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ORIGINAL ARTICLE

Changing Concepts and Current Definition of Majocchi's Granuloma

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Abstract Dermatophytic granuloma characterized by perifollicular granulomatous inflammation was first described by Domenico Majocchi and was later named after him, Majocchi's granuloma (MG). Although the initial description was related to a dermatophyte *Trichophyton tonsurans*, later reports linked MG to non-dermatophytes (*Phoma*, *Aspergillus*, *Malbranchea*), which led to a confusion of disease patterns caused by cutaneous pathogens and general opportunistic microorganisms. Furthermore, several causative agents of MG described in the literature were not confirmed as such. Our review addressed the following aspects: (1) significance of histopathological finding for MG diagnosis, (2) dermatophytes as exclusive agents of MG, (3) spectrum of etiological agents causing different types of invasive dermatophytic infections, and (4) treatment options.

Keywords Dermatophyte · Fungi · Granuloma · Histopathology · Invasive infection · Mycetoma

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Introduction

Majocchi's granuloma (MG) was first described by an Italian dermatologist Prof. Domenico Majocchi (1849–1929) in 1883, when he published a report on a case of dermal granuloma due to *Trichophyton tonsurans* [1]. Histopathology analysis of the case revealed hair follicle (perifollicular) granulomatous inflammation and Majocchi named the newly observed disease "granuloma tricofitico" [1]. Later, Majocchi published five more papers on perifollicular granulomatous inflammation caused by dermatophytes. The following three criteria were used for the diagnosis of "granuloma tricofitico": (1) histopathological evidence of perifollicular granulomatous inflammation, (2) lesions resulting from

infections due to dermatophytes, and (3) presence of dermatophytes not only in the superficial layer but also in the dermis [1, 2]. In subsequent years, dermatophytic infections accompanied with perifollicular granulomatous inflammation have been termed after Majocchi, MG [2].

Our preliminary literature review revealed some gaps in the knowledge related to MG diagnosis. For example, although reliable diagnosis of MG should be based on histopathological findings, it is sometimes made without histopathology analysis [3–10], and some cases have been reported as MG even though they were not caused by dermatophytes [11–13].

In the current mini-review, we incorporated and expanded the analysis presented in our earlier literature reviews [2, 14]. The aim was to summarize the currently available information on the diagnostic methods and criteria of MG in order to draw attention of clinical microbiologists, dermatologists, and pathologists and prevent terminological confusion, misdiagnosis, and underdiagnosis of this important disorder.

Search Strategy

We searched PubMed (MEDLINE) and Google Scholar databases for descriptions of MG cases published in the English-language literature up to September, 2018, using key words "Majocchi's granuloma," "trichophytic granuloma," and "dermatophytic granuloma." In our previous studies, we reviewed MG cases reported up to 2011 [2] and 2017 [14]. Here, we re-reviewed the literature and included findings reported after November 2017 [15–17], with a specific focus on the diagnostic criteria specified in Majocchi's original description. Other types of invasive or disseminated dermatophyte infections were excluded from the present review.

Is Histopathological Examination Required for MG?

Dermatophytic infections may be superficial or invasive. The two infection types have distinct features with respect to the area infected, infection depth, and host response. In superficial dermatophytic infections of the glabrous skin (tinea glabrosa), including tinea corporis, tinea pedis, tinea cruris, and tinea manuum, fungal pathogens are present only in the outermost layer of the epidermis (stratum corneum) without dermal invasion [18]. Invasive dermatophytic infections can be either localized to perifollicular sites, such as MG, or spread beyond the perifollicular area (sometimes into deep skin layers). In dermatophytic infections of the hair follicle, including tinea capitis and tinea barbae, the hyphae invade hair shafts [19], which can occur both in ectothrix (hair surface) and endothrix (deep hair layer) infections; however, dermatophytes may not be detected in hairs with endothrix infection because superficial hyphae rapidly break up into arthrospores and destroy keratin of the hair shaft. Although there are no fungi in the dermis, various degrees of immune response reactions such as perifollicular mononuclear cell infiltration can be observed. Multinuclear giant cells may also be seen after hair follicle deterioration. Furthermore, pronounced interfollicular tissue inflammation can develop as a result of excessive reaction to fungal structures in kerion celsi, an inflammatory type of tinea capitis [20].

