Medical Mycology July 2012, **50,** 449–457

informa
healthcare

Review Article

Majocchi's granuloma: a symptom complex caused by fungal pathogens

MACIT İLKIT*, MURAT DURDU† & MEHMET KARAKAŞ‡

**Division of Mycology, Department of Microbiology, ‡Department of Dermatology, Faculty of Medicine, University of Çukurova, Adana, and †Department of Dermatology, Faculty of Medicine, Başkent University Adana Hospital, Adana, Turkey*

Majocchi's granuloma (MG) is a well-recognized but uncommon infection of dermal and subcutaneous tissues that is caused by mold fungi. Although primarily caused by keratinophilic dermatophytes such as anthropophilic *Trichophyton rubrum*, species from the *Aspergillus* and *Phoma* genera have been occasionally detected as etiologic agents of MG. In both healthy individuals and immunocompromised hosts, MG often presents as nodules, plaques, and papules on areas that are prone to trauma. Although MG generally appears on the upper and lower extremities (forearms, hands, legs, or ankles), it occasionally appears on the scalp and face. The clinical, mycologic, and/or cytologic diagnosis should be confirmed by the demonstration of perifollicular granulomatous inflammation by histologic examination. This review focuses on the clinical presentation, pathogenesis, laboratory diagnostic methods (including the Tzanck smear test), etiologic agents, histopathologic characteristics, and therapeutic approaches to the treatment of MG.

Keywords dermatophytes, immunodeficiency, tinea pedis, transplantation, *Trichophyton rubrum*, Tzanck smear

Introduction

Dermatophytic fungi compose three anamorphic (asexual, conidial, or imperfect) genera: *Epidermophyton*, *Trichophyton,* and *Microsporum*. Each genus includes several recognized species. These fungi are keratinophilic and colonize or infect the superficial keratinized tissues (the skin, nails, and hair) of humans and animals. The organisms are usually restricted to the non-living cornified layer of the epidermis and do not invade beyond the epidermis. In an immunocompetent host, these fungi are usually unable to penetrate into viable tissues [1]. There are four well-described forms of invasive dermatophytic infections: (i) Majocchi's granuloma (MG), which is also known as nodular granulomatous perifolliculitis; (ii) deeper dermatophytosis; (iii) disseminated dermatophytosis; and (iv) mycetoma and pseudomycetoma caused by dermatophytes [2–5]. MG was first described in 1883 by Professor Domenico Majocchi (1849–1929) as an intracutaneous or subcutaneous granulomatous inflammation that arose as a result of invasion by a dermatophytic fungus (*T. tonsurans*); he termed the condition '*Granuloma tricofitico*' [2].

This review provides information regarding the different clinical presentations and underlying mechanisms of MG; additionally, accurate diagnostic and management strategies for microbiologists, dermatologists, and pathologists are discussed. For this review, PubMed (Medline) and Google Scholar were searched for clinical and mycologic studies published in English (prior to July 2011) using the key words 'Majocchi's granuloma', 'trichophytic granuloma', and 'dermatophytic granuloma'. The reports retrieved within these search criteria were reviewed for inclusion in the study. However, papers concerning other forms of invasive dermatophytic infections, such as deeper or disseminated dermatophytosis, mycetoma, and pseudomycetoma, were excluded.

Received 30 November 2011; Received in final revised form 6 February 2012; Accepted 21 February 2012

Correspondence: Macit İlkit, Division of Mycology, Department of Microbiology, Faculty of Medicine, University of Çukurova, Adana, 01330, Turkey. Tel.: +90 532 286 00 99; Fax: +90 322 457 30 72; E-mail: milkit@cu.edu.tr

DOI: 10.3109/13693786.2012.669503

MG: an overview

MG is a fungal disease that may result from a modified local and/or systemic response or a damaged skin barrier [6–8]. Dermatophytic MG is characterized by the presence of inflammatory papular, pustular, or nodular lesions, usually on the limbs [7]. Briefly, it is a folliculitic and perifolliculitic dermatophyte infection of the dermis [9,10]. There are two forms of MG: (i) the small, perifollicular papular form, which is a localized dermal infection that usually occurs in healthy individuals (Fig. 1a) and (ii) the form featuring deep subcutaneous plaques or nodular lesions that occur in immunosuppressed hosts [8–13].

The superficial perifollicular form occurs predominately on the legs of otherwise healthy young women who repeatedly shave their legs and develop hair follicle occlusions that directly or indirectly disrupt the follicle and allow for passive introduction of the organism into the dermis. Keratin and/or necrotic material can also be introduced into the dermis with the infectious organism [9,14–17]. MG of the beard may have a similar etiology. Razor trauma may result in introduction of the infectious organism beneath the skin [18]. Because keratinophilic dermatophytes digest keratin, the introduction of keratin into the dermis may act as a medium for continued growth [3].

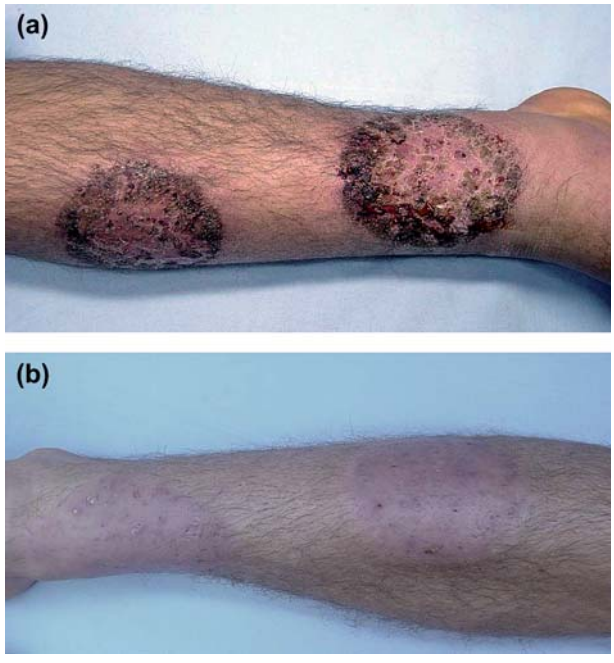

Fig. 1 (a) A 46-year-old immunocompetent man diagnosed with MG with well-demarcated, non-tender, indurated erythematous plaques, pustules, and crusts on the right shin; the lesion had been present for 4 weeks at the time of the photo. (b) Lesions were completely improved with the use of oral terbinafine (250 mg/day) and topical terbinafine cream for 4 weeks.

