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CLINICAL CASE REPORT

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A Case Report of Majocchi's Granuloma Associated with Combined Therapy of Topical Steroids and Adalimumab

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Abstract: Currently, tumor necrosis factor alpha (TNF-alpha) inhibitors are widely used for many autoimmune disorders. However, they cause an immunocompromised status that sometimes leads to many cutaneous side effects including atypical infections. Herein, we report the first case of adalimumab-related Majocchi's granuloma.

A 43-year-old Taiwanese male patient with chronic plaque-type psoriasis developed numerous tender nodules 1 month after adalimumab injection. The nodules responded poorly to bacterial folliculitis treatment. After repeated skin biopsies for pathology and tissue fungal culture, Majocchi's granuloma was confirmed. Adalimumab was withheld, and 12 weeks of terbinafine treatment was given. On completion of treatment, the nodular skin lesions and dystrophic nail lesions improved dramatically.

The information, including time span, clinical features, histological findings, and improvement following withdrawal of adalimumab and treatment with an oral antifungal agent, indicates that Majocchi's granuloma was adalimumab-related. Psoriasis patients are more susceptible to dermatophyte infection due to local and systemic immunosuppressant therapy. It is important to perform a thorough examination for latent dermatophyte infection, including skin and nail lesions, before treatment with TNF-alpha inhibitors and during traditional psoriasis treatment. When atypical presentation together with treatment failure is noted in psoriasis patients prescribed biologics, clinicians should investigate evidence of dermatophyte infection and provide proper treatment. Sometimes, multiple skin biopsies and tissue fungal cultures are required to establish a correct diagnosis.

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Abbreviations: CARD9 = caspase recruitment domain–containing protein 9, GMS = Grocott's Methenamine Silver, ICAM-1 = intercellular adhesion molecule 1, IFN-γ = interferon gamma, IL = interleukin, KOH = potassium hydroxide, MHC = major histocompatibility complex, p38 MAPK = p38 mitogen-activated protein kinase, PAS = periodic acid–Schiff, PASI = psoriasis area severity index, PCR = polymerase chain reaction, S100A8 = S100 calcium binding protein A8, STAT = signal transducers and activator, TNF-alpha = tumor necrosis factor alpha.

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INTRODUCTION

Currently, tumor necrosis factor alpha (TNF-alpha) inhibitors are widely used for many kinds of autoimmune disorders.[1] Among them, adalimumab (HUMIRA, AbbVie Inc, North Chicago, IL) is used worldwide in treating plaque-type psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, Crohn disease, and ulcerative colitis.[2] Because of the immunocompromised status of patients who use TNF-alpha inhibitors, risk management plans including tuberculosis and viral hepatitis tests must be done before prescription. Our objective was to relate a case of Majocchi's granuloma induced by adalimumab, which has not been previously reported. Clinicians should know the possible infection risk and treat infections immediately.

CASE REPORT

A 43-year-old Taiwanese businessman with chronic plaque-type psoriasis developed numerous mildly tender skin nodules 1 month after receiving adalimumab. He had been diagnosed as having plaque-type psoriasis for 2 years with thick, scaling plaques on the scalp, neck, lower back, and all 4 limbs. Nail changes including nail pitting, leukonychia, oil stains, distal ungual crumbling, and subungual hyperkeratosis were also found (Figure 1A). Initially, topical steroids, Daivobet ointment (calcipotriol with betamethasone, LEO Pharma, Ballerup, Denmark), oral methotrexate, acitretin, and narrow-band ultraviolet radiation B were the main therapy. During treatment, a short period of tinea infection presented as annular erythematous scaly patches and plaques with central clearing on the right forearm, face, and neck. This was confirmed by septated hyphae observed on microscopic examination with 10% potassium hydroxide (KOH). Most of the annular lesions were located on previous psoriatic plaque areas. The tinea corporis was gone after the patient received topical ketoconazole treatment for 1 month. No remnant annular lesions were seen. However, many psoriatic plaques persisted despite many kinds of traditional psoriatic treatment. His psoriasis area severity index (PASI) score was as high as 24.4. Thus, adalimumab was prescribed at the standard dosage and intervals.