Dermal hyphae and spores may be detected in four types of dermatophyte infections: (1) MG, (2) deeper dermatophytosis, (3) disseminated dermatophytosis, and (4) mycetoma and pseudomycetoma associated with dermatophytes. Although the clinical symptoms of these invasive forms may be similar, the histopathological findings are different [2].

In MG, fungal elements are found not only in the hair follicle but also in the perifollicular infiltrate of the dermis, which is due to the rupture of the hair follicle wall. The diameter of spores within the hair follicle (approximately 2 μm) is smaller than those of spores in the dermis, especially in multinuclear giant cells (up to 6 μm). Although histopathology analysis allows detection of fungal components, it cannot provide identification of fungal pathogens at the species or even genus levels. To differentiate MG from the other invasive dermatophytic infections, perifollicular granulomatous inflammation should be observed. Furthermore, in MG dermal infiltrates include lymphoid cells, macrophages, epithelioid cells, and multinucleated giant cells, which cause central necrosis (Fig. 1). If no infected hair follicle is detected during histopathological examination, MG and other invasive dermatophytic infections cannot be differentiated [20].

Unlike MG, deeper dermatophytosis and disseminated dermatophytosis are characterized by dermal

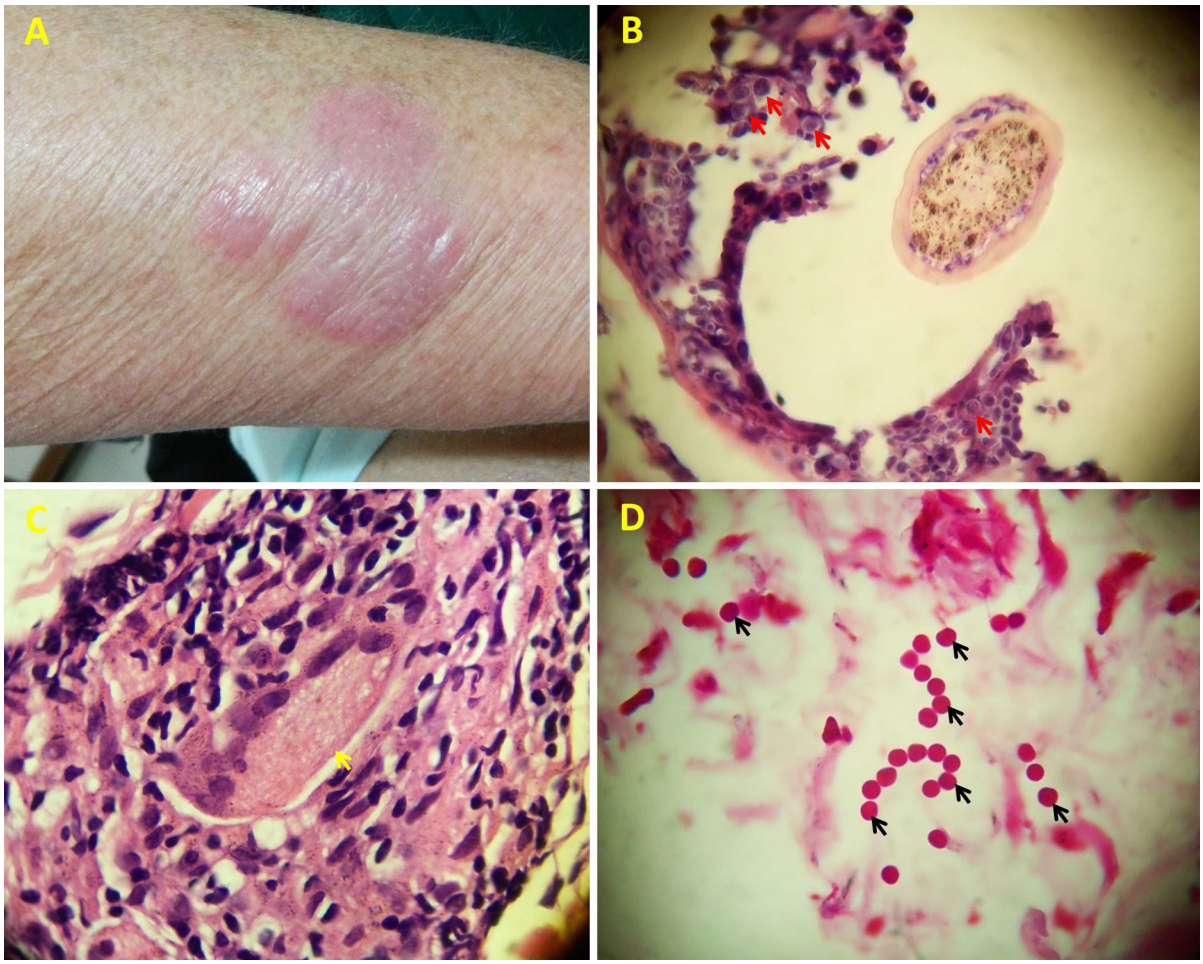

Fig. 1 Clinical and histopathological findings in a patient with Majocchi's granuloma. **a** Erythematous plaque on the lateral side of the forearm in a patient with Majocchi's granuloma. **b** Histopathology analysis by hematoxylin and eosin (HE) staining revealed perifollicular spores (arrows; × 1000). **c** Granuloma formation with Langhans-type multinucleated giant cells was seen at high magnification (HE staining, × 1000). **d** Perifollicular spores (arrows) were revealed by periodic acid-Schiff (PAS) staining (× 1000)

inflammation, which spreads not only to the perifollicular but also to the interfollicular area [21]. Extracutaneous spreading to other organs is observed in disseminated dermatophytosis but not in deeper dermatophytosis [22]. Furthermore, pseudomycetoma usually affects the scalp but rarely causes numerous non-scalp lesions [23, 24]. Similar to MG, pseudomycetoma may, albeit very rarely, occur in the perifollicular region; however, MG is limited to the perifollicular area, whereas pseudomycetoma spreads beyond it. Characteristic histopathological findings in pseudomycetoma cases include filamentous structures embedded in homogeneous eosinophilic radiate structures (so-called Splendore–Hoeppli phenomenon), suggesting a chronic nature of the disorder; the accompanying infiltrate includes neutrophils and multinuclear giant cells [24–26]. For unambiguous identification of invasive dermatophytosis type, MG or pseudomycetoma, thorough histopathological analysis should be performed.

