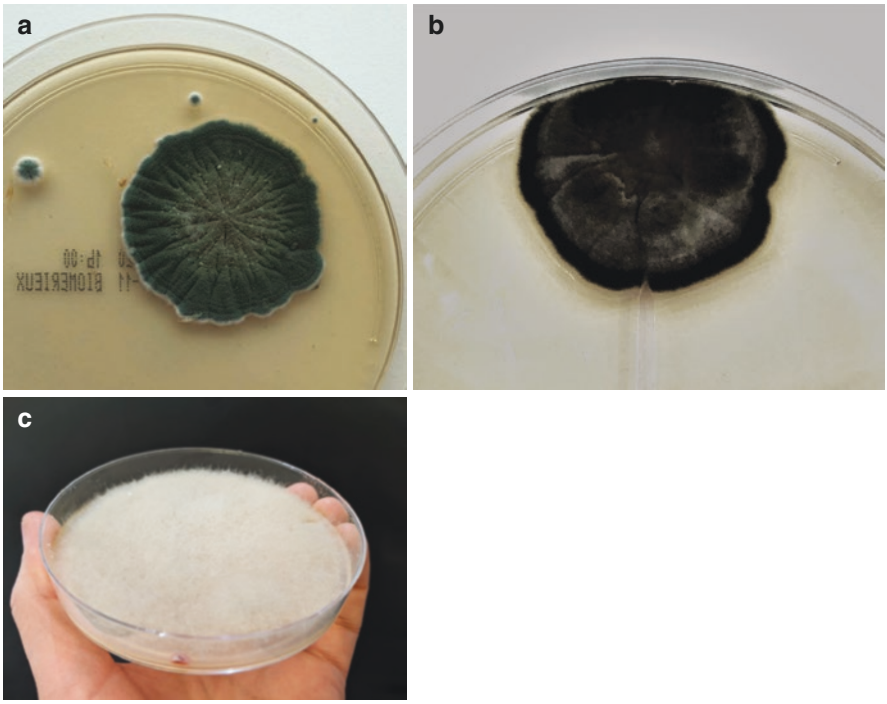


Fig. 5.15 (**a**–**c**) Molds: (**a**) *Penicillium*, (**b**) *Aspergillus*, (**c**) *Mucor*

Guevara-Suarez et al. obtained a total of 118 isolates thought to belong to the genus *Penicillium* based on morphological features obtained from the Fungus Testing Laboratory at the University of Texas Health Science Center in San Antonio (USA). Antifungal susceptibility testing was performed for nine antifungal drugs. The potent in vitro activity of amphotericin B and terbinafine against *Penicillium* species might offer a good therapeutic option for the treatment of infections caused by these fungi [52].

5.3.2 *Aspergillus* spp.

Aspergillosis is a fungal infection of usually the lungs [53] caused by the genus *Aspergillus*, a common mold that is inhaled from ambient air. Most people are thought to inhale thousands of *Aspergillus* spores daily but without effect due to an efficient immune response.

Chronic colonization or infection can cause complications in people with underlying respiratory illnesses, such as asthma [54], cystic fibrosis [55], sarcoidosis [56], tuberculosis, or chronic obstructive pulmonary disease [57]. Most commonly, aspergillosis occurs in the form of chronic pulmonary aspergillosis, aspergilloma, or allergic bronchopulmonary aspergillosis.

Other noninvasive manifestations include fungal sinusitis, otomycosis, keratitis, and onychomycosis. Rarely, it can affect skin.

People who are immunocompromised, such as patients undergoing hematopoietic stem cell transplantation, chemotherapy for leukemia, or AIDS, are at an increased risk for invasive aspergillosis infections. Poorly controlled aspergillosis can disseminate through the blood to cause widespread organ damage. The person may develop kidney failure, liver failure, and breathing difficulties, and death can occur quickly.

Aspergillosis is estimated to affect more than 14 million people worldwide [58] with allergic bronchopulmonary aspergillosis (>4 million), severe asthma with fungal sensitization (>6.5 million), and chronic pulmonary aspergillosis (~3 million), being considerably more prevalent than invasive aspergillosis (>300,000). Other common conditions include *Aspergillus* bronchitis, *Aspergillus* rhinosinusitis (many millions), otitis externa, and *Aspergillus* onychomycosis (10 million).

During the COVID-19 pandemic (2020/2021), COVID-19-associated pulmonary aspergillosis was reported in some people who had been admitted to the hospital and received long-term corticosteroid treatment [59].