Chronic psoriatic plaques improved gradually, manifesting decreased thickness and scaling. Three months later, most psoriatic plaques were barely visible except for 2 palm-sized plaques on the lower legs. However, several acute skin eruptions appeared on the nape of the neck 1 month after the first dose of adalimumab. These lesions presented as erythematous, mildly tender nodules, and the locations roughly corresponded to the previous tinea corporis sites (Figure 1B). Even though these lesions were nonpruritic, the patient tried to reduce the lesions by scratching sometimes. These new skin eruptions

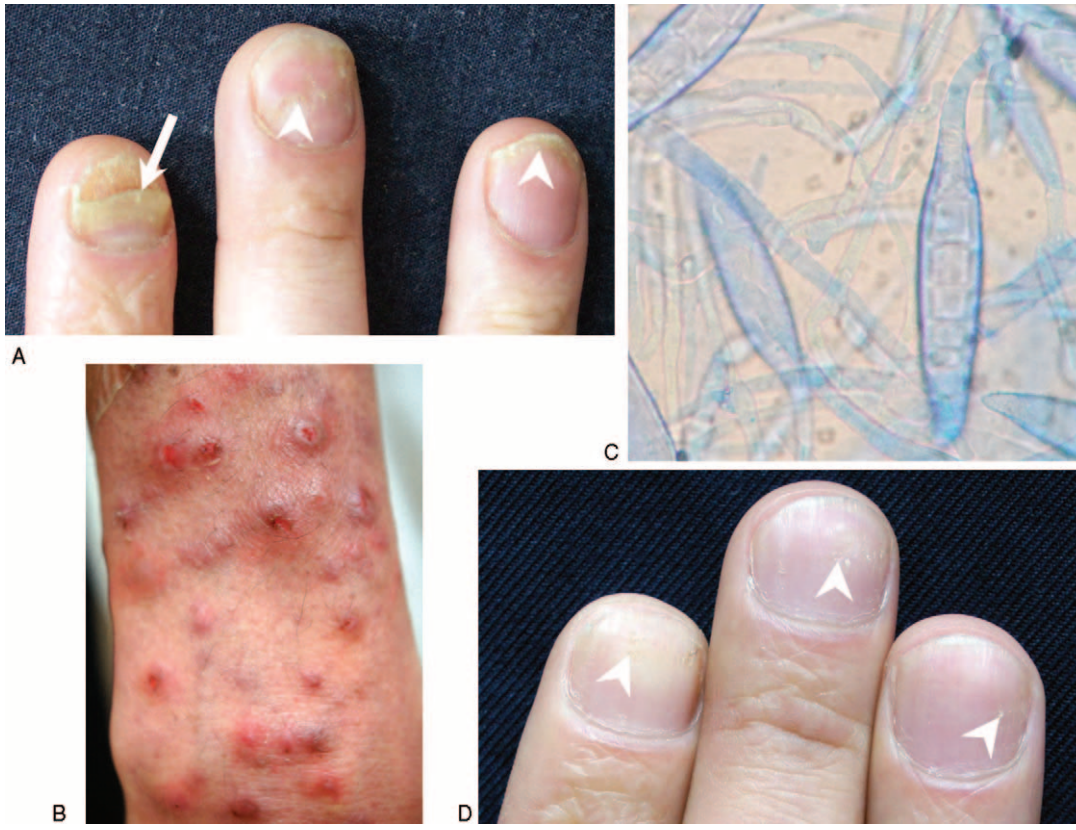

FIGURE 1. A, Nail lesions before adalimumab injection: nail pitting (arrowheads), leukonychia, oil stains, distal ungual crumbling, and hyperkeratosis (arrow). B, Clinical presentation of Majocchi's granuloma: multiple erythematous papulonodules developed 1 month after adalimumab injection. C, *Microsporum gypseum*: fungal hyphae (arrowheads) highlighted with Grocott's Methenamine Silver (GMS) stain (original magnification ×400). D, Nail lesions after 12-week terbinafine treatment: almost all hyperkeratotic nails havereturned to normal except for mild nail pitting on a few nails (arrowheads).

progressed during the course of treatment with the biologic agent and extended rapidly to the face and 4 limbs.

We prescribed oral minocycline and topical benzoyl peroxide for 1 month under an initial diagnosis of folliculitis or furunculosis, but lesions still increased. Skin biopsy was prescribed due to the poor response to treatment. Biopsies were performed 3 times because the initial pathological diagnosis was inconclusive. The first biopsy showed a ruptured epidermal infundibular-type cyst involving the hypodermis with suppurative abscess formation. However, inflamed ruptured epidermal cysts neither appeared in a cluster nor spread out over a short period of time.