Firm or fluctuant subcutaneous nodules or abscesses represent a second form of MG that is generally observed in immunosuppressed hosts. Nodules may develop in any hair-bearing part of the body but are most often observed on the forearms, hands, and legs of infected individuals. Involvement of the scalp and face is rarely observed. Lesions start as solitary or multiple well-circumscribed perifollicular papulopustules and nodules with or without background erythema and scaling. In rare circumstances, the lesions may have keloidal features [7,8,10,19,20].

Clinical manifestations

In this study, 79 (48 men, 31 women) cases of MG were reviewed (Table 1) [7–10,12,13,17,19–49]. The mean patient age was 42 years (range, 3–87 years). The mean duration of the lesions prior to diagnosis was 10 months (range, 1 week–96 months). In the related literature, most cases with MG (62%) were immunocompetent patients. In the patient cohort that was reviewed, dermatophytic MG was characterized by inflammatory nodular (60.7%), papular (17.7%), or pustular (16.4%) lesions that generally occurred on the limbs (72%). Discrete or grouped papules (0.3–0.5 cm in size) and nodules (0.5–2 cm in size) can occur on the more active border of the erythematous plaques or alone; additionally, they can rarely be keloidal or verrucous in nature. The application of pressure does not usually cause the lesions to extrude pus. Unlike kerions, MG lesions do not suppurate until late in their course, unless secondary impetigo occurs. Pustules (16.4%) and crusts (4.1%) are observed on the erythematous plaques. Red-purple or occasionally brown papular and nodular lesions may resolve spontaneously without cutaneous scarring; however, lesions may result in eventual atrophic and hypertrophic scar formation [7,50]. The features of cellulitis, such as indurated plaques without papules, nodules, or pustules, are observed in 5.4% of all cases. Although subjective complaints are usually not reported, pruritus (10.9%) and slight tenderness following the application of pressure (9.5%) have been observed. Vulvar swelling was reported in one case [30]. MG may have a variable clinical presentation, such as abscess formation, especially when occurring in an immunodeficient host [10,16]. It was also reported that MG lesions on the right ankle of a patient became worse during pregnancy [9].

Importantly, our review of the literature found that nodular lesions were reported in 65.3% of MG cases in healthy individuals, 58.1% of which were nodular lesions that were not associated with papular lesions. Nodular lesions were detected in 53.3% and 65.3% of cases in immunosuppressed hosts and healthy individuals, respectively. For papular lesions, incidence rates of 23.3% and 14.3% were reported in immunosuppressed hosts and healthy individuals,

Table 1 Clinical characteristics of Majocchi's granuloma patients reviewed from the related literature.

	Immunocompetent cases	Immunosuppressed cases
Number of cases	49	30
Male/Female	24/25	24/6
The mean age (range)	40 (3–87)	48 (20–70)
Mean duration of lesions	13 months	6 months
Localizations		
Lower extremities	22	12
Upper extremities	17	8
Trunk	2	1
Scalp	1	–
Face	4	1
Genital region	2	3
Multiple anatomic localization	1	5
Type of lesion		
Papule	7	7
Nodule	32	16
Plaque	16	13
Pustule	8	5
Abscess	–	1
Associated diseases		
Solid organ transplant recipients	–	15
AIDS	–	1
Iatrogenic Cushing syndrome	–	1
CREST syndrome	–	1
Systemic lupus erythematosus	–	1
Rheumatoid arthritis	–	1
Chronic lymphocytic leukemia	–	2
Lymphoma	–	3
Behçet's disease	–	1
Leucocytosis	–	1
Chronic obstructive lung disease	–	1
Use of topical steroid	9	1

respectively. Lesions were most commonly located on the lower extremities (43.1%) with 24% of the lesions occurring on only one leg. Only two (10.5%) cases involving the leg were treated with immunosuppressive therapy, whereas leg involvement alone was reported in 34.2% of MG cases in healthy individuals. In immunocompetent patients (62%), the second most common area of localization was the upper extremities (34.7%), particularly the forearm (12.6%) and the back of the hand (12.6%). In immunosuppressed hosts, lesions most commonly occurred on the upper (40%) and lower (26.6%) extremities. Other locations of MG lesions included the face (6.8%), groin and gluteal region (4.1%), trunk (4.1%), ear (2.7%), vulva (1.3%), and scrotum (1.3%).

Only the scalp was affected in one (1.2%) adult case of MG [22]. Additionally, scalp involvement was reported in two of six cases with lesions in multiple anatomic areas. Among cases with multiple sites of involvement, five occurred in immunodeficient patients. Face-only involvement was reported in five (6.3%) cases. The first case was a patient with chronic obstructive lung disease who received oral corticosteroid treatment, and the second case was a patient without any underlying medical problems who had a lesion on the jaw [8]. The remaining face-only cases involved a 40-year-old man with alcohol-induced liver disease [20], an immunocompetent 53-year-old man who developed MG caused by *T. tonsurans* on the lower part of his right ear that subsequently spread to the right cheek [31], and an immunocompetent woman who used clothes to hide her face [37]. Additionally, two cases with facial involvement were reported in cases with lesions in multiple anatomic sites [17,21].

MG of the genital organs only, an unusual presentation, has been reported in only two case reports to date [30,36]. First, Chang *et al*. [30] reported a case of MG caused by *T. mentagrophytes* on the vulva of a 23-year-old woman with chronic eczematous disease. The patient had used topical steroids for approximately five years. Her dog was described as a possible source of the infection. Second, Cho *et al*. [36] observed a case of the superficial perifollicular form of MG that was caused by *T. rubrum* in a 66-year-old male; the lesions were located on the scrotal skin of an otherwise healthy man with tinea cruris. The involvement of the groin and gluteal region was present in three (3.8%) individuals who used immunosuppressive therapy after solid organ transplantation (SOT) [12,21,33].

