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Case Report

Refractory Infection of *Mycobacterium abscessus*: Skin and Soft Tissue Infection Recurred under Combination Therapy of Surgery and Outpatient Antibiotics

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Abstract

Mycobacterium abscessus (*M. abscessus*) is a nontuberculous mycobacterium that causes skin and soft tissue infections. Treatment methods for these infections, including the type and duration of antimicrobial agents, have not been established. The function of surgery is also unknown. We report a case of skin and soft tissue infection of the left upper arm in a healthy 47-year-old Japanese man who was treated with complete surgical excision and antimicrobial therapy as feasible on an outpatient basis, which resulted in relapse <1 month later. Given the possibility of developing antibiotic-resistant bacteria, insufficient antimicrobial treatment should not be administered without careful consideration. There are currently few effective oral antimicrobial agents against *M. abscessus*, so careful antimicrobial therapy along with hospitalization (at least during the early treatment phase) is preferred, regardless of the use/nonuse of surgical treatment.

Keywords

Mycobacterium abscessus, skin and soft tissue infection, surgery, antibiotics

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Introduction

Mycobacterium abscessus (*M. abscessus*) is a nontuberculous mycobacterium that occasionally causes skin and soft tissue infections. As *M. abscessus* bacteria have sometimes been multidrug-resistant and the optimal treatment for *M. abscessus* infections has not yet been established[1], it has been proposed that the treatment plan should be carefully chosen in consultation with a mycobacterial disease specialist. At present, the most important treatment strategy for *M. abscessus* infections appears to be multidrug antibiotic therapy including intravenous-only antibiotics, in the inpatient setting[1,2]. The utilization of supplementary surgical therapy in difficult cases has been suggested[2], but this is based on only a very few reports. We have found no published reports of an examination of the extent to which antibacterial therapy can be reduced when surgical excision is performed for an *M. abscessus* infection. We present the case of a skin and soft tissue *M. abscessus* infection of the left upper arm of a healthy adult male who was treated with surgical excision and as much antimicrobial therapy as possible on an outpatient basis, which resulted in relapse at 3 weeks postoperatively.

Case Report

First treatment

A 47-year-old Japanese man with no noteworthy medical history came to our hospital for the examination of a subcutaneous mass and discomfort in his left upper arm that he had been aware of for 1 month. The clinical examination revealed a 40 × 30-mm subcutaneous mass palpated on the left upper arm, with a 4-mm erythematous dermal nodule on the surface skin (**Figure 1**). Laboratory data showed no increase in white blood cells or serum C-reactive protein (CRP) (WBC 8,100/μL, RBC 514 × 10^4/μL, Hb 15.0 g/dL, Ht 44.9%, Plt 231,000/μL, CRP 0.11 mg/dL). Ultrasonography and MRI indicated a cold abscess (**Figure 2 and 3**), and a puncture was thus performed, with the result of purulent fluid.

M. abscessus was found in the culture test of the purulent fluid. Mycobacterial blood cultures were negative, and a contrast-enhanced CT examination showed no disseminated lesions in other parts of the body. A diagnosis of localized

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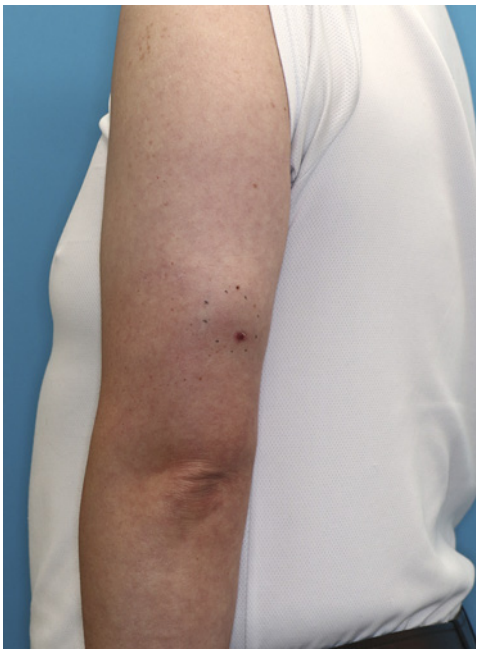

Figure 1. Physical findings. A 40 × 30 mm subcutaneous mass was palpated on the left upper arm, with a 4-mm erythematous dermal nodule on the surface skin.