Fungal infections from *Aspergillus* spores remain one theory of sickness and untimely death of some early Egyptologists and tomb explorers. Ancient spores which grew on the remains of food offerings and mummies sealed in tombs and chambers may have been blown around and inhaled by the excavators, ultimately linked to the notion of the curse of the pharaohs [60]. Ultimately, the death of Lord Carnarvon (1866–1923), 6 weeks after the opening of Tutankhamun's tomb, resulted in many curse stories in the press, which were fueled further by author Sir Arthur

Conan Doyle's (1859–1930) suggestion that Carnarvon's death had been caused by "elementals" created by Tutankhamun's priests to guard the royal tomb [61].

Aspergillus has been reported in kerion-type scalp mycosis [62], in a non-healing scalp wound [63], scalp necrotizing fasciitis with osteomyelitis of the skull [64], and mycetoma of the scalp [65].

Specifically, Chokoeva et al. identified *Aspergillus niger* as a possible etiopathogenic agent in tinea capitis and suggested that pathogenic molds should be considered as a potential source of infection in some geographic regions, which require rationalization of the former therapeutic conception, regarding the molds' higher antimycotic resistance compared to the dermatophytes. Molds-induced tinea capitis should be also considered in clinically resistant and atypical cases, with further investigations of the antifungal susceptibility of the respective alternative pathogens [66].

The diagnosis of aspergillosis is based on medical history, risk factors, symptoms, physical examination, and lab tests. Depending on the location of the suspected infection, imaging such as a chest X-ray or a CT scan of the lungs or other anatomic sites is performed. Tissue biopsies are needed to provide the evidence for *Aspergillus* infection microscopically or in a fungal culture (Fig. 5.15b). On microscopy, *Aspergillus* species are reliably demonstrated by silver stains, e.g., Gridley stain or Gomori methenamine silver [67]. These give the fungal walls a gray-black color. Finally, a respective blood test can help diagnose invasive aspergillosis early in people who are severely immunocompromised.

The current medical treatments for aggressive invasive aspergillosis include voriconazole and liposomal amphotericin B in combination with surgical debridement as indicated [68]. A growing proportion of infections are resistant to the triazoles [69]. *A. fumigatus*, the most commonly infecting species, is intrinsically resistant to fluconazole [70].

5.3.3 Mucormycosis

Mucormycosis, also known as black fungus, is a serious opportunistic fungal infection, usually seen in debilitated hosts, 70% having diabetes mellitus with persistently high blood sugar levels or diabetic ketoacidosis, but patients with low white cells due to hematologic malignancy or cancer therapy, immunosuppression, extensive burn patients, and severe malnutrition are also at risk. Only 4% of infections occur without an underlying condition.

The infectious agent belongs to the taxonomic class *Zygomycetes*, family *Mucoraceae*. *Rhizopus* (mucormycosis), *Mucor* (zygomcosis), and *Absidia* genera are involved, in decreasing frequency.

During the COVID-19 pandemic, an association between mucormycosis and COVID-19 has been reported. This association is thought to relate to reduced immune function during the course of the illness and may also be related to glucocorticoid therapy for COVID-19. A rise in cases was particularly noted in India.

Symptoms depend on the anatomical site of infection. It most commonly infects the nose, sinuses, eye, and brain, resulting in a runny nose, one-sided facial swelling and pain, headache, fever, blurred vision, proptosis, and tissue necrosis by fungal invasion into the blood vessels resulting in thrombosis and infarction.

It is spread by spores of the respective molds, most often through inhalation, contaminated food, or contamination of open wounds. These fungi are common in soils; decomposing organic matter, such as rotting fruit and vegetables; and animal manure, but usually do not affect people. It is not transmitted between people. The condition tends to progress rapidly and is fatal in about half of sinus cases and almost all cases of the widespread type.

Rhizopus is a genus of common saprophytic fungi on plants and specialized parasites on animals. Some *Rhizopus* species are opportunistic human pathogens that potentially cause fatal disease.

Diagnosis requires identifying the mold in the affected tissue by biopsy and confirming it with a fungal culture and medical imaging to help determine the extent of disease, such as CT scan of the lungs and sinuses.

In culture, *Rhizopus oryzae* is characterized to be a fast-growing fungus where growth under optimal temperatures is fast at 1.6 mm per hour (nearly 0.5 μm per second, enough to be able to directly visualize hyphal elongation in real time under the microscope), covering the surface of the agar. Rapidly growing colonies fade from white to dark during sporulation. The colonies have a dense cottony growth or candy flossy or fairly floss in texture (Fig. 5.15c).

