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CASE REPORT

Cutaneous *Mycobacterium intracellulare* infection presenting as multiple asymptomatic papulonodules in an immunocompetent adult: A case report and review of the literature

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ABSTRACT

Disseminated cutaneous nontuberculous mycobacteria infection is rare in immunocompetent hosts. We report a case of *Mycobacterium intracellulare* infection in an immunocompetent patient presenting with simultaneously developing multiple asymptomatic cutaneous papulonodules. The possibility of lung lesions as the primary focus is suspected. We review the literature for other cases of multiple cutaneous *M avium* complex infections in immunocompetent hosts. There are differences in the virulence of M avium and M intracellulare, and hence in the underlying immune status of the hosts.

Introduction

Nontuberculous mycobacteria (NTM) are opportunistic pathogens that can cause lung, skin/soft tissue, lymphatic, or disseminated infections, mainly in immunocompromised patients. *Mycobacterium avium* complex (MAC) consists of several closely related slow-growing nonchromogens of NTMs, including *M intracellulare*. MAC accounts for the largest portion of all NTM infections in most epidemiologic series.[1,2] They are environmental organisms widely distributed in soil, water, and animals. The routes of infection include inhalation, ingestion, or direct inoculation by trauma or medical procedures. Disseminated NTM infections usually occur in patients with acquired immunodeficiency syndrome (AIDS), and they have been reported sporadically in patients with other forms of immunosuppression. We report a rare case of disseminated cutaneous MAC infection in an immunocompetent patient.

Case report

A man aged 54 years was referred to our clinic for slowly progressing asymptomatic eruptions. The lesions began first on the right arm 2 years ago and additional lesions developed shortly after. On inspection, erythematous indurated papules and nodules were present on his right arm, left cheek, right ankle, and back (Figure 1). None of the lesions showed surface changes of erosion, ulceration, or desquamation. The skin biopsy in the referring hospital showed granulomatous inflammation of the dermis and subcutis with negative periodic acid-Schiff (PAS) and acid-fast stain for microorganisms. The tissue cultures for bacteria, fungi, and mycobacteria were all negative. Under the diagnosis of granuloma of unknown causes, methotrexate and thalidomide were prescribed without improvement.

The patient had been a truck driver dealing with waste recycling for many years, but he did not recall any related trauma experiences on the affected sites. He had a history of pulmonary tuberculosis about 30 years ago, and he had received a complete antituberculosis treatment course at that time. He was also a heavy smoker for more than 30 years. One year before the first presentation of his right arm lesion, he had been hospitalized for 6 days due to atypical pneumonia with fever, chills, dyspnea, weight loss, and hypoalbuminemia. However, no specific pathogen was identified during the hospitalization. The clinical symptoms and pulmonary infiltrations improved after clarithromycin and amoxicillin/clavulanic acid treatment, yet there were calcified fibronodular interstitial infiltrates left in the left upper lobe of lung in the follow-up chest X-ray. He was otherwise healthy and was not under any

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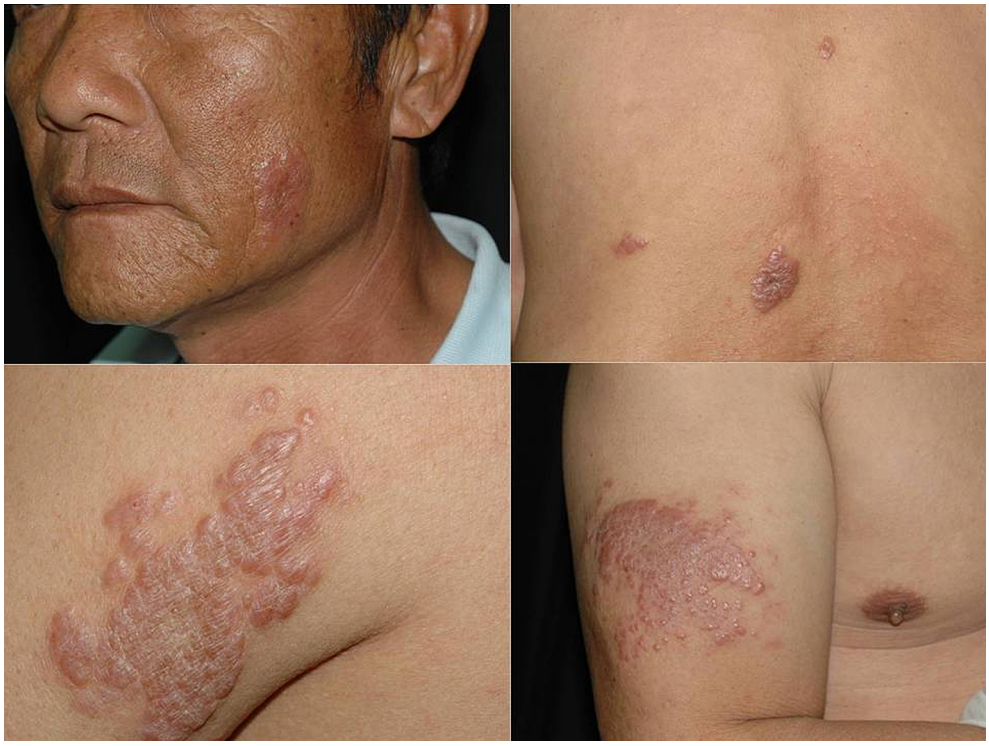