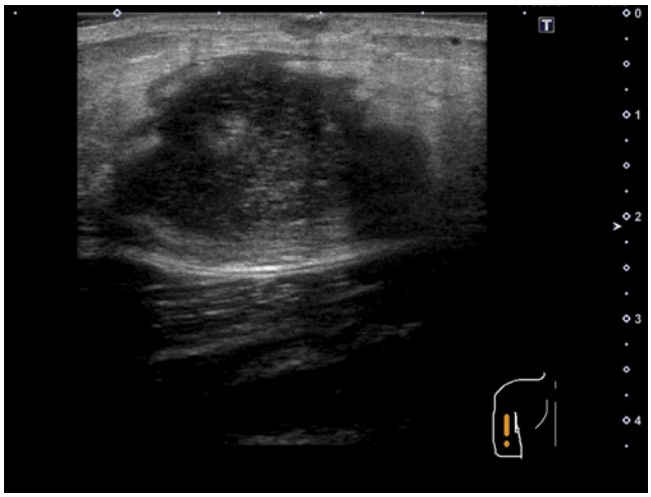

Figure 2. Ultrasound scan of the patient's left arm showing the 30-mm borderline indistinct mass. The internal echo was heterogeneous and showed no blood flow.

skin and soft tissue *M. abscessus* infection was thus created. We consulted with a specialist in infectious diseases, and hospitalization for multidrug therapy was recommended, but the patient preferred outpatient treatment for his own convenience. We therefore decided to surgically remove the abscess with surrounding tissue, lower the amount of bacteria, and treat the patient with a 3×/weekly intravenous infusion of amikacin (1,000 mg/dose) and daily oral medications (azithromycin 250 mg/day + levofloxacin 500 mg/day).

Intraoperatively, the abscess (surrounded by scar-like fibrous tissue) was firmly attached to the surrounding tissue, and purulent fluid was released from some delicate areas. The abscess was totally removed (**Figure 4 and 5**), and the incision was properly cleaned with saline. A Penrose drain was positioned and sutured in two layers. The drain was removed 3 days postoperatively, and stitches were removed at 1 week. The course of the patient seemed to be favorable until 2 weeks postoperatively, but swelling and pain manifest 3 weeks after the surgery.

Second treatment

At that timepoint, ultrasound revealed fluid retention, and the patient was taken to the hospital for recurrence of the infection. Laboratory tests again showed no increase in white blood cells or serum CRP (WBC 5,500/μL, RBC 467 × 10^4/μL, Hb 13.7 g/dL, Ht 41.2%, Plt 261,000/μL, CRP 0.03 mg/dL). Anti-interferon gamma autoantibodies were also examined and found negative. Incision and drainage were performed, and the wound was left open to debridement of the harmful granulation tissue and slough accordingly (**Figure 6**). Regarding antibiotic therapy, in addition to oral azithromycin (250 mg/day), intravenous amikacin (800 mg/day) and imipenem/cilastatin (3 g/day) were given. Thereafter, symptoms of swelling and pain in the patient's upper arm subsided, and he was released from the hospital 7 weeks after admission with a minor remaining ulcer.

Following his release from the hospital, the patient was treated with an intravenous infusion of amikacin (1,000 mg/dose) 3×/week and daily oral antibiotics (azithromycin 250 mg/day + sitafloxacin 100 mg/day) for 2 weeks. The wound gradually healed, and the amikacin was stopped. Azithromycin 250 mg/day + sitafloxacin 100 mg/day was continued for 4 weeks, and the antimicrobial therapy was stopped after complete epithelialization of the wound was determined (**Figure 7**). No recurrence was observed after 6 months, and the treatment was considered successful. The clinical course is displayed in **Figure 8**.