Treatment is generally with amphotericin B and surgical debridement.

Harman et al. reported a rare case of mucormycosis of the scalp: a 54-year-old woman patient presented with a wound in the scalp with purulent discharge. An ulcerated discharging lesion with necrotic hemorrhagic crusts in the left parietal region of the scalp and wheals with fluctuation from this lesion to the left periorbital area was observed. The patient had vision loss in the left eye. Biochemical investigations revealed elevated blood sugar level and urine ketone bodies. In the smears, thick-walled non-septate hyphae were detected, and *Rhizopus* spp. were isolated from culture. Antidiabetic therapy and liposomal amphotericin B were initiated with consecutive improvement of the scalp lesion [71].

Zaman et al. observed a case of pediatric scalp mucormycosis in 9-year-old diabetic girls caused by *Rhizopus oryzae*. She was successfully treated with amphotericin B deoxycholate and wound debridement. At 3 months' follow-up, the patient was stable, although she had lost her vision [72].

Rao et al. reported on deep mycosis of the scalp caused by *Rhizopus oryzae* mimicking kerion in a 5-year-old immunocompetent boy who presented with multiple painful boggy swellings with discharging sinuses on the scalp of 4 months' duration. Purulent discharge from the swelling cultured on Sabouraud's dextrose agar yielded *R. oryzae* species, which was confirmed by molecular analysis by polymerase chain reaction. The child was managed with parenteral liposomal amphotericin B, which helped in clearance of infection [73].

Melsom and Knahgure observed a case of craniofacial *Mucor* infection following assault to the forehead with a spanner. The female diabetic developed periorbital

cellulitis adjacent to the scalp wound, which progressed to a necrotizing fasciitis. This did not respond to treatment. Subsequently the patient developed hemiparesis, with CT imaging showing periorbital and paranasal sinus inflammatory changes, evidence of cavernous sinus invasion, and development of a middle cerebral artery territory infarction. The scalp wound was debrided, and *Mucor* spp. were isolated from the debrided tissue. The patient died shortly afterward despite intravenous amphotericin B. Postmortem examination showed fungal invasion of the right cavernous sinus with *Mucor* spp. and thrombosis of the right internal carotid artery and right cerebral infarction [74].

Invasive fungal infection in burn injury is caused by inoculation of fungal spore from patient skin or respiratory tract or from the caregiver. The risk factors for acquiring fungal infection in burns include age of burns, total burn size, full-thickness burns, inhalational injury, prolonged hospital stay, late surgical excision, open dressing, central venous catheters, antibiotics, steroid treatment, long-term artificial ventilation, fungal wound colonization, hyperglycemic episodes, and other immunosuppressive disorders. Invasive fungal infection with *Absidia corymbifera* is a rare opportunistic infection encountered in patients with burn injury. Moon and Jithendran reported on a case of invasive fungal infection with *A. corymbifera* in an immunocompetent patient who sustained high voltage electrical contact burn of the scalp and presented late after 10 days of injury [75].

In general, burn wound infection is primarily caused by bacteria (70%), followed by fungi (20–25%) and virus (5–10%) [76]. Cutaneous invasive fungal infection is a devastating condition in which delay in diagnosis and treatment may lead to high morbidity and mortality.

5.4 Dimorphic Fungi

Dimorphic fungi are organisms that have the ability to switch between two morphologies during their life cycle: yeast and hyphae. They usually have natural habitat in soil where they grow as a mold, and when fungal propagules are inhaled or inoculated by injury in the susceptible mammalian host, they undergo a complex process and convert into pathogenic yeasts, causing deep mycoses that are usually endemic to specific geographical areas. The ability to convert to the yeast form is essential for this class of fungal agents to produce disease. Temperature change is one key stimulus that triggers the phase transition from mold (25°) to yeast (37°) (in medical mycology, the memory aid "Mold in the Cold, Yeast in the Heat" helps students remember that among human pathogens, dimorphism largely reflects temperature) (Fig. 5.16a). This morphological transition is crucial to pathogenicity.

After the AIDS pandemic and with the increase in number of patients undergoing immunosuppressive therapy due to cancer, for organ transplantation, and in autoimmune diseases, the incidence of endemic mycosis has been progressively rising.