Source of infection

MG occurs when a long-standing superficial fungal infection (e.g., dermatophytosis of the buttock, foot, or toenail) progressively disseminates into the subcutaneous tissues as a complication of the long-term use of potent topical corticosteroids, chemotherapeutic agents, or systemic immunosuppression [7,8,10,16,21,42,50]. Generally, the source of the infection can be found in the patient's skin or nails [9,33,42,51]. However, most cases that have been described in the literature were not associated with tinea pedis [11,30,31]. In one case, the infection may have been transmitted from a bedmate's infected toenails [11].

Predisposing factors

MG is a rare fungal infection. The available literature revealed either no specific data on the actual incidence of MG or its increasing frequency. However, some predisposing factors were addressed. The various immunosuppressed conditions that have been described in 79 patients with MG include the following: malnutrition (1.3%), leukemia (2.5%), lymphoma (3.8%), AIDS (1.3%), and Cushing's

syndrome (1.3%). Additionally, the use of immunosuppressive drugs that affect cell-mediated immunity and the inflammatory response, including neutrophil production, function, and chemotaxis, can be associated with nodular dermatophytic infections [10,12,16,39].

Our review revealed that 28 of 79 (35.4%) patients with MG had received immunosuppressive therapy, and 17 of these 28 patients received two or more immunosuppressive drugs, including the following: systemic corticosteroids (25 cases), tacrolimus (nine cases), azathioprine (six cases), mycophenolate mofetil (five cases), cyclosporine (four cases), systemic chemotherapy (three cases), methotrexate (one case), and anti-thymocyte globulin (one case). Among these cases, 15 were SOT recipients who underwent kidney (seven cases), heart (six cases), or liver (two cases) transplantation. The other patients treated with immunosuppressive drugs had CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, or telangiectasia; one case), systemic lupus erythematosus (one case), rheumatoid arthritis (one case), Behçet's disease (one case), and leukocytosis (one case) (Table 1). Therefore, because the presence of MG may be a sign of immunosuppressant overdose, serum drug levels should be examined [35]. MG is a rare opportunistic infection in SOT recipients. However, because of increases in the numbers of SOTs and the administration of immunosuppressive therapies, microbiologists and dermatologists should consider the possibility of MG [12,49]. Because immunosuppressive therapy lowers cellular immunity, SOT recipients are highly predisposed to opportunistic infections and to aggressive and atypical clinical courses of infections with common pathogens [49]. In the literature, several cases of MG were reported in SOT recipients who underwent renal [8,12,16,29,32,33,35], cardiac [8,17,19,49], and liver transplants [42,44]. In a case report, Ma *et al*. [42] observed a 48-year-old female patient with MG who had undergone liver transplantation 9 months earlier. She presented with red papules and nodular lesions on her back, buttock, and thigh that were caused by *T. rubrum* with a '*raubitschekii*' morphotype and persisted for 2 months. She also had onychomycosis of the toenail that was due to the same organism. Onychomycosis persisted for several years and worsened during the post-transplant period. Recently, 11 cases of SOT recipients with MG were reviewed, and potential risk factors, pathogens, clinical presentations, therapeutic approaches, and outcomes were comprehensively analyzed. Most of the patients were males who presented with nodules or plaques on the lower extremities; these were predominantly caused by *T. rubrum* [49].

Although rarely reported, individuals can be predisposed to MG by the long-standing natural occlusion of the hair follicle (such as that occurring in the groin area) or the long-term use of topical corticosteroids for pre-existing tinea [46,47,51,52]. In the literature, 10 of 79 MG cases (12.7%) had used topical corticosteroids to treat a pre-existing condition (e.g., eczema). It has been demonstrated that strong topical steroids can increase the number of hyphae present on the surface of the skin in fungal infections and modify the appearance of lesions [10,47]. Moreover, particularly when occlusion occurs, MG may present as tinea incognito, the clinical manifestations of which are highly variable and non-specific [46,52]. Therefore, topical steroids should be applied to areas of the skin with follicular occlusions only when one is confident that the eruption is not a dermatophytosis, as the use of potent steroids under these conditions may predispose an individual to the development of MG [23,52,53].

Pathogenesis

In an earlier report, it was noted that the pathogenesis of MG is puzzling because the mycelia are present in moist, living tissues as opposed to their usual localization in non-living, keratinized tissues [21]. However, the pathogenesis of MG has been well delineated. In an immunocompetent person, multiple factors prevent deep invasion by dermatophytes, including physical factors, antimicrobial peptides, and innate and adaptive immunity [54]. First, the physical barrier of the skin is important because it prevents the penetration of microorganisms [54]. Physical factors that play a major role in inhibiting dermal invasion include the interplay among keratin production, the rate of epidermal turnover, the degree of hydration and lipid composition of the stratum corneum, CO_2 levels, and the presence or absence of hair [14,55,56]. Notably, trauma may lead to impairment of the epidermal barrier. The initiating factor in MG is thought to be physical trauma that either directly or indirectly leads to follicle disruption and passive introduction of the organism into the dermis; keratin and/or necrotic material can also be introduced into the dermis at the same time, which may provide a substrate for survival of the organism [8,14,57]. For example, Cho *et al*. [36] suggested that physical trauma from tinea cruris-induced scratching caused follicular disruption of the scrotal skin, leading to the migration of *T. rubrum* into the dermis and the development of MG. Additionally, dermatophytic fungi may directly invade the skin [17]. However, Rippon [58] reported that dermatophytes can be converted to yeast-like forms, which is a feature of dimorphic fungi. Notably, the dermal environment is more alkaline than the epidermis, and the dermis does not represent the ideal substrate for the growth process outlined above [57]. Keratinous material that is introduced into the dermis after follicular disruption can potentially provide a substrate for dermatophytic fungi; however, this should not affect non-dermatophytic

molds, such as those of the *Alternaria* and *Aspergillus* genera [14,57]. Cellular destruction associated with fungal growth and the increased amounts of stromal acid mucopolysaccharides that are produced by inflammation reduce the dermal pH, making the dermal environment more suitable for survival of the fungal pathogen [8,57].

Second, antimicrobial peptides such as cathelicidins play a role in skin defense against dermatophytes and may help to limit the dermal invasion of dermatophytes [59]. Toll-like receptor (TLR)-mediated activation of keratinocytes and monocytes by dermatophytes causes the degradation of cathelicidins [60]. However, levels of cathelicidins are reduced in patients with atopic dermatitis [61]. For this reason, severe generalized MG in a patient with atopic dermatitis is here reported [60].