Discussion

M. abscessus is a type of nontuberculous mycobacteria that is commonly found in the natural world (i.e., soil, water pipes)[2], and it is among the rapidly growing mycobacteria in the Runyon classification[3]. *M. abscessus* is differentiated into three subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, and *M. abscessus* subsp. *massiliense*[4]. Clinical manifestations of skin and soft tissue *M. abscessus* infections are subcutaneous nodules, abscesses, papules, and erythema[1,2]. These infections have been associated with nail salon footbaths[5], tattoos[6], public bathing facilities[7], and surgery[8]. Immunosuppressive diseases such as diabetes and the presence of anti-interferon gamma autoantibodies are also considered possible causes of *M. abscessus* infections[9]. Our patient had no history of trauma or immunosuppressive disease, and the source of the infection remains unknown.

For the management of serious *M. abscessus* skin and soft tissue infections, it has been proposed that oral clarithromycin (or azithromycin) in combination with other medications such as amikacin plus imipenem, cefoxitin, or tigecycline

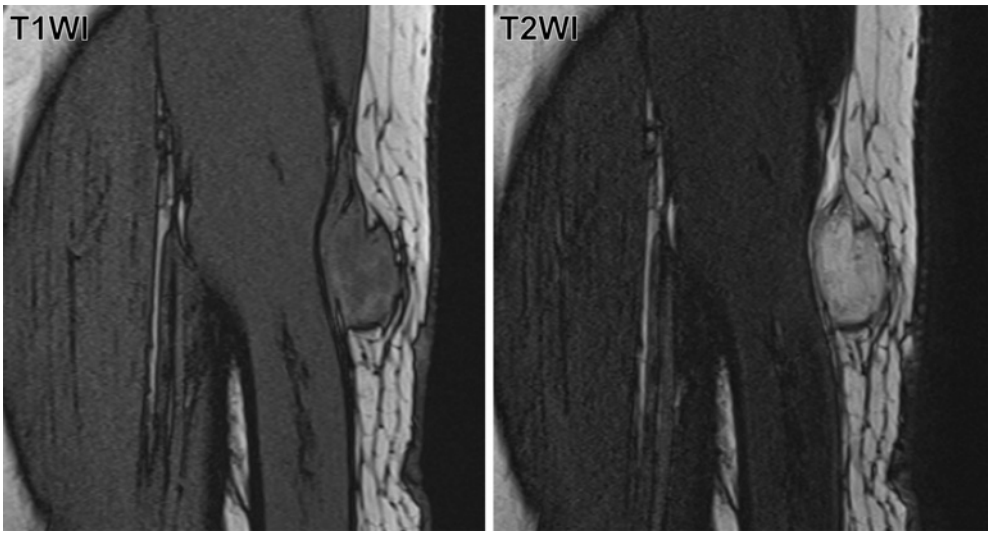

Figure 3. MRI of the patient's left arm. A 22-mm nodule was seen subcutaneously along the fascia in the left upper arm. The signal intensity was moderate on T1WI and high confidence on T2WI. There was no intramuscular invasion.

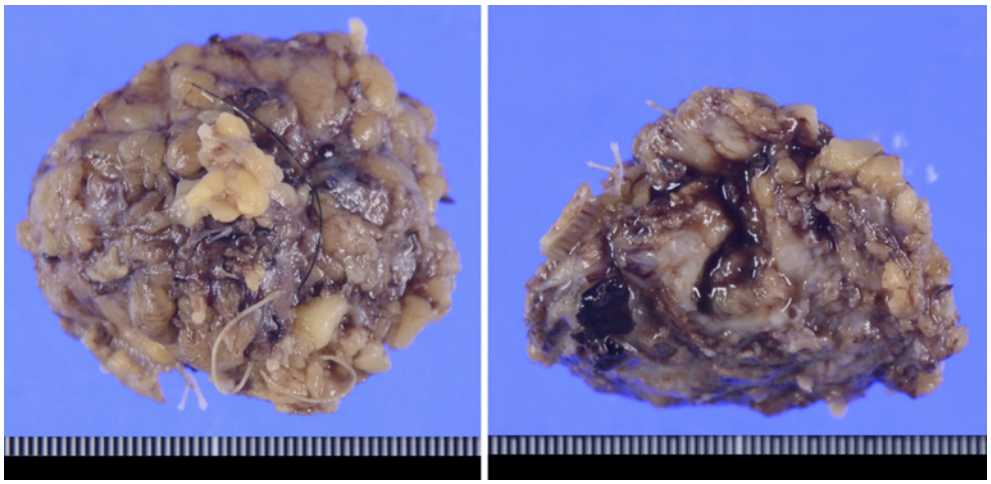

Figure 4. The abscess was totally eradicated.