Two subsequent biopsies were arranged. The pathology of the second biopsy demonstrated a small locus of clustered and partially yellow-pigmented fungal hyphae surrounded by suppurative granulomatous inflammation in the deep reticular dermis. The third biopsy revealed destroyed hair follicles containing some septated fungal hyphae surrounded by mild, deep folliculitis, and fibrotic granuloma formation. These intrafollicular fungal spores and hyphae were confirmed using periodic acid–Schiff (PAS) and Grocott's Methenamine Silver (GMS) stains. *Microsporum gypseum* complex grew in the soft tissue culture (Figure 1C). However, both fingernail and toenail fungal cultures yielded negative results.

Adalimumab was discontinued after a diagnosis of Majocchi's granuloma was established. By this time, the patient had already received adalimumab biweekly for 5 months. All other psoriatic treatment was suspended, including the topical steroid, Daivobet ointment, and narrow-band ultraviolet radiation B. Meanwhile, we initiated a systemic antifungal therapy of terbinafine (250 mg) once daily. After 12 weeks of treatment with systemic terbinafine, cutaneous nodules had almost disappeared, and all the nails were almost normal except for minimal pitting (Figure 1D). We performed cryotherapy and prescribed topical 1% butenafine hydrochloride cream for the few remaining lesions on the scalp and thighs. The patient felt no discomfort during the entire treatment course.

DISCUSSION

Adalimumab-induced deep fungal infections, including pulmonary and disseminated histoplasmosis, coccidioidomycosis, aspergillosis, and blastomycosis, have rarely been reported.[3] One case reported a patient with rheumatoid arthritis and severe asthma who developed an invasive *Trichophyton rubrum* infection after she received infliximab (REMICADE) and long-term prednisolone.[4] Herein, we report the first case of Majocchi's granuloma associated with a combined therapy of topical steroids and adalimumab.

Majocchi's granuloma (Majocchi granuloma, granuloma trichophyticum, nodular granulomatous perifolliculitis), first described in 1883, may develop on any hair-bearing area, most

TABLE 1. Majocchi's Granuloma in Immunocompetent and Immunocompromised Patients

Characteristics	Immunocompetent Patients	Immunocompromised Patients
Locations	Follicular type	Follicular or subcutaneous nodular type
Mechanism	Trauma or local immunosuppression	Trauma or systemic immunosuppression
Clinical presentations	Clustered erythematous, perifollicular papules or small nodules or pustules	Clustered erythematous, perifollicular papules or small nodules or subcutaneous nodules with abscesses. Rare systemic dissemination
Associated conditions	Atopic dermatitis, topical steroid use, occlusion, leg shaving, scratching	Leukemia or lymphoma, autoimmune diseases, high-dose chemotherapy, post–organ transplantation, inherited CARD9 deficiency, biologics

often the scalp, face, forearms, hands, and legs.[5] It is an uncommon, deep fungal folliculitis related to cutaneous dermatophyte infection.[6] The fungi disrupt hair follicles and spread into the dermis producing a granulomatous inflammation.[7]

Causative fungi for Majocchi's granuloma are *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton epilans, Trichophyton violaceum, Microsporum audouinii, Microsporum gypseum, Microsporum ferrugineum, and Microsporum canis*. The most common one is *Trichophyton rubrum*.[8] Both immunocompetent and immunocompromised patients may develop Majocchi's granuloma with different clinical presentations (Table 1).[5,6,8–10] In immunocompetent patients, trauma such as scratching or leg shaving, and local immunosuppression such as topical steroid use are predisposing factors to Majocchi's granuloma. Topical steroids, which are potent inhibitors of T-lymphocyte proliferation that modify the functions of epidermal/dermal cells and leukocytes, are well-known agents that increase the risk of dermatophyte infection.[11]

Why did our patient develop Majocchi's granuloma? First, before developing the granuloma, our patient received potent topical steroids and Daivobet ointment, which led to local immunosuppression. Second, adalimumab, which can cause systemic immunosuppression, was administered for better control due to inadequate clinical response to topical agents and phototherapy. Adalimumab, a TNF-alpha inhibitor, suppresses cell-mediated immunity and inflammatory response, thereby compromising defenses against invasion by dermatophytes.[1]