Third, the nonspecific phagocytic functions of neutrophils and macrophages appear to be crucial for the control of deep or invasive forms of fungal infections [16]. Fungal hyphae can activate complement via the alternative pathway and generate chemotactic factors for neutrophils. Neutrophils and monocytes have been demonstrated to ingest and kill the spores of *T. rubrum*; additionally, neutrophils destroy *Aspergillus* hyphae. Therapeutic immunosuppression with corticosteroids inhibits the resident tissue macrophage-mediated killing of spores (but not via the inhibition of phagocytosis) and impairs the neutrophil-mediated killing of hyphae [16]. Th2-associated humoral immunity is not protective against the dermatophytes, but Th1-mediated adaptive immunity is important in dermatophytic infections [62]. Therefore, immunosuppressive therapy lowers cellular immunity, resulting in generalized MG lesions [10,12].

Laboratory diagnosis

A high index of suspicion will facilitate the diagnosis of this uncommon and treatable disease and of any previously unknown underlying immunodeficiencies [45]. The presence of non-tender, usually unilateral, erythematous or purple nodules, papules, and plaques that are refractory to the initial treatment should elicit a high degree of suspicion [7,10,13].

Mycologic examination

Fungal hyphae can be observed by the potassium hydroxide (KOH) test. Upon direct microscopic examination of the extracted hairs, the fungi were detected mostly as an ectothrix mosaic mantle of rather large spherical or oval spores. However, on most hairs, an endothrix element was also present. This structure consisted of short hyphal segments and chains of oval or rounded arthrospores that were longitudinally directed in relation to their shaft [7]. In the majority of patients (76.7%), the KOH examination was positive. However, in some MG cases (23.3%), KOH preparations of scales and pustules may reveal no hyphal structures [6,13]. Gram stains, calcofluor stains, scale cultures, and exudate or tissue biopsy samples may reveal hyphae when the KOH test result is negative [6].

Furthermore, if the KOH examination is negative, cytologic examination can also be performed. Samples may be taken by a slit-skin smear or fine-needle aspiration and can then be quickly stained using the May-Grünwald-Giemsa method (20–25 s) [63,64]. Hyphae and spores can be detected in foreign body-type giant cells and/or in the background (Fig. 2a and 2b). In suspected cases of MG, confirmatory stains, such as periodic acid-Schiff (PAS) or Gomori's methenamine silver (GMS) staining, can be performed [65]. In general, tissue homogenate cultures are more sensitive than special stains [6].

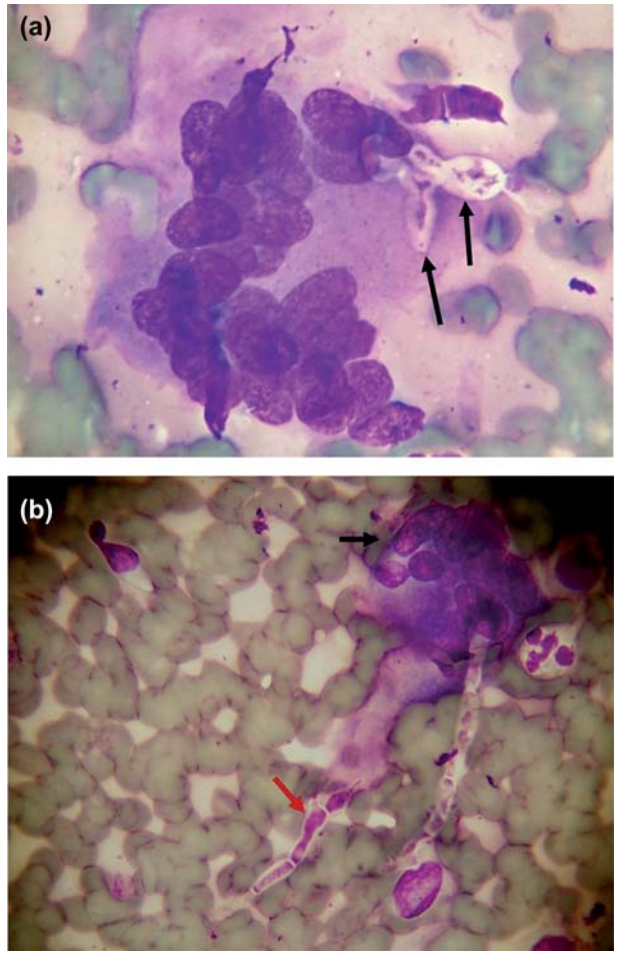

Fig. 2 (a) Hyphae (arrows) in a Langhans-type giant cell in a trunk scale from a 37-year-old immunocompetent man with MG (May-Grünwald-Giemsa stain; magnification, × 1000). (b) Hyphae in the background (red arrow) and a foreign body-type giant cell (black arrow) in a trunk scale from a 37-year-old immunocompetent man with MG (May-Grünwald-Giemsa stain; magnification, × 1000).

The pathogen must be identified by culture [7] or by specific PCR [35]. For this purpose, fresh tissue should be collected from the dermal granulomas. In one study, *T. rubrum* was detected using an ELISA-PCR of unstained tissue specimens and paraffin sections [35]. As discussed below, the clinical picture of MG is mostly caused by dermatophytes but can also be caused by other molds that may require treatment with particular antimycotic agents. Therefore, an unambiguous identification of the fungus is mandatory, especially in immunocompromised patients.

Etiologic agents

Dr Majocchi [2,66–70] worked at a time when anthropophilic *T. rubrum* was uncommon in Europe and almost always recovered *T. tonsurans* or *T. violaceum* from MG cases. Currently, however, the most common dermatophyte species that causes MG in both immunocompetent and immunosuppressed individuals is *T. rubrum*. Additionally, *T. rubrum* is the most common fungal cause worldwide of both acute and chronic cutaneous and nail dermatophytosis [7–10,13,17,18,20,21,23,24,28,29,33,35–38,41,42,44,45,49,53]. Other causative agents include *T. rubrum* with the '*raubitschekii*' morphotype [42], *T. mentagrophytes* [8,30,39], *T. tonsurans* [19,22,31,32,34], *T. verrucosum* [27], *Microsporum canis* [8,16,43,46], and *Epidermophyton floccosum* [26]. Moreover, Smith *et al.* [8] identified the following dermatophytic fungi from patients with MG: *T. violaceum*, *M. audouinii*, *M. gypseum*, and *M. ferrugineum*.