may be effective[1,2]. Additionally, new guidelines for pulmonary lesions by ATS/ERS/ESCMID/IDSA permit the use of clofazimine and linezolid[10]. Of the above, amikacin, imipenem, cefoxitin, and tigecycline can only be administered intravenously and are occasionally challenging to manage on an outpatient basis. The duration of antibiotic treatment is a matter of controversy and varies depending on the report. Kothavade et al. advised 2-8 weeks of intensive multidrug therapy, including intravenous-only antimicrobials, followed by maintenance therapy with susceptible oral agents to the extent that the total duration of antibiotic therapy is 6 months[1]. Griffith et al. suggested amikacin combined with cefoxitin or imipenem for a minimum of 2 weeks as the initial treatment for an *M. abscessus* infection and antimicrobials for a minimum of 4 months in extreme situations[2].

The maintenance-phase strategy depends on whether or not the isolate is macrolide-susceptible. There are two categories of resistance: mutant resistance caused by mutations in the 23S ribosomal RNA gene and inducible resistance due to acquisition of the *erm* gene[11]. Since the majority of *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii* isolates exhibit active inducible *erm* genes, but *M. abscessus* subsp. *massiliense* does not (with rare instances)[11], it is vital to distinguish clinical *M. abscessus* isolates at the subspecies level, if possible.

Antimicrobials used to treat nontuberculous mycobacteria are frequently associated with adverse reactions, which is one crucial component of long-term antimicrobial therapy. Therefore, warning patients about possible responses and monitoring for them are crucial parts of care. Adverse responses and monitoring techniques of the main antimicrobial agents are listed in **Table 1**[10].

In our patient's case, the first treatment consisted of a three-drug combination of amikacin, azithromycin, and levofloxacin. As at least three medications are recommended in combination, in addition to the dependable amikacin and macrolide, levofloxacin was chosen because it is an oral