Several species of dimorphic fungi are important pathogens in humans, including *Sporothrix schenckii*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*,

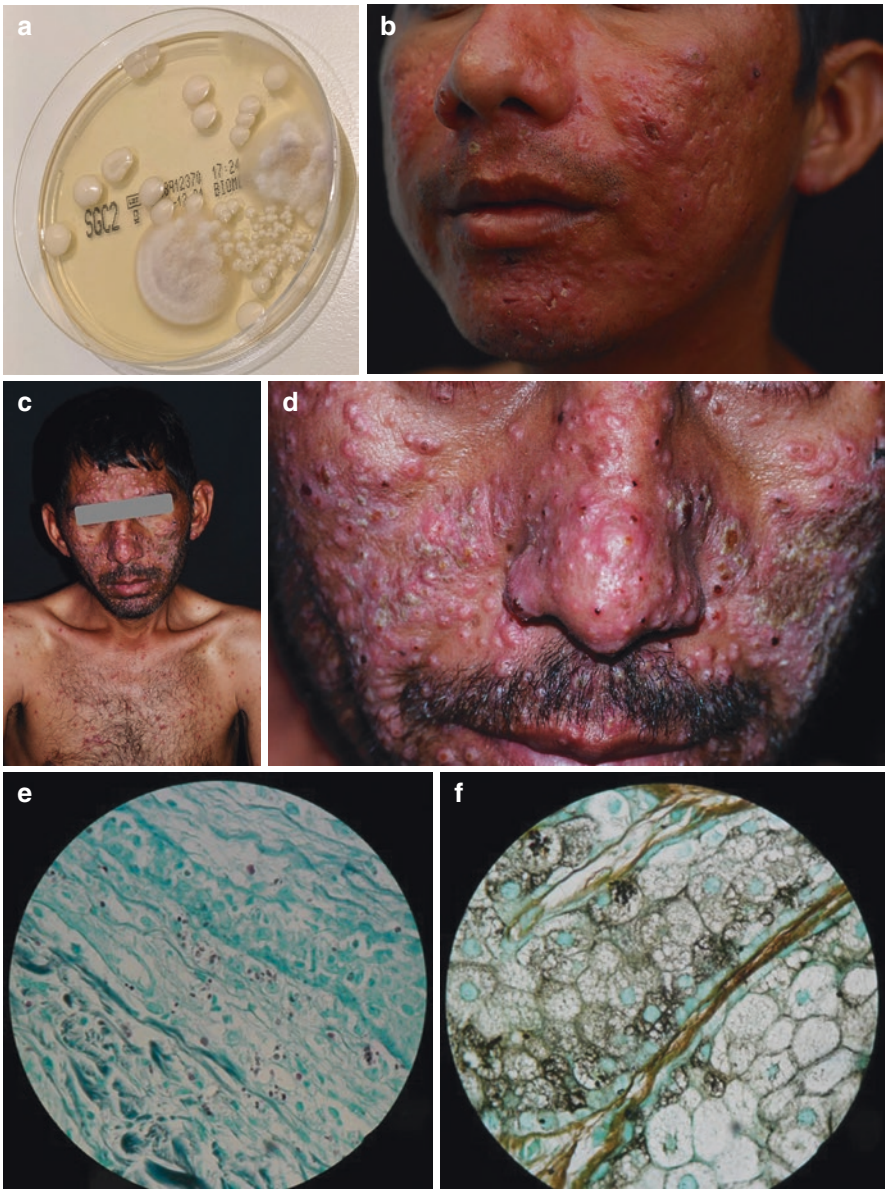


Fig. 5.16 (**a**–**f**) Dimorphic fungi: (**a**) Two morphologies of *Candida albicans* on Sabouraud medium, mold and yeast. (**b**–**f**) Disseminated histoplasmosis (courtesy of Prof. Fábio Francesconi, Federal University of Amazonas, Brazil): (**b**) acneiform, (**c**, **d**) molluscum contagiosum-like in a patient with AIDS (courtesy of Prof Sinesio Talhari, Department of Infectious Diseases, Amazonas Foundation of Tropical Medicine, Brazil), (**e**, **f**) methenamine silver stain showing histopathologic changes of histoplasmosis. Note the presence of typical yeast cells, some of which are undergoing replication by budding

Coccidioides immitis, *Paracoccidioides brasiliensis*, and *Candida albicans*. Some diseases caused by fungi are:

- Sporotrichosis
- Blastomycosis
- Histoplasmosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Candidiasis

Of these, scalp involvement has been observed in blastomycosis [77], histoplasmosis [78], coccidioidomycosis [79], paracoccidioidomycosis [80], and candidiasis [24].