Majocchi [2] clearly thought that '*Granuloma tricofitico*' was a dermatophyte-related problem. However, more than a century after his initial report, an infection caused by a saprophytic dematiaceous *Phoma* sp. found in soil and plants was reported in a 53-year-old Hispanic man receiving tacrolimus treatment for a renal transplant [12]. Furthermore, Saadat *et al.* [40] recovered *Aspergillus fumigatus* from the left lower flank of a 27-year-old man with AIDS (Table 3).

Histopathologic characteristics

The diagnosis of MG should be made by histopathologic examination [8]. Histopathologic sectioning reveals perifollicular granulomatous inflammation with dermal abscesses. Severe inflammation of hair follicles and shafts is also seen in kerion. In both instances, giant cells can be present. In kerion, perifollicular infiltrates spread rapidly to the interfollicular areas, and the infiltrate primarily includes neutrophils. However, MG is associated with chronic inflammation with lymphocytes, macrophages, epithelioid cells, and scattered multinucleated giant cells [71]. Like MG, pseudomycetomas may arise through extension from hair follicles. However, pseudomycetomas represent granulomatous infiltrations with hyphal aggregates that form basophilic structures (grains) similar to eumycotic granules [5]. Clear granuloma is usually observed in cutaneous alternariosis, but this infiltration is not strictly perifollicular [72].

It has been reported that no specific features were characteristic of particular etiologic agents, and no specific

Table 2 Differential diagnosis in Majocchi's granuloma according to lesion type.

Type of lesion	Differential diagnosis
Papule	Folliculitis
	Acne vulgaris
	Lupus miliaris disseminatus facii
	Insect bite
	Cutaneous leishmaniasis
	Granulomatous rosacea
	Disseminated toxoplasmosis
	Kaposi sarcoma
Nodule	Erythema nodosum
	Erythema induratum Bazin
	Furunculosis
	Sarcoidosis
	Cutaneous leishmaniasis
	Kaposi sarcoma
	Foreign body granuloma
	Lymphocytoma cutis
	Thrombophlebitis
	Squamous cell carcinoma
Plaque	Bacterial cellulitis
	Eosinophilic cellulitis
	Chemical cellulitis
	Sarcoidosis
	Lupus vulgaris
	Cutaneous leishmaniasis
	Stasis dermatitis
	Psoriasis
	Contact dermatitis

Table 3 Etiologic agent of 79 cases of Majocchi's granuloma and their frequency.

Causative fungi	Frequency (%)
Dermatophytic fungi	97.4
Trichophyton rubrum[§]	70.8
T. mentagrophytes	6.3
T. tonsurans	7.5
T. verrucosum	1.3
T. violaceum	1.3
Microsporum canis	5
M. audouinii	1.3
M. ferrugineum	1.3
M. gypseum	1.3
Epidermophyton floccosum	1.3
Non-dermatophytic molds	2.6
Aspergillus fumigatus	1.3
Phoma sp.	1.3

[§]*T. rubrum* also includes *T. rubrum* of the '*raubitschekii*' morphotype.

changes are known to reflect the degree of immune suppression of the infected patient. However, more extensive tissue necrosis and abscess formation with less extensive epidermal acanthosis and a less granulomatous reaction were characteristic features of the specimens derived from immunocompromised patients [8]. Importantly, fungal elements are not the typical slender hyphae found within the stratum corneum during superficial infections; instead, fungal elements include thicker, shorter hyphae and arthrospores. Although some of the hyphae are large and can be up to 6 μm in diameter, variations in their size and shape do exist. However, the presence of large hyphae can lead to the incorrect diagnosis of mucoraceous species such as *Mucor* sp. and *Rhizopus* sp. Segmented hyphae form rectangular to ovoid arthrospores that vary in size from 10–40 μm. These arthrospores exhibit single or multiple budding sporulation and areas of internal segmentation, occasionally with capsular sialomucin. In addition, some of the microconidia exhibit double walls or single budding sporulation [8].

Detecting fungal elements is difficult when histopathologic examination is performed with the hematoxylin-eosin stain. However, PAS and GMS staining can facilitate the detection of fungal spores, hyphae, and arthrospores within hairs, hair follicles, and in dermal infiltrates [8,16,30,36]. If these confirmatory stains are also negative, the histopathologic findings may be confused with other granulomatous diseases, such as granulomatous rosacea, sarcoidosis, cutaneous tuberculosis, or cutaneous leishmaniasis [7]. If eosinophils are prominent and the fungal elements are negative, the diagnosis may be eosinophilic cellulitis [30]. In this condition, tissue homogenate cultures and molecular-based techniques, such as PCR, may be used to detect dermatophytic fungi [6,35].

Differential diagnosis

We now consider MG as a localized 'dermatophytic granuloma'. Therefore, the correct diagnosis of MG relies upon a high degree of clinical suspicion followed by skin biopsy with pathologic correlation and fungal cultures of biopsy materials. The disease should be differentiated from several diseases that present with papules, nodules, or plaques (Table 2) [6,10,35,45,50,57,73]. Additionally, when *Phoma* sp. [12] and *A. fumigatus* [40] are included as the etiologic fungi contributing to MG, a differential diagnosis to distinguish it from other diseases, such as hyphomycosis and phaeohyphomycosis, is required.

Treatment

Historically, antifungal therapy has been successful in controlling MG in most instances. The therapies utilized have included oral potassium iodide, mildly filtered local X-radiation, and topical applications of 2-dimethylamino-6-(β-diethylaminoethoxy)-benzothiazole (Asterol) as a fungicide in both tincture and ointment forms [7]. In modern medicine, systemic antifungals, such as griseofulvin [9,16,17,21–24,31,32,34,48], ketoconazole [10], itraconazole [ITR; 17,27–30,37,38,45,49], and terbinafine [TER; 12,20,25,35,39], are the mainstays of therapy, as they are safe and effective. The duration of therapy should be at least 4–8 weeks, and treatment should be continued until all lesions are cleared. In the literature, nearly all lesions resolved without scarring at the end of 6 weeks of antifungal therapy (Fig. 1b). Specifically, Sequeira *et al*. [12] treated a case of MG due to *Phoma* sp. with 2 months of ITR (250 mg b.i.d.) therapy. ITR was discontinued due to a lack of response, and treatment with TER (250 mg daily) was started; significant clinical improvement was observed after 4 weeks. A case of MG caused by *A. fumigatus* was treated with intravenous amphotericin B (1.5 mg/kg/day), and the cutaneous lesions exhibited some clinical improvement after 2 weeks. However, this patient died from respiratory failure 6 weeks after admission [40].