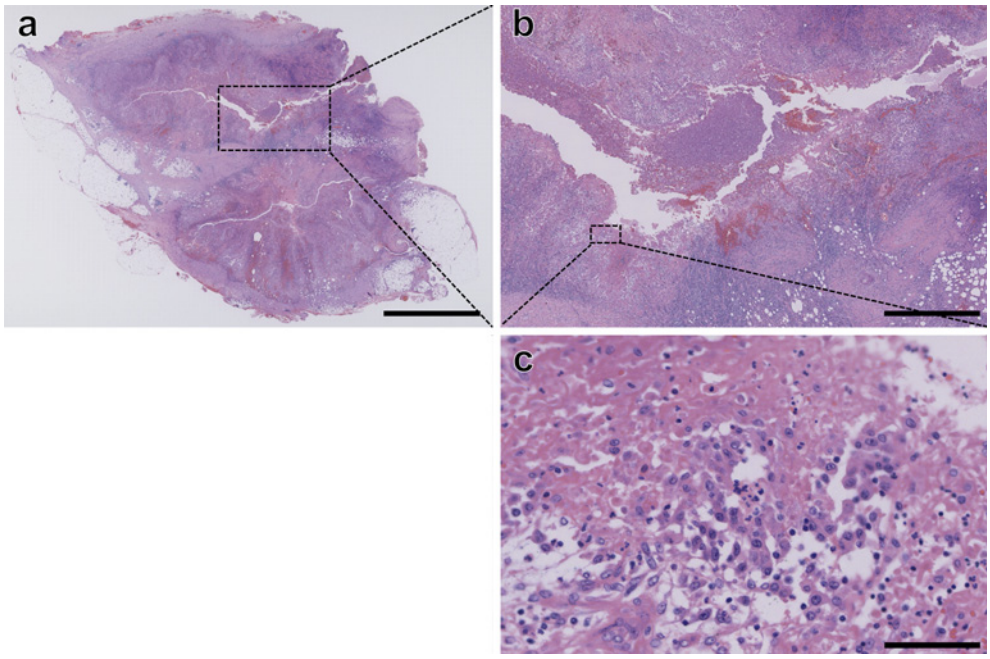

Figure 5. Pathological findings of abscess (hematoxylin–eosin staining). (a) Loupe image of the center. The lesion was surrounded by fibrofatty tissue of the subcutaneous tissue at the margins, and a hollow development was seen in the middle. (b) Enlarged image of the inset in panel (a). The central cavity revealed an accumulation of inflammatory exudate and was surrounded by granulation tissue, suggesting abscess formation. (c) Enlarged image of the inset in panel (b). Neutrophils and lymphocytes were present, interspersed with fibrin-like exudates. Epithelioid histiocytes were present; some clustered to form granulomas. Scales = 8 mm (a); 2 mm (b); 100 μm (c).

Figure 6. The progress during the second treatment. The incision was left open, and debridement of poor granulation tissue and slough was performed as needed.

Figure 7. At the end of the second treatment. Hypertrophic scarring was developed.

drug that could be susceptible and has very minimal adverse effects[1,2,10]. However, the outcome was failure. During the second treatment phase, we implemented the suggested triple therapy involving daily intravenous infusions for 7 weeks as the intensive phase, followed by a 6-week maintenance phase of antibiotic medication, which was successful. There was no apparent adverse effect in either treatment.

Although there have been numerous examples of antimicrobial therapy for *M. abscessus* infections and resistance to antimicrobial medicines, surgery for an *M. abscessus* infection has only been documented as sometimes being required in combination with antimicrobial agents, and we have located no published report of a thorough analysis of the efficacy of surgical treatment in this situation. The only study that examined the effectiveness of surgery in a large number of patients was the report by Villanueva et al. of an outbreak caused by local injection in Barranquilla, Colombia[12]. They

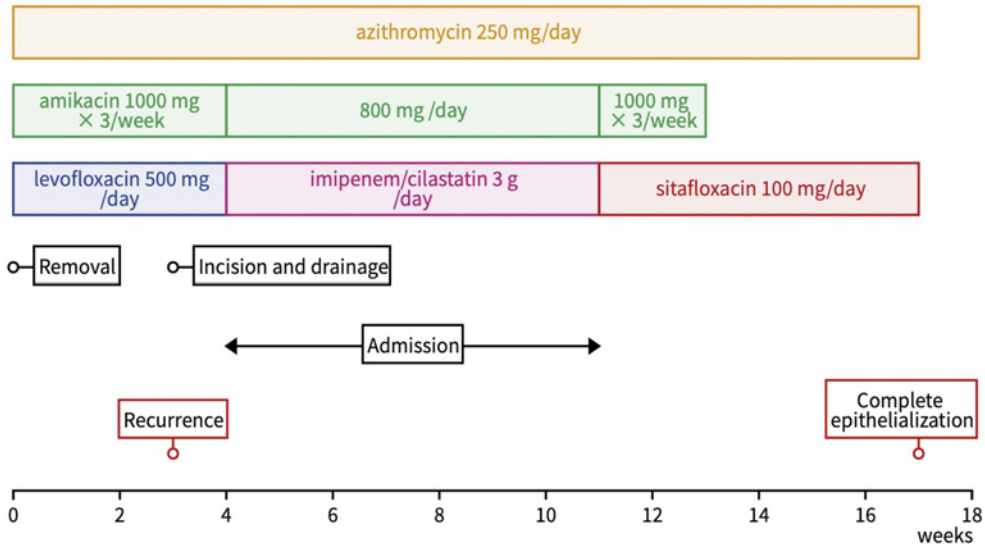

Figure 8. Clinical course of the patient.

Table 1. Common Adverse Drug Reaction and Monitoring.