Is It Necessary to Isolate the Causative Agent to Diagnose MG?

Treatment of fungal infections depends on the etiologic agent. Dermatophytic granulomas usually respond well to terbinafine treatment. However, non-dermatophyte species such as *Aspergillus* may be

resistant to antifungal antibiotics. Thus, it was reported that a patient with MG-like infection due to *Aspergillus* died in spite of amphotericin B therapy [12].

The present literature review revealed that fungal pathogens had been isolated in 108 of 115 reported cases of MG [2, 14]. The identified etiologic agents were usually dermatophytes (97.2%). Among them, *Trichophyton rubrum* was the most common species (65.7%), followed by *T. mentagrophytes* (10.2%), *T. tonsurans* (7.4%), *Microsporum canis* (3.7%), *Nannizzia gypsea* (2.8%), *T. violaceum* (1.9%), *T. interdigitale* (1.9%), *M. ferrugineum* (0.9%), *T. verrucosum* (0.9%), *M. audouinii* (0.9%), and *Epidermophyton floccosum* (0.9%). The remaining cases (2.8%) were caused by non-dermatophytic molds, such as *Phoma*, *Aspergillus*, and *Malbranchea* species [2, 14]. Identification of the fungal pathogen at the species level was not performed in seven MG cases [9, 10, 16, 27–29].

A similar problem, i.e., inability to offer efficient treatment because the specific causative agent was not identified, has been reported for fungal infections of the nails, which can be caused by both dermatophytes (tinea unguium) and non-dermatophyte molds and yeasts (onychomycosis) [30]. It is important to note that by their behavior, dermatophytes should be regarded as intrinsic (true) pathogens, because during host infection they develop adaptive traits that can be transmitted to subsequent generations to increase species' fitness. In contrast, non-dermatophytes are opportunistic fungi with no specific behavior upon infection [31]. Therefore, we suggest that different names should be used for fungal perifollicular granulomatous infections depending on the causative fungus. Thus, the term "MG" should be limited to dermatophyte-related conditions, whereas perifollicular granulomatous disorders due to non-dermatophyte species may be called "MG-like non-dermatophytic infections." To distinguish between the diseases, causative agents should be identified by reliable methods such as molecular biology techniques.