Systemic antifungals, such as TER given at a dose of 250 mg/day for 4–6 weeks, are being used successfully. Following therapy with TER (250 mg/day), the drug can be detected in the stratum corneum as early as 24 h after administration, having diffused from the vascular system and through the deeper structures of the skin. The response of MG to oral TER can be explained on the basis of its pharmacokinetics [74]. Attention should be paid to possible interactions between antifungals and immunosuppressants. In addition to its superior efficacy in eliminating dermatophytes, TER also has a lower risk of drug interactions and is preferable to azole antifungals for treating MG [25]. In another study by Gupta *et al*. [27], seven patients with MG were treated up to three times with ITR pulse therapy (200 mg twice daily for 1 week with 2 weeks between pulses). All seven patients responded to therapy; clinical and mycologic cures were achieved, with no patient relapsing over a 6- to 18-month follow-up period. The authors suggest that one pulse may be sufficient in some patients.

Topical antifungals are usually ineffective therapeutically because of insufficient drug penetration into the deeper skin layers [27]. However, Cho *et al*. [36] successfully treated superficial and perifollicular forms of scrotal MG with a topical antifungal agent alone (cloconazole hydrochloride) for one month. In addition, surgical treatment may be an option when the lesions are either solitary or discrete and involve a limited area and when wound healing is not a concern [19,33,42]. However, recurrence is expected in many instances because foci of dermatophytosis remain uncured in nails, feet, or other anatomic sites [7]. In addition, in immunocompromised patients, prolonged treatment may be advisable as relapses have been

reported [21]. Therefore, clinical and mycological clearance is crucial for the follow-up of patients with MG. Avoiding follicular occlusions, topical steroids, and leg- shaving may help to prevent MG [6].

Conclusions

Described more than a century ago, MG is an infection of dermal and subcutaneous tissues that is related to the disruption of hair follicles and spillage of fungi into the dermis, which produces granulomatous inflammation. Briefly, changes in the dermal environment induced by the introduction of foreign material and morphologic changes in the organisms, including the production of sialomucin, may enable the dermatophytes to persist and grow in areas other than the epidermis. MG can occur in both immunocompetent (62%) and immunosuppressed (38%) hosts. Patients receiving immunosuppressive treatments that lead to a reduction of cellular immunity are at increased risk for MG.

Importantly, clinical and/or mycologic diagnoses should be verified by the histologic examination of biopsy material. *T. rubrum* is the most commonly recovered fungal pathogen; however, in contrast to Majocchi's original description in 1883, non-dermatophytic molds, including those from the *Aspergillus* and *Phoma* genera, have occasionally been implicated. It should be noted that the Tzanck smear method is a rapid, easily performable diagnostic test that is routinely used. Histopathologic examinations reveal a deep suppurative and granulomatous folliculitis in patients with MG. Systemic antifungals given at an adequate dose and for an appropriate duration are the drugs of choice; in general, topical antifungals alone do not clear the fungal infections. Patients should be educated about the causative fungus of MG as well as the predisposing and exacerbating factors.

Acknowledgements

This study is dedicated to our leader and dear friend, Professor Süleyha Hilmioğlu-Polat, an outstanding researcher and highly distinguished clinical mycologist whose spirit touched all and who completely devoted her life to a large number of graduate and undergraduate students and mycologists in Turkey.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References