Administration Route	Drug	Adverse Reactions	Monitoring
Oral (or Parenteral)	Azithromycin	Gastrointestinal	Clinical monitoring
		Tinnitus/hearing loss	Audiogram
		Hepatotoxicity	Liver function tests
		Prolonged QTc	ECG (QTc)
	Clarithromycin	Gastrointestinal	Clinical monitoring
		Tinnitus/hearing loss	Audiogram
		Hepatotoxicity	Liver function tests
		Prolonged QTc	ECG (QTc)
	Linezolid	Peripheral neuropathy	Clinical monitoring
		Optic neuritis	Visual acuity and color discrimination
		Cytopenias	Complete blood count
	Clofazimine	Tanning of skin and dryness	Clinical monitoring
		Hepatotoxicity	Liver function tests
		Prolonged QTc	ECG (QTc)
Parenteral	Amikacin	Vestibular toxicity	Clinical monitoring
		Ototoxicity	Audiograms
		Nephrotoxicity	BUN, creatinine
		Electrolyte disturbances	Calcium, magnesium, potassium
	Cefoxitin	Cytopenias	Complete blood count
		Hypersensitivity	Clinical monitoring
	Imipenem	Rashes	Clinical monitoring
		Cytopenias	Complete blood count
		Nephrotoxicity	BUN, creatinine
	Tigecycline	Nausea/vomiting	Clinical monitoring
		Hepatitis/pancreatitis	Liver function tests, amylase, lipase

conducted a retrospective study of postinjection abscesses of *M. abscessus* (n = 240), contrasting the course of treatment with clarithromycin alone, surgery alone, surgery plus clarithromycin, and no therapy. The surgery plus clarithromycin group was successful for 95% of 148 patients, the highest response rate, compared to 23% of the 35 patients treated with clarithromycin alone and 32% of the 22 patients treated with surgery alone. As limitation of that study, the surgical operations included both the drainage of abscesses and the resection of nodules and fistulae, and the protocol of each procedure was not clear. Furthermore, since the study was based on an outbreak, it is very probable that the same strain of bacteria was responsible and the findings may be skewed. More data is required in order to reach a decision about surgical treatment for *M. abscessus* infections.

In our patient's case, the lesion was contained and there

were no signs of inflammation in the surrounding area, and we thus surmised that majority of the bacteria could be removed by surgery. Although complete removal of the abscess was performed and azithromycin plus amikacin and levofloxacin were used, the abscess returned. It is believed that bacteria were extensively distributed not only throughout the abscess but also in the surrounding scar and subcutaneous tissue. If surgical treatment that does not rely on antibiotics is the goal, then extended resection involving muscles, tendons, and other normal tissues may be necessary, which is occasionally overly invasive. The culture submission of the edges of removed tissue may be helpful, as in osteomyelitis surgery[13,14], in assessing the efficacy of surgery.

There are very few reports on the clinical course of the infection treated with surgery and antibiotic therapy, which is a valuable aspect of this report. The recurrence of the disease, despite the local lesions and absence of immunodeficiency status, suggests the difficulty of treating *M. abscessus* infections. In cases of skin and soft tissue infections in healthy individuals, the patients frequently have no symptoms other than wound discomfort, and because they are of working age, many are reluctant to be hospitalized for treatment. However, given the possibility of producing antibiotic-resistant bacteria, insufficient antimicrobial therapy should not be used carelessly, which is a point for reflection. In the current situation in which there are few effective oral antibacterial medications against *M. abscessus*, it is recommended to provide cautious antimicrobial therapy with hospitalization at least in the early treatment phase, regardless of the presence of surgical treatment. Then, in facilities where drug susceptibility testing is available, de-escalation may be considered for a maintenance phase after the test results are received.

Conclusion

The subcutaneous abscess reappeared in the left arm of our patient, a healthy adult who had been treated unsuccessfully with surgical excision and outpatient antibiotic medication. To eradicate the microorganism solely via surgery in a *M. abscessus* infection of the skin and soft tissues (even if it is a localized lesion), it could be required to have a border beyond at least visually visible lesions. There are currently few effective oral antibacterial medications against *M. abscessus*, so cautious antibiotic therapy combined with hospitalization at least during the first treatment phase is ideal, regardless of the use/nonuse of surgical treatment or immunodeficiency status of the patient. This study was approved by the Internal Review Board of our hospital, and the patient gave his written informed consent for the release of his data and images.

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Conflicts of Interest: There are no conflicts of interest.

Consent for Publication: Written informed consent for publication of images and information about the patients was obtained.

Ethical Approval: The study was reviewed and approved by the Clinical Trial Review Committee at Toranomon Hospital. The approval number is 2486.

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