Figure 1 Discrete and confluent red brown papulonodules on the face, limbs, and trunk.

immunosuppressive medication. The routine laboratory data were unremarkable.

We performed a skin biopsy from the right arm lesion that showed noncaseating granulomatous inflammation involving superficial dermis and subcutis with scattered multinucleated giant cells (Figures 2 and 3). The PAS and acid-fast stains were negative. Two months later, the tissue culture grew a nontuberculous mycobacterium. The isolate was negative for niacin accumulation, catalase at 68°C, hydrolysis of Tween 80, or arylsulfatase at 14 days. The colonies of the isolates were buff after 14 days of incubation. Confirmation of these isolates to the species level was performed by partial 16S rRNA gene (1464 bp) analysis using two primers (primers 8FPL and 1492) as described previously.[3] The sequences were compared with known 16S rRNA gene sequences in the GenBank database of the National Center for Biotechnology Information using the basic local alignment search tool (BLAST) algorithm. The species of all the isolates with the best match was *M intracellulare* (accession number AY859027.1, 98% identity). No lymphadenopathy was present, and the tests for human immunodeficiency virus (HIV) and antinuclear antibody were negative. Serum protein electrophoresis revealed normal immunoglobulin levels. After a 4-month treatment with oral clarithromycin 500 mg twice daily and levofloxacin 500 mg daily, the lesions resolved with residual hyperpigmentation (Figure 4). There was no recurrence of the lesions 2 years after completion of the treatment. The follow-up chest X-ray and computer tomography showed focal areas of fibroreticular shadows within the bilateral upper lungs consistent with old tuberculosis.

Discussion

Disseminated NTM infections usually occur in patients with AIDS or other forms of immunosuppression. The typical manifestations of disseminated MAC infections are fever, night sweats, and weight loss, with fever being the most common presentation.[4] Disseminated cutaneous MAC infections have an extremely rare occurrence rate in immunocompetent patients, and most of the reports are from Japan (Table 1).[5–16] Concurrent non-cutaneous foci, including lymph nodes, joints, bone marrow, or lung were present in one-half of the cases (seven out of 14). Six out of the seven cases with isolated cutaneous MAC infections had ulcers,

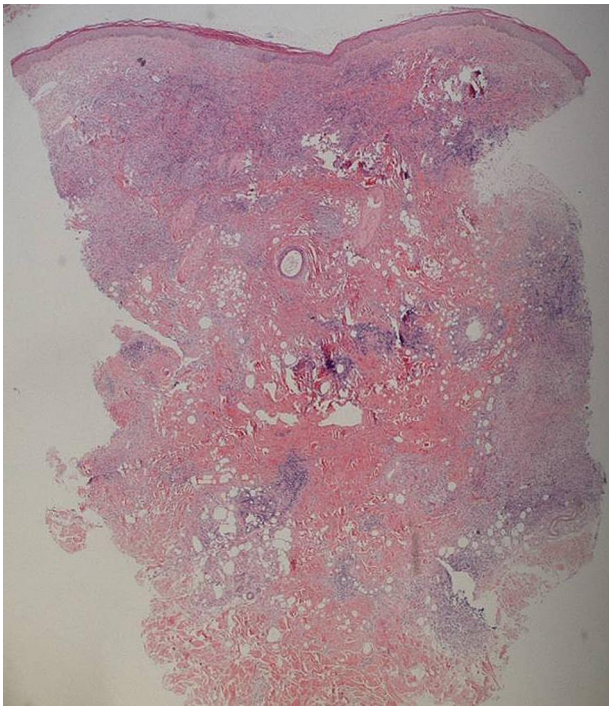

Figure 2 Nodular inflammation involving the superficial dermis and subcutis with uninvolved epidermis.