Specifically, disseminated candidiasis in intravenous heroin abusers with skin lesions confided to the scalp and other hair-bearing areas, such as the beard, seems to represent a distinctive clinical presentation. Histological examination of scalp biopsy specimens shows infiltration of hair follicles with chronic inflammatory cells and *C. albicans*. Pseudohyphae of *C. albicans* are also identified in and around hair shafts [19].

Although rare, the incidence of scalp involvement is an alert to include dimorphic fungi as a differential diagnosis of lesions on the scalp, particularly in the respective endemic areas.

Blastomycosis is endemic to the eastern United States, especially the Ohio and Mississippi River valleys, the Great Lakes, and the St. Lawrence River. It is also endemic to some parts of Canada, including Quebec, Ontario, and Manitoba.

H. capsulatum is found throughout the world. It is endemic in certain areas of the United States, particularly in States bordering the Ohio River valley and the Lower Mississippi River. It is also common in caves in Southern and East Africa. In Canada, the St. Lawrence River Valley is the site of most frequent infections. A review of reported cases in 2018 showed disease presence throughout Southeast Asia. In India, the Gangetic West Bengal is the site of most frequent infections. The humidity and acidity patterns of soil are associated with endemicity. Bird and bat droppings in soil promote the growth of *Histoplasma*. Contact with such soil aerosolizes the microconidia, which can infect humans. It manifests by the presence of fever as the only symptom in most individuals. The disease may present as self-limited pneumonia or as a hematogenous widespread fungal infection with a potentially fatal outcome in elderly individuals and people with compromised T-cell mediated immunity. If symptoms of histoplasmosis infection occur, they start within 3 to 17 days after exposure; the typical time is 12–14 days. Most affected individuals have clinically silent manifestations and show no apparent ill effects. The acute phase of histoplasmosis is characterized by nonspecific respiratory symptoms, often cough or flu-like. Chest X-ray findings are normal in 40–70% of cases. Chronic histoplasmosis cases can resemble tuberculosis. In fact, while *Histoplasma* was

discovered in 1905, only in the 1930s was it discovered to be a widespread infection. Before then, many cases were mistakenly attributed to tuberculosis and patients admitted to tuberculosis sanatoria, where some contracted tuberculosis. Disseminated histoplasmosis affects multiple organ systems and is fatal unless treated. Severe infections can cause hepatosplenomegaly, lymphadenopathy, and adrenal enlargement. Cutaneous manifestations of disseminated disease are diverse and often present as a nondescript rash with systemic complaints. Disseminated histoplasmosis is a relatively common and AIDS-defining illness, occurring in almost 4% of patients living in endemic areas where it may be the first clinical expression of the HIV infection. A broad spectrum of clinical skin lesions associated with *Histoplasma capsulatum* infection have been described in AIDS patients, such as erythematous macules, papules, nodules, and pustules, herpetic, acneiform (Fig. 5.16b), erythema multiforme-like, molluscum contagiosum-like (Fig. 5.16c, d), vasculitic, and exfoliative forms.

Kucharski et al. [81] reported a case of disseminated cutaneous histoplasmosis in a 33-year-old male homosexual patient and intravenous drug user. The patient had been diagnosed with HIV infection 5 years earlier. Although in apparently good health, he had developed erythematous papules and pustules in the skin of the scalp, face, back, thighs, abdomen, palms, and soles. He was placed on antiretroviral therapy, fluconazole, for mucosal candidiasis, trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, and antibiotics for the skin pustules. The skin lesions improved remarkably within 14 days. He was discharged and soon lost to follow-up. After his discharge, skin biopsy and fungal culture results revealed *H. capsulatum*. He was seen again 1 year later. The interim history revealed that he had taken fluconazole 100 mg/day for 1 month and fluconazole 150 mg/week for 7 months. He had not continued antiretroviral therapy, nor taken other antifungal drugs. The clinical evolution of the disease was exceptional in that there was disappearance of all the skin lesions attributed to histoplasmosis with fluconazole, although itraconazole is the drug of choice for histoplasmosis.

Régnier-Rosencher et al. [78] report on an imported case of *Histoplasma capsulatum* var. *duboisii* (*H. duboisii*) infection in a white French woman revealed by cutaneous lesions of the scalp, 18 years after her last stay in West and Central Africa. Asymptomatic bilateral pulmonary infiltrates were discovered on thoracic computed tomography. Skin biopsy allowed the positive diagnosis showing the typical yeast morphology (Fig. 5.16e,f), and culture of biopsy specimens was positive for *H. capsulatum*. In the absence of criteria of severity, the patient was treated for 1 year with oral itraconazole 400 mg/day. The outcome was favorable, and skin and pulmonary lesions resolved slowly. The follow-up is 5 years without relapse after the end of treatment. This case illustrates the possibility of late occurrence of *H. duboisii* infection, many years after exposure, and the major importance of asking any patient for travelling or residency in tropical countries.