Can Invasive Dermatophytic Infections be Distinguished on the Basis of Clinical Findings?

Although patients with MG respond well to terbinafine therapy, those with the other invasive dermatophytic infections may not [23, 24], which is another reason why MG should be distinguished from unrelated invasive dermatophyte- and non-dermatophyte-related disorders. MG is presented by clinically variable symptoms and may not be recognized based only on clinical manifestations, which creates a problem in diagnosing and treating MG and accounts for the lack of reliable epidemiological data.

The most common lesion type in patients with MG is nodules (63.5%); other types are plaques (43.5%), papules (24.3%), ulcers (3.5%), and abscess (2.6%). Approximately one third (29.6%) of patients have pustules on these lesions [10, 15, 29]. Palmoplantar keratoderma, erythroderma, and cellulitis-like lesions have also been reported [15]. Other conditions such as deeper dermatophytosis, disseminated dermatophytosis, and pseudomycetoma may also cause variable lesions which could be similar to those in MG, whereas disease-specific symptoms such as sinus tracts and fungal grains in dermatophyte mycetoma may sometimes be missed [32]. These data indicate that fungal infections cannot be easily differentiated by clinical manifestations; therefore, histopathological examination is necessary for accurate diagnosis [18].

The patient's immune status plays a critical role in determining the type of invasion. Thus, among the mentioned diseases, only MG and pseudomycetoma are observed in immunocompetent individuals [32]. MG can be detected in both immunocompromised (37.4%) and immunocompetent (62.6%) patients, whereas almost all patients with deeper and disseminated dermatophytosis have a tendency to immunosuppression [2, 14]. Therefore, distinguishing among deep dermatophytic infections is particularly important for immunocompromised hosts.

Is Identification of the Causative Pathogen Important for Treatment of Invasive Dermatophytosis?

Among dermatophytes, the rate of antifungal drug resistance, either natural or acquired, has been increasing in the last decade, which explains a growing number of cases refractory to treatment. Indiscriminate application of antifungal drugs may promote the loss of sensitivity to appropriate antibiotics; therefore, it is essential to identify the causative pathogen so that target-specific treatment can be used. The majority of such infections are caused by

T. rubrum and the species of the *T. mentagrophytes* complex [33, 34]. In general, terbinafine (250 mg/day) is the preferred systemic antifungal drug for the treatment of MG applied in 40.8% of cases. Other systemic antifungal drugs are itraconazole (100–200 mg/day) (36.8%), griseofulvin (250–500 mg/day) (11.8%), ketoconazole (8.6%), voriconazole (1%), and posaconazole (1%) [2, 14–17]. When the causative agent cannot be isolated, terbinafine should be the first-choice drug because cases resistant to itraconazole or griseofulvin were reported to be responsive to terbinafine [8, 11]. The duration of MG treatment should be longer than that of superficial dermatophytic infections [35]; depending on disease severity and the patient's immune status, it can last between 1 and 6 months.

Not only the causative agent but also the type of invasive dermatophytosis is important in determining the treatment. While in case of MG, terbinafine is the drug of choice, and other invasive dermatophytic infections are difficult to treat. Thus, the therapeutic response of patients with mycetoma and pseudomycetoma is rather poor [23, 24]. Therefore, it is of key importance to accurately diagnose the diseases, especially in immunocompromised patients.

Conclusions

- There are four different types of invasive dermatophytic infections, and it is important to distinguish among them in order to apply correct treatment and assess prognosis.
- MG is exclusively caused by dermatophytes.
- To diagnose MG, the causative agent should be isolated and identified as dermatophyte by fungal culture or molecular methods.
- Histopathology is an important diagnostic method, which should be applied to reveal perifollicular granulomatous inflammation in order to confirm MG diagnosis.

Compliance with Ethical Standards

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

Ethical Approval This article does not describe any studies with human participants or animals performed by the authors.

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