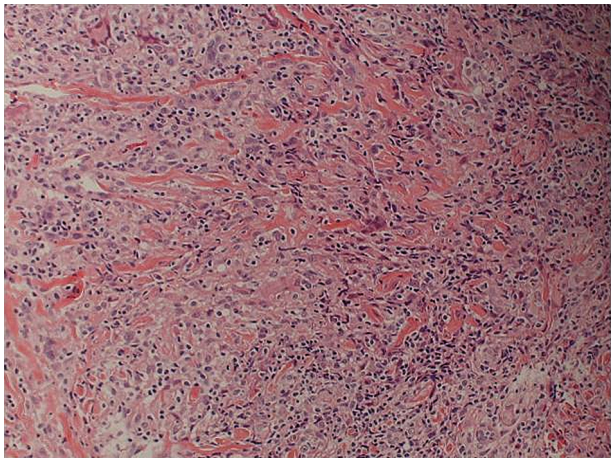

Figure 3 Noncaseating granulomatous inflammation with scattered multinucleated giant cells.

discharge, or fistula. Thus in some of these patients, the development of multiple skin lesions may represent autoinoculation and not true dissemination.[13,14,16] Papulonodules without surface changes, as seen in our patient, were present in four cases (Cases 1, 6–8). In three out of the four cases (Cases 1, 6–7), cervical lymphadenopathy was also present.

Our patient had skin *M intracellulare* infections involving different skin areas within a short period. In view of the simultaneous occurrence of multiple lesions and the absence of related local skin trauma histories, we suspected that his skin infections might result from a hematogenous or lymphatic spreading. The atypical pneumonia one year before the skin eruptions might be the source of his primary infection, which was partially controlled by the antibiotics. In a study conducted by Reed and colleagues,[17] the most significant environmental risk factor for MAC infections was cumulative occupational exposure to soil. The cumulative exposure to recycled wastes, the prior pulmonary tuberculosis, and the history of decades of smoking might contribute to the vulnerability to MAC pulmonary infection in our patient.[18] The pathogenesis of disseminated MAC infections in patients without recognizable underlying immunosuppression is not well known. Congenital or acquired defects in the interferon (IFN)-γ/ interleukin (IL)-12 pathways had been observed in some of these patients.[19,20]

Although in most literature, *M avium* and *M intracellulare* were not differentiated due to their similar biochemical characteristics, some epidemiologic studies implicated that these two organisms exhibited different virulence. Most of the MAC infections in AIDS patients were caused by *M avium*, whereas *M intracellulare* was responsible for a larger portion of MAC lung diseases in non-HIV patients.[21] Moreover, among non-AIDS patients with MAC isolated, only 16.2% of the patients with *M avium* had an American Thoracic Society-defined probable to definite infection, which is in contrast with 63.1% of the *M intracellulare* group.[22] An ecologic study revealed that *M intracellulare* tended to form biofilm more often than *M avium*.[23] This attachment and growth ability might provide an explanation for the higher pathogenic property of *M intracellulare*.

Currently, an established principle for treatment of MAC infections is a macrolide based two- or three-drug regimen for 6–12 months.[18] In our case, because of the clinical resolution, the patient refused further treatment after 4 months of clarithromycin and levofloxacin. No relapse was observed after a 2-year follow-up. As the current MAC treatment guideline is mainly based on pulmonary infection, whether a shorter course is acceptable for isolated multiple cutaneous MAC infection remains unknown due to the rarity of such cases. The prognosis varies widely and may be affected by the underlying diseases, affected sites, and early treatment.