Finally, Corti et al. [82] reported on a peculiar presentation of disseminated histoplasmosis in a patient with AIDS, the rupioid lesion. The term rupioid has been used to describe well-demarcated, cone-shaped plaques with thick, dark, lamellate, and adherent crusts on the skin that somewhat resemble oyster or limpet shells.

Rupioid manifestations have been clinically observed in a variety of conditions, including:

- Disseminated histoplasmosis
- Keratotic scabies
- Secondary syphilis
- Rupioid psoriasis
- Photosensitive skin lesions in association with aminoaciduria

Therefore, to diagnose the underlying infectious or inflammatory disease beneath the thick crusts, skin biopsy and a blood test for syphilis are recommended [83].

Coccidioidomycosis is a common cause of community-acquired pneumonia in the endemic areas of the United States. Coccidioidomycosis is endemic to the Western Hemisphere between 40°N and 40°S. The ecological niches are characterized by hot summers and mild winters with an annual rainfall of 10–50 cm. The species are found in alkaline sandy soil, typically 10–30 cm below the surface. In harmony with the mycelium life cycle, incidence increases with periods of dryness after a rainy season. This phenomenon, termed "grow and blow," refers to growth of the fungus in wet weather, producing spores, which are spread by the wind during the succeeding dry weather. In the United States, *C. immitis* is endemic to southern and central California with the highest presence in the San Joaquin Valley. *Coccidioides posadasii* is most prevalent in Arizona, although it can be found in a wider region spanning from Utah, New Mexico, Texas, and Nevada.

Paracoccidioidomycosis, also known as South American blastomycosis, is endemic to Central and South America and is considered a type of neglected tropical disease while causing around 200 deaths per year alone in Brazil.

5.5 Piedra

Piedra is a hair disease caused by a fungus, which causes formation of nodules on the hair shaft. Piedra is the Spanish word for stone. Piedra appears as minute stones that attach to the hair shaft and may group to form clusters. Types include white piedra and black piedra.

Since piedra is a superficial fungal infection and is restricted to the stratum corneum, it usually causes no inflammation.

5.5.1 White Piedra

White Piedra is a superficial mycosis of the hair caused by several species of fungi in the genus *Trichosporon* and characterized by white-to-tan gelatinous, pearly nodules surrounding the hair shaft (Fig. 5.17a–d). These nodules are typically found in