Dermatophyte species and *Candida* spp. share common cell wall carbohydrates and are recognized by the same innate immune mechanisms, such as Dectin-1 and Dectin-2; they also induce a similar adaptive response.[12] Antimicrobial mechanisms include innate immunity, adaptive immunity, and phagocytosis. These mechanisms and immune deficiencies associated with dermatophyte and *Candida* infection are listed in Table 2.[12–19]

There are 3 possible mechanisms of TNF-alpha inhibitor related dermatophyte and *Candida* infection. First, S100 calcium binding protein A8 (S100A8), the antimicrobial peptide, is upregulated in psoriatic skin and exerts antifungal activity. TNF-alpha and interleukin (IL)-17A induced S100A8 mRNA and protein via the p38 mitogen-activated protein kinase (MAPK) pathway. Significant decreases in S100A8 mRNA at treatment Day 14 are seen in psoriasis patients who have received adalimumab.[13]

Second, transforming growth factor beta 1, interferon gamma (IFN-γ), IL-6, and IL-22 induce podoplanin-expression in keratinocytes, which may be involved in the pathogenesis of psoriatic hyperproliferative epidermis. IFN-γ, IL-6, and IL-22 upregulate the podoplanin expression in both signal transducers and activator (STAT)-1- and STAT-3-dependent manners.[20] Patients with deficiencies in innate (dectin-1, CARD9, IL12RB1) or adaptive immunity (interleukin (IL)17-F, IL-17 receptor, STAT1, STAT3, antibodies to Th-17 cytokines) that disrupt the Th-17 pathway cannot fight superficial Candida or

TABLE 2. Antimicrobial Mechanisms and Immune Deficiencies Associated With Dermatophyte and *Candida* Infection

	Antimicrobial Mechanisms	Immune Deficiencies
Innate immunity	Antimicrobial peptide S100A8[13]	TNF-alpha inhibitor[13,*]
	Dectin-1[12]	Dectin-1 deficiency[12]
	CARD9[12,14,15]	Inherited CARD9 Deficiency[12]
Adaptive immunity	STAT1, STAT3[14]	TNF-alpha inhibitor: increase phospho-STAT4 and 6[16,*]
	Th-17 pathway, IL-17, TNF-alpha[14,17,18]	TNF-alpha inhibitor[*]
	MHC alleles[12]	
Phagocytosis	Oxidative killing[14]	
	Neutrophils[14]	Neutropenia[14]
	ICAM-1[12]	ICAM-1 deficiency[12]
	Dendritic cells, macrophages, T cells[19]	TNF-alpha inhibitor[19,*]

CARD9 = caspase recruitment domain–containing protein 9, ICAM-1 = intercellular adhesion molecule 1, IL = interleukin, MHC = major histocompatibility complex, p38 MAPK = p38 mitogen-activated protein kinase, S100A8 = S100 calcium binding protein A8, STAT = signal transducers and activator.

[*] TNF-alpha inhibitor related.

dermatophyte infections.[14] Though TNF-alpha inhibitors suppress the activity of psoriasis via increasing phospho-STAT4 and 6,[16] no previous studies report the relationship between TNF-alpha inhibitors and STAT 1 and 3. The exact interaction between TNF-alpha inhibitors and STAT 1 and 3 requires further study.

Third, peripheral mononuclear cells release IFN-gamma in response to dermatophyte compound stimulation with elevated serum levels of TNF-alpha.[17] TNF-alpha inhibitors decrease the TNF-alpha level, and may impair the response to dermatophyte infection.