1 Weitzman I, Summerbell RC. The dermatophytes. *Clin Microbiol Rev* 1995; **8**: 240–259.
2 Majocchi D. Sopra una nuova tricofizia (*Granuloma tricofitico*), Studi clinici e micologici [A new trichophytic granuloma: clinical and mycologic studies]. *Bull R Acad Med Roma* 1883; **9**: 220–223.
3 Smith KJ, Welsh M, Skelton H. *Trichophyton rubrum* showing deep dermal invasion directly from the epidermis in immunosuppressed patients. *Br J Dermatol* 2001; **145**: 344–348.
4 Marconi VC, Kradin R, Marty FM, Hospenthal DR, Kotton CN. Disseminated dermatophytosis in a patient with hereditary hemochromatosis and hepatic cirrhosis: case report and review of the literature. *Med Mycol* 2010; **48**: 518–527.
5 Isa-Isa R, Arenas R, Isa M. Inflammatory tinea capitis: kerion, dermatophytic granuloma, and mycetoma. *Clin Dermatol* 2010; **28**: 133–136.
6 Schwartz RA, Janniger CK, Fivenson DP, *et al*. Majocchi granuloma. http//emedicine.medscape.com. 2011: updated, May 27.
7 Wilson JW, Plunkett OA, Gregersen A. Nodular granulomatous perifolliculitis of the legs caused by *Trichophyton rubrum*. *AMA Arch Dermatol Syphilol* 1954; **63**: 258–277.
8 Smith KJ, Neafie RC, Skelton HG 3rd, *et al*. Majocchi's granuloma. *J Cutan Pathol* 1991; **18**: 28–35.
9 Allen GE. Majocchi's granuloma. *Br J Dermatol* 1966; **78**: 544.
10 Radentz WH, Yanase DJ. Papular lesions in an immunocompromised patient. *Trichophyton rubrum* granulomas (Majocchi's granuloma). *Arch Dermatol* 1993; **129**: 1189–1190.
11 Lepage GC. Source of Majocchi's granuloma. *J Am Acad Dermatol* 1983; **8**: 260.
12 Sequeira M, Burdick AE, Elgart GW, Berman B. New-onset Majocchi's granuloma in two kidney transplant recipients under tacrolimus treatment. *J Am Acad Dermatol* 1998; **38**: 486–488.
13 Tan E, Goh CL. Unusual papular lesions in a healthy man. *Arch Dermatol* 2002; **138**: 117–122.
14 Dahl MV. Dermatophytosis and the immune response. *J Am Acad Dermatol* 1994; **31**: s34–s41.
15 Sherwin WK, Rose TH, Rosenthal CM, Petrozzi JW. An immunosuppressive serum factor in widespread cutaneous dermatophytosis. *Arch Dermatol* 1979; **115**: 600–604.
16 Novick NL, Tapia L, Bottone EJ. Invasive *Trichophyton rubrum* infection in an immunocompromised host. Case report and review of the literature. *Am J Med* 1987; **82**: 321–325.
17 Grossman ME, Pappert AS, Garzon MC, Silvers DN. Invasive *Trichophyton rubrum* infection in the immunocompromised host: report of three cases. *J Am Acad Dermatol* 1995; **33**: 315–318.
18 Conti-Diaz IA, de la LIosa LA, Colman R. Majocchi's granuloma of the beard caused by *Trichophyton rubrum*. *Med Cutan Ibero Latin Am* 1974; **2**: 433–436.
19 Liao YH, Chu SH, Hsiao GH, *et al*. Majocchi's granuloma caused by *Trichophyton tonsurans* in a cardiac transplant recipient. *Br J Dermatol* 1999; **40**: 1194–1196.
20 Gupta S, Kumar B, Radotra BD, Rai R. Majocchi's granuloma trichophyticum in an immunocompromised patient. *Int J Dermatol* 2000; **39**: 140–141.
21 Blank H, Smith JG Jr. Widespread *Trichophyton rubrum* granulomas treated with griseofulvin. *AMA Arch Dermatol Syphilol* 1960; **81**: 779–789.
22 McNamara RJ. *Trichophyton tonsurans* granuloma in the scalp of an adult. *Cutis* 1977; **20**: 55–57.
23 Carter RL. Majocchi's granuloma. *J Am Acad Dermatol* 1980; **2**: 75.
24 Alteras I, Feuerman EJ, David M, Shvili D. Unusual aspects of granulomatous dermatophytosis. *Mycopathologia* 1984; **86**: 93–97.
25 Gupta AK, Prussick R, Sibbald RG, Knowles SR. Terbinafine in the treatment of Majocchi's granuloma. *Int J Dermatol* 1995; **34**: 489.
26 Seddon ME, Thomas MG. Invasive diesase due to *Epidermophyton floccosum* in an immunocompromised patient with a Behçet's syndrome. *Clin Infect Dis* 1997; **25**: 153–154.
27 Gupta AK, Groen K, Woestenborghs R, de Doncker P. Itraconazole pulse therapy is effective in the treatment of Majocchi's granuloma: a clinical and pharmacokinetic evaluation and implications for possible effectiveness in tinea capitis. *Clin Exp Dermatol* 1998; **23**: 103–108.