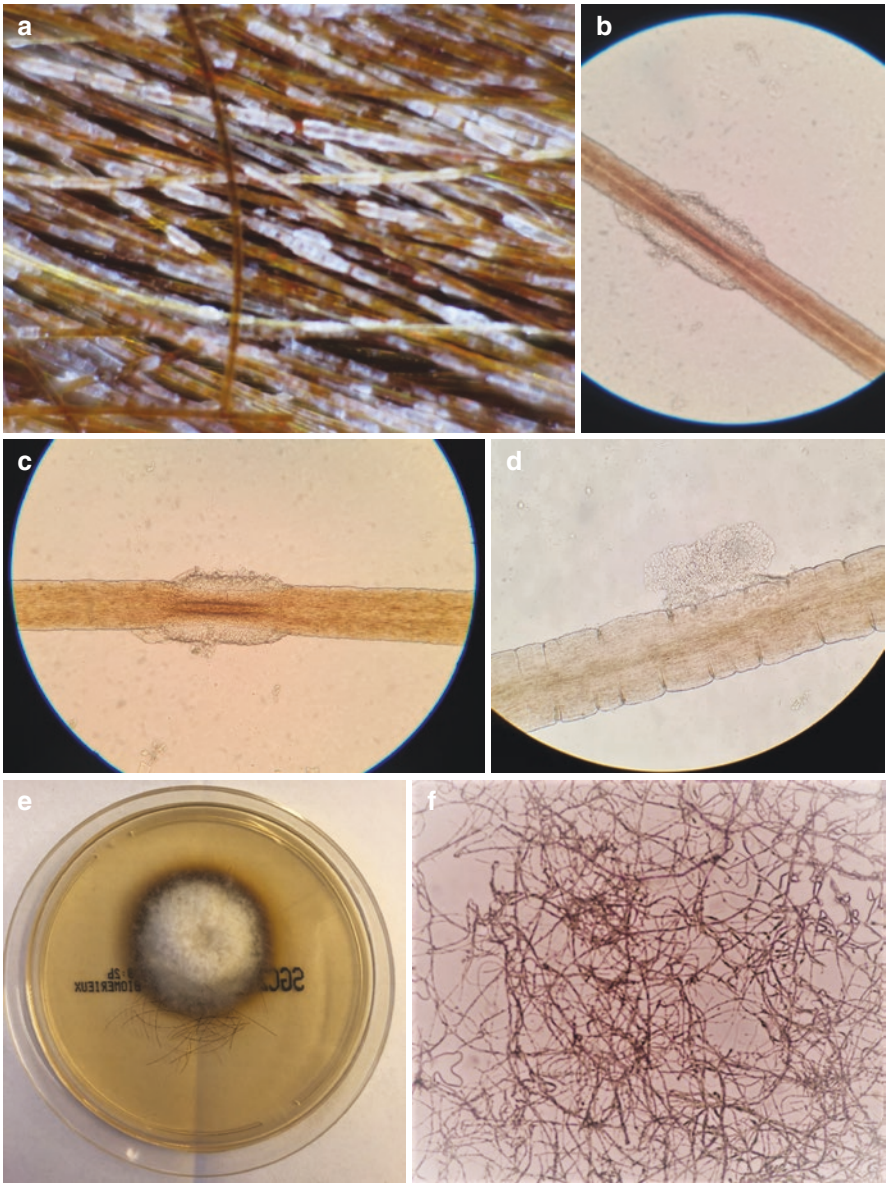


Fig. 5.17 (**a**–**f**) White piedra (*Trichosporon* spp.): (**a**–**d**) white-to-tan gelatinous, pearly nodules surrounding the hair shaft. (**e**) Colony morphology: yeast-like, at first cream colored, moist, and soft. The surface becomes irregularly wrinkled, rather powdery and crumb-like, and the color often darkens to yellowish gray. (**f**) Microscopic morphology: true hyphae and pseudohyphae with blastoconidia singly or in short chains

facial hair and body hair, for example, in mustaches and beards, on eyelashes and eyebrows, and in armpit and pubic hair. The nodules are about 1 mm or greater in diameter and are fairly easy to remove. However, removal may cause the affected hair shafts to split or break.

Trichosporon ovoides is likely the cause of white piedra of the scalp hair, while *Trichosporon inkin* is mainly associated with white piedra of the pubic hair [84]. The obsolete name *Trichosporon beigelii* was formerly applied to all or any of these species.

The spread of white piedra directly from person to person is uncommon. White piedra is more common in the temperate and semitropical climates of South America, Africa, Europe, the Middle East, Southeast Asia, India, Japan, and southeastern United States. After a person is exposed, the fungus needs the right conditions to survive and colonize human hair. Practices that can lead to colonization and result in white piedra infection include:

- Infrequent bathing or poor personal hygiene
- Frequent use of oil applications to the hair
- Irregular combing habits or matted hair
- Covering wet hair with a veil or turban

The most common complication of white piedra is brittle hair. People who are immunosuppressed, have HIV, or are undergoing chemotherapy can have pruritic or necrotic nodules or papules. These can cause intense itching and discomfort.

Much more serious opportunistic infections, collectively called trichosporonosis, have also been reported in immunocompromised individuals [85]. *Trichosporon asahii* is the most common isolate in these cases, followed by *Trichosporon mucoides*. The relative resistance of these organisms to amphotericin B is important to note, and azole-based treatment regimens should be considered the first-line treatment.

The rate of growth of *Trichosporon* spp. in culture is moderately rapid, with maturity in 5–7 days. Colony morphology is yeast-like, at first cream colored, moist, and soft. The surface becomes irregularly wrinkled, rather powdery and crumb-like, and the color often darkens to yellowish gray (Fig. 5.17e). On cornmeal-Tween 80 agar at 25 °C for 72 h, true hyphae and pseudohyphae with blastoconidia singly or in short chains are seen (Fig. 5.17f).

The preferred treatment of white piedra is having the affected area shaved. Medicated shampoos and lotions, such as 1% clotrimazole, 2% miconazole, 2% ketoconazole shampoo or lotion, ciclopirox, or 2% selenium sulfide, may be effective when shaving is not an option for cosmetic, personal, or cultural reasons.

Topical medications do not work for some individuals. In these cases, oral itraconazole 100 mg twice a day after a meal, with a citrus drink for 1 to 2 weeks, can be prescribed to treat persistent white piedra [86].