Whether psoriasis patients have a higher incidence of dermatophyte infection remains a debated issue. Researchers who have found an increased incidence of dermatophyte infection posit the hypothesis that morphological abnormalities in psoriatic nails (eg, hyperkeratosis and onycholysis) and the use of systemic and topical immunosuppressive drugs are predisposing factors for invasion of the nail by microorganisms.[21] They believe that abnormal capillary units in psoriatic nails impair the defense normally supplied by healthy hyponychium and weakens the nail defense system against invading microorganisms. In contrast, other researchers who observed a decreased incidence of dematophyte infection think that immune response against microbial skin infections is stronger with psoriasis.[21] Moreover, psoriatic nails have a higher turnover and desquamation rate and may lower the rate of nail keratin invasion by fungal organisms. A systemic review conducted by Klaassen et al indicated that the prevalence of onychomycosis in psoriatic patients seems to be increased when compared with control groups and literature on healthy populations, although conclusive evidence is lacking.[21] In addition, psoriasis patients frequently receive systemic and topical immunosuppressive drugs that may facilitate the development of dermatophyte infections.[21]

Majocchi's granuloma usually begins as a nonpruritic solitary patch or as multiple well-circumscribed oval patches. Then, it becomes clustered perifollicular papulopustules, nodules, or erythematous, granulomatous lesions.[6] Onychomycosis is a huge reservoir of dermatophytes.[7] Thus, inquiry should be made about a history of tinea pedis, corporis, or onychomycosis in susceptible patients.[6] Sometimes, skin and nail lesions associated with psoriasis and tinea infection share similar clinical presentation; therefore, KOH preparation and fungal culture could be useful tools for differentiation between psoriatic nails and onychomycosis and between annular resolving psoriatic plaques and annular tinea plaques. Because KOH preparation can only detect fungi located in the stratum corneum, the result may be negative for Majocchi's granuloma due to deeper invasion of the fungi into the dermal follicular component. In such circumstances, a skin biopsy with special staining (PAS or GMS) and tissue fungal culture may be more diagnostic.[6] A negative result on microscopy cannot exclude the diagnosis of Majocchi's granuloma.[5] Other tests, such as the trichophytin skin test and anti-body (anti-Mycobacteriumand anti-Trichophyton antibodies) and polymerase chain reaction (PCR)-based molecular typing, could yield variable results.[7]

Treatment of Majocchi's granuloma includes removing predisposing factors (such as topical steroid use, occlusion, and leg shaving) and prescribing a combination of topical and systemic antifungal therapy.[6] Most antifungals exert only fungistatic activity and only temporarily inhibit fungal growth. Recurrence will be noted if this treatment is too short. Newer antifungal agents such as terbinafine provide fungicidal and likely immuno-stimulating activity on neutrophils.[5] If onychomycosis is identified, a 12-week course of terbinafine treatment is indicated. Dermatophytosis may respond slowly to therapy at first and have a tendency to relapse.[8] Cryotherapy can be considered in refractory cases.[5]

In conclusion, atypical clinical behavior such as progressive and rapid development of newer lesions and treatment failure in psoriasis patients who have been prescribed biologics should alert care providers to investigate symptoms of dermatophyte infection. Longer treatment and potentially toxic antifungals may be needed if delayed diagnosis causes more extensive involvement.[6] Surgical debridement may also be required in severe cases.[6,7] Sometimes, multiple skin biopsies and tissue fungal cultures are needed to establish a correct diagnosis. As a result, a thorough physical examination and additional tests for latent dermatophyte infection, including skin and nail lesions, before treatment with TNF-alpha inhibitors and during traditional psoriasis treatment are important.

The limitation of our report is that we have only 1 case. Therefore, the incidence of this significant adverse effect requires further investigation. The information, including time span, clinical features, histological findings, and improvement following withdrawal of adalimumab and taking an oral antifungal agent, indicates that Majocchi's granuloma was adalimumab-related.

CONCLUSION

Psoriasis patients seem to be susceptible to dermatophyte infection due to local and systemic immunosuppression therapy. A thorough physical examination and additional tests for latent dermatophyte infection, including skin and nail lesions, before treatment with TNF-alpha inhibitors and during traditional psoriasis treatment are important. During treatment with biologics, when acute skin lesions develop with atypical clinical morphology and persist even under ongoing biologic treatment, clinicians should investigate evidence of dermatophyte infection and provide proper treatment as soon as possible. Multiple skin biopsies and tissue fungal cultures are sometimes required to establish the diagnosis. To our knowledge, this is the first case of adalimumab-related Majocchi's granuloma.

ETHICAL REVIEW AND PATIENT CONSENT

The Institutional Review Board (IRB) of China Medical University Hospital has stated that it is not necessary to achieve IRB approval for this case report and this report requires obtaining patient consent since this study is dealt with only the patient's medical record and related images. The informed consent of this case report and associated images was obtained from the patient for the publication.

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