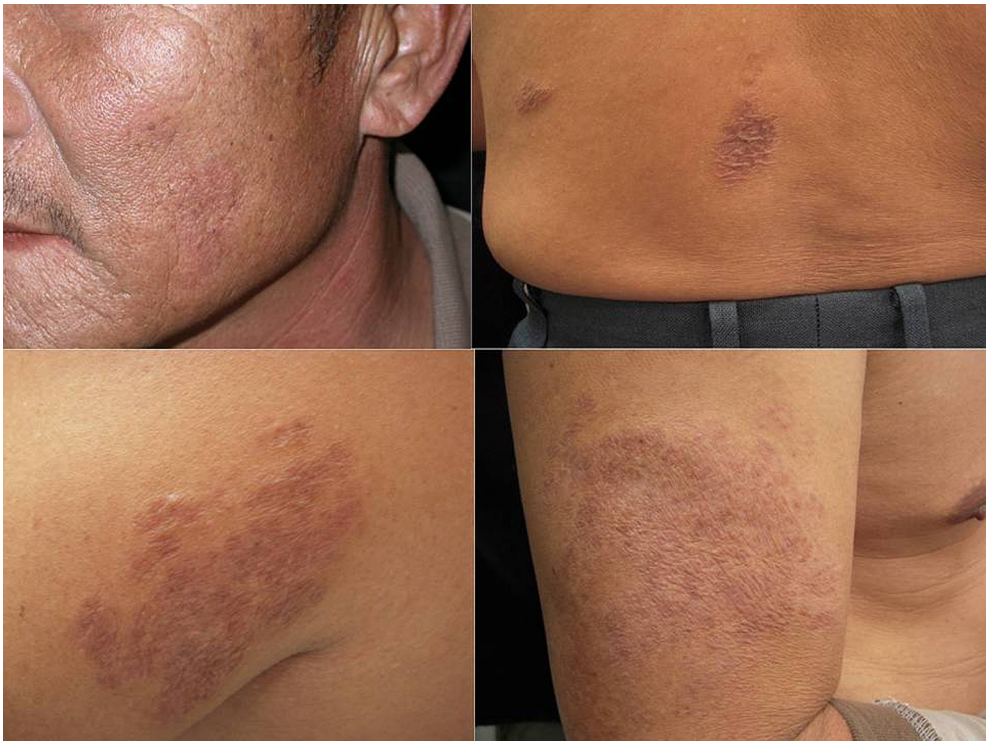

Figure 4 The papulonodular lesions resolved with residual hyperpigmentation after a 4-month treatment with oral clarithromycin and levofloxacin.

Table 1 MAC infections in immunocompetent hosts with multiple cutaneous lesions.

Age/Sex	Species	Disease duration	Involved skin areas	Appearance of lesions	Systemic involvement	Treatment/response
1. 65/F[5]	MI	13 yr	Back, face, neck, chest, Rt forearm, loin	Violaceous and brown plaques	Neck LAP	DDS, INH, RFP 1 y/CR
2. 11/F[6]	MAC	3 yr	Lt foot, Rt ankle, Rt hand, Lt infraorbital	Subcutaneous plaques with draining sinuses, crust	Osteomyelitis, cervical LAP	NA
3. 20/M[7]	MAC	4 mo	Face, Rt arm	Violaceous edematous patch, pustules, scar	Nil	Clofazimine 6 mo, then EB + RFP 2 y/PR
4. 40/M[7]	MA	8 yr	Face, upper back	Eroded, crusted plaques	Neck LAP, lung,	INH, RFP, EB, clofazimine, SM, 5 m/CR
5. 6/M[8]	MAC	1 mo	Thighs, abdomen, Lt buttock, Lt forearm	Nodules, ulcers	Nil	INH + excision/CR
6. 62/F[9]	MAC	7 yr	Face, ears, neck, abdomen, back	Papules, nodules, plaques	Cervical LAP	CAM, ciprofloxacin, EB, 8 m/CR
7. 52/F[9]	MAC	3 yr	Face, waist, back	Pruritic papules and nodules	Cervical LAP, bone marrow, lung	SM, RFP, INH, EB, clofazimine/PR
8. 2/F[10]	MA	2 mo	Lt axilla, Lt chest, Lt arm, Lt leg,	Nodules	Nil	INH, RFP, cycloserine + excision/CR
9. 10/F[11]	MA	6 mo	Back, Buttocks, thighs	Nodules, ulcers, pus	Inguinal LAP	CAM, INH/PR
10. 48/M[12]	MA	31 yr (skin 1 yr)	Lt shoulder, Rt thigh	Scaly plaques	Knee and ankle arthritis	CAM, EB/CR
11. 11/F[13]	MA	1 yr	Trunk, buttocks, thighs	Nodules with discharge, ulcers, hypertrophy scars	Nil	CAM, 9 m/CR
12. yr9/F[14]	MA	4 mo	Abdomen, hip, thighs	Nodules, ulcers	Nil	Cycloserine, INH, CAM + excision/CR
13. 12/F[15]	MA	4 mo	Buttocks, thighs	Subcutaneous nodules with fistula	Nil	Excision + CAM/CR
14. 60/M[16]	MAC	10 yr	Thighs, buttocks groin, legs, abdomen	Erythematous squamous patches with pustules	Nil	TC + ciprofloxacin, then CAM/PR

CAM = clarithromycin; CR = complete response; DDS = dapsone; EB = ethambutol; Ext = external; F = female; INH = isoniazid; LAP = lymphadenopathy; LN = lymph node; Lt = left; M = male; MA = *Mycobacterium avium*; MAC = *Mycobacterium avium* complex; MI = *Mycobacterium intracellulare*; NA = not available; PR = partial response; RFP = rifampicin; Rt = right; SM = streptomycin; TC = tetracycline; TMP/SMX = trimethoprim-sulfamethoxazole.

We report a rare presentation of disseminated *M intracellulare* infection. It is interesting to note that most cases of disseminated cutaneous MAC infection in immunocompetent hosts are reported from Japan. However, it remains unknown whether this is due to a report bias or there is a true racial or geographic difference. The diagnosis of nonulcerated MAC infection without an identifiable concurrent primary focus remains challenging and a correct diagnosis is often delayed. More clinical vigilance is required for such cases.

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