White piedra of the genitals often recurs, so combining shaving with a short course of a topical antifungal is often necessary for a complete cure.

The fungus may remain in clothing and bedding. A person should throw infected underwear away and disinfect other garments, linen, and towels to help prevent reinfection.

Following good personal hygiene and hair care practices can help prevent future recurrences of white piedra.

5.5.2 Black Piedra

Black piedra is a superficial mycosis of the hair caused by *Piedraia hortae*, which is characterized by the formation of black nodules of less than 1 mm size on the hair of the scalp, moustache, or pubic hair (Fig. 5.18a). The nodules are hard and gritty, which produces a metallic sound when the hair is combed. The nodules colonize the hair shaft, which causes progressive weakness of the hair and leads to breakage of the hair in severe cases.

Hairs with black piedra isolated from Brazilian Indians were investigated by studying serial sections with light and transmission electron microscopy. *P. hortae* showed strong keratolytic activity; it was able to destroy both the cuticle and the hair cortex [87].

In histological sections or 10% potassium hydroxide (KOH) mounts, the nodules are observed to be made up of closely packed brown hyphae held in a mass by a viscous or cement-like substance (Fig. 5.18b–c). The cementing extracellular material that holds the nodule together is probably the main factor responsible for preserving the fungus against environmental attack and desiccation. Moreover, this compact organization can also impair successful treatment, which may explain why an untreated black piedra may run a very chronic course.

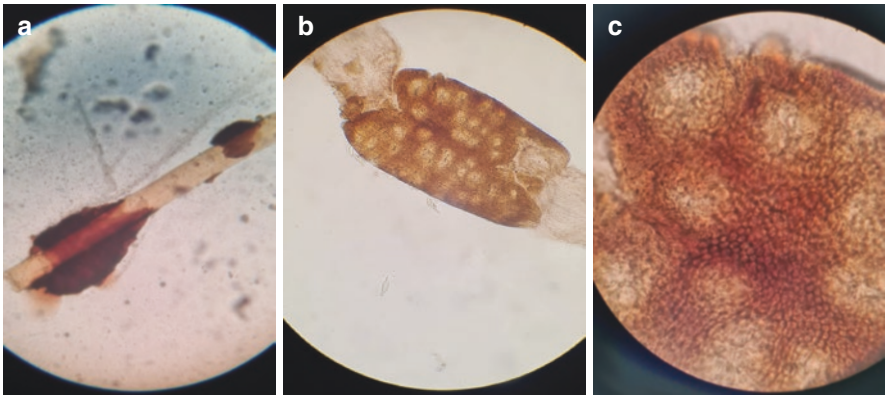


Fig. 5.18 (**a**–**c**) Black Piedra (*Piedraia hortae*) (courtesy of Elisabeth Maria Heins, Lusiada Foundation, Santos, Brazil)

Table 5.3 Black piedra. Treatment plan (from [89])

• Shaving the head
• 2% ketoconazole or 2% miconazole shampoo or 1% to 1.5% ciclopirox shampoo applied once to twice a week for 3 to 4 weeks
• Oral terbinafine 250 mg once daily for 6 weeks
• Oral itraconazole 100 mg twice a day after a meal, with a citrus drink for 1 to 2 weeks
• Counseling on the maintenance of good scalp hygiene, avoidance of sharing combs, etc.

Black piedra is usually seen in tropical regions. The source of the infection is usually in soils, while poor hygiene, long hair, cultural use of veils, and the application of plant oils to wet hair favor the growth of the infection.

The exact mode of spread of piedra is not clear. The use of an infected comb or sharing of pillows and bedsheets may be the possible factors for transmission. There are also reports of sexual transmission.

In culture on Sabouraud dextrose agar medium at room temperature, *P. hortae* shows a smooth greenish-black colony with a raised and cerebriform center. The reverse side of the colonies is blackish.

Piedra is usually treated with cutting or shaving of the hair, if culturally appropriate and with patient's willful consent, followed by the application of topical antifungal agents, such as 2% ketoconazole or 2% miconazole shampoo applied once a week for 3 weeks. 0.77% ciclopirox lotion or 1% to 1.5% shampoo has also been used successfully. Topical keratolytics such as 1% salicylic acid may also be added in cases nonresponsive to monotherapy with antifungal shampoos.

Oral terbinafine has been used successfully in black piedra resistant to topical treatment. A course of 250 mg of oral terbinafine once daily for 6 weeks was found to be effective [88].

Family members should avoid sharing personal care items with the infected individual.

The treatment plan of black piedra is summarized in Table 5.3.

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