28 Akiba H, Motoki Y, Satoh M, Iwatsuki K, Kaneko F. Recalcitrant trichophytic granuloma associated with NK-cell deficiency in a SLE patient treated with corticosteroid. *Eur J Dermatol* 2001; **11**: 58–62.
29 Tse KC, Yeung CK, Tang S, *et al*. Majocchi's granuloma and post-transplant lymphoproliferative disease in a renal translant patient. *Am J Kidney Dis* 2001; **38**: e38.
30 Chang SE, Lee DK, Choi JH, Moon KC, Koh JC. Majocchi's granuloma of the vulva caused by *Trichophyton mentagrophytes*. *Mycoses* 2005; **48**: 382–384.
31 Chen HH, Chiu HC. Facial Majocchi's granuloma caused by *Trichophyton tonsurans* in an immunocompetent patient. *Acta Derm Venereol* 2003; **83**: 65–66.
32 Rajpara V, Frankel S, Rogers S, Nouri K. *Trichophyton tonsurans* associated tinea corporis infection with the development of Majocchi's granuloma in a renal transplant patient. *J Drugs Dermatol* 2005; **4**: 767–769.
33 Burg M, Jaekel D, Kiss E, Kliem V. Majocchi's granuloma after kidney transplantation. *Exp Clin Transplant* 2006; **4**: 518–520.
34 Feng WW, Chen HC, Chen HC. Majocchi's granuloma in a 3-year-old boy. *Pediatr Infect Dis J* 2006; **25**: 258–259.
35 Brod C, Benedix F, Röcken M, Schaller M. Trichophytic Majocchi granuloma mimicking Kaposi sarcoma. *J Dtsch Dermatol Ges* 2007; **5**: 591–593.
36 Cho HR, Lee MH, Haw CR. Majocchi's granuloma of the scrotum. *Mycoses* 2007; **50**: 520–522.
37 Gill M, Sachdeva B, Gill PS, *et al*. Majocchi's granuloma of the face in an immunocompetent patient. *J Dermatol* 2007; **34**: 702–704.
38 Gong JQ, Liu XQ, Xu HB, *et al*. Deep dermatophytosis caused by *Trichophyton rubrum*: report of two cases. *Mycoses* 2007; **50**: 102–108.
39 Kim ST, Baek JW, Kim TK, *et al*. Majocchi's granuloma in a woman with iatrogenic Cushing's syndrome. *J Dermatol* 2008; **35**: 789–791.
40 Saadat P, Kappel S, Young S, Abrishami M, Vadmal MS. *Aspergillus fumigatus* Majocchi's granuloma in a patient with acquired immunodeficiency syndrome. *Clin Exp Dermatol* 2008; **33**: 450–453.
41 Coelho WS, Diniz LM, Sousa Filho JB, Castro CM. Granuloma trichophyticum (Majocchi's granuloma). *An Bras Dermatol* 2009; **84**: 85–86.
42 Ma L, Li R, Yu J, *et al*. Majocchi's granuloma in a liver transplant recipient caused by *Trichophyton* spp., phenotypically consistent with *Trichophyton rubrum* var. *raubitschekii*. *Med Mycol* 2009; **47**: 312–316.
43 Ratajczak-Stefańska V, Kiedrowicz M, Maleszka R, Różewicka M, Mikulska D. Majocchi's granuloma caused by *Microsporum canis* in an immunocompetent patient. *Clin Exp Dermatol* 2009; **35**: 445–447.
44 Gega A, Ketsela G, Glavin FL, Soldevilla-Pico C, Schain D. Majocchi's granuloma after antithymocyte globulin therapy in a liver transplant patient. *Transpl Infect Dis* 2010; **12**: 143–145.
45 Mahajan R, Dogra S, De D, Kanwar AJ, Saikia UN. Multiple nodules on the forearms. *Clin Exp Dermatol* 2010; **35**: 929–930.
46 Bae BG, Kim HJ, Ryu DJ, Kwon YS, Lee KH. Majocchi granuloma caused by *Microsporum canis* as tinea incognito. *Mycoses* 2011; **54**: 361–362.
47 Collins MA, Lloyd R. Treatment-resistant plaque on the thigh. Majocchi granuloma. *Am Fam Physician* 2011; **83**: 753–754.
48 Husein-Elahmed H, Orgaz-Molina J, Soriano-Hernández MI, Burkhardt-Perez P, Naranjo-Sintes R. Majocchi granuloma on the hand successfully treated with griseofulvin. In: American Academy of Dermatology 69th Annual Meeting, February 4–8, 2011, New Orleans, Louisiana, USA. *J Am Acad Dermatol* 2011: **64** (Suppl. 2); AB102 (P2400).
49 Romero FA, Deziel PJ, Razonable RR. Majocchi's granuloma in solid organ transplant recipients. *Transpl Infect Dis* 2011; **13**: 424–432.
50 Janniger CK. Majocchi's granuloma. *Cutis* 1992; **50**: 267–268.
51 Jacobs PH. Majocchi's granuloma (due to therapy with steroid and occlusion). *Cutis* 1986; **38**: 28.
52 Meehan K. A growing, pruritic plaque on the thigh. Majocchi's granuloma with secondary tinea incognito. *JAAPA* 2002; **15**: 16, 65.
53 Nolting C, Vennewald I, Seebacher C. Tinea follicularis presenting as trichophytic Majocchi granuloma. *Mycoses* 1997; **40**: 73–75.
54 Brasch J. Pathogenesis of tinea. *J Dtsch Dermatol Ges* 2010; **8**: 780–786.
55 Svejgaard EL. Immunologic investigations of dermatophytoses and dermatophytosis. *Semin Dermatol* 1985; **4**: 201–221.
56 Marsh TW, Artis WM. Host defence mechanisms and the superficial fungal infections. *Dermatol Clin* 1984; **2**: 67–79.
57 Elgart ML. Tinea incognito: an update on Majocchi's granuloma. *Dermatol Clin* 1996; **14**: 51–55.
58 Rippon JW. Medical mycology: the pathogenic fungi and the pathogenic actinomycetes. 2nd edn. Philadelphia: WB Saunders, 1982: 167.
59 López-García B, Lee PH, Gallo RL. Expression and potential function of cathelicidin antimicrobial peptides in dermatophytosis and tinea versicolor. *J Antimicrob Chemother* 2006; **57**: 877–882.
60 Tateishi Y, Sato H, Akiyama M, *et al*. Severe generalized deep dermatophytosis due to *Trichophyton rubrum* (trichophytic granuloma) in a patient with atopic dermatitis. *Arch Dermatol* 2004; **140**: 624–625.
61 Bangert C, Brunner PM, Stingl G. Immune functions of the skin. *Clin Dermatol* 2011; **29**: 360–376.
62 Almeida SR. Immunology of dermatophytosis. *Mycopathologia* 2008; **166**: 277–283.
63 Durdu M, Seçkin D, Baba M. The Tzanck smear test: rediscovery of a practical diagnostic tool. *Skinmed* 2011; **9**: 23–32.
64 Barboza-Quintana O, Garza-Guajardo R, Assad-Morel C, Méndez-Olvera N. Pseudomycetoma for *Microsporum canis*: report of a case diagnose by fine needle aspiration biopsy. *Acta Cytol* 2007; **51**: 424–428.
65 Durdu M, Baba M, Seçkin D. More experiences with the Tzanck smear test: cytologic findings in cutaneous granulomatous disorders. *J Am Acad Dermatol* 2009; **61**: 441–450.
66 Majocchi D. Sul granuloma tricofitico. In: Atti del VIII riunione della Società Italiana di dermatologia e sfilolgia, Settembre, Milano, Italy, 1906 (p. 17). *Gior Ital Mal Ven E Pelle* 1906; **41**: 567–574.
67 Majocchi D. Alcune considerazioni clinico-critiche e ricerche sperimentali intorna al granuloma tricofitico [Some critical clinical considerations and experimental researches on trichophytic granuloma]. *Gior Ital Mal Ven E Pelle* 1908; **49**: 198–209.
68 Majocchi D. Contribuzione clinica, istologica e micologica sul granuloma tricofitico [Clinical, histologic, and mycologic contributions on trichophytic granuloma]. *Gior Ital Mal Ven E Pelle* 1920; **61**: 397–403.
69 Majocchi D. Associazone del granuloma trichophyticum col kerion Celsi e indipendenza di sviluppo delle due forme tricofitiche sullo stesso soggetto [Association of trichophytic granuloma with kerion celsi and independent development of the two types of trichophytosis on the same patient]. *Gior Ital Dermat E Sfi* 1926; **67**: 250–253.
70 Majocchi D. Granuloma trichophyticum. Cited in Miescher G. (1929). Trichophytosis profunda. In: *Handbuch für Haut und Geschlectskrankheiten*. Berlin: Julius Springer, 11, 140.
71 Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev* 2011; **24**: 247–280.
72 Gilaberte M, Bartralot R, Torres JM, *et al*. Cutaneous alternariosis in transplant recipients: clinicopathologic review of 9 cases. *J Am Acad Dermatol* 2005; **52**: 653–659.
73 Hellier FF. Trichophytic granuloma simulating Bazin's disease. *Br Med J* 1962; **2**: 644–645.
74 Faergemann J, Zehender H, Jones H, Maibach I. Terbinafine levels in serum, stratum corneum, dermis-epidermis (without stratum corneum), hair, sebum and eccrine sweat. *Acta Derm Venereol* 1991; **71**: 322–326.

This paper was first published online on Early Online on 23 March 2012.