



Rapidly growing Mycobacterium infections after cosmetic surgery in medical tourists: the Bronx experience and a review of the literature



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ABSTRACT

Background: Medical tourism is increasingly popular for elective cosmetic surgical procedures. However, medical tourism has been accompanied by reports of post-surgical infections due to rapidly growing mycobacteria (RGM). The authors' experience working with patients with RGM infections who have returned to the USA after traveling abroad for cosmetic surgical procedures is described here.

Methods: Patients who developed RGM infections after undergoing cosmetic surgeries abroad and who presented at the Montefiore Medical Center (Bronx, New York, USA) between August 2015 and June 2016 were identified. A review of patient medical records was performed.

Results: Four patients who presented with culture-proven RGM infections at the sites of recent cosmetic procedures were identified. All patients were treated with a combination of antibiotics and aggressive surgical treatment.

Conclusions: This case series of RGM infections following recent cosmetic surgeries abroad highlights the risks of medical tourism. Close monitoring of affected patients by surgical and infectious disease specialties is necessary, as aggressive surgical debridement combined with appropriate antibiotic regimens is needed to achieve cure. Given the increasing reports of post-surgical RGM infections, consultants should have a low threshold for suspecting RGM, as rapid diagnosis may accelerate the initiation of targeted treatment and minimize morbidity.

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Introduction

Medical tourism for cosmetic surgery procedures is on the rise, and approximately four million Americans travel abroad annually to receive medical care (Singh, 2016). The rapid availability of affordable treatments, perceived quality, and familiarity with one's host country all factor into the decision to travel for medical care, especially for cosmetic procedures (Singh, 2016; Hanefeld, 2015; Franzblau, 2013). However, there has been significant debate concerning the health outcomes of these patients and the financial burden that this imposes on the resident country's healthcare system. Increasing reports of post-surgical rapidly growing

Mycobacterium (RGM) infections have become a public health concern, and timely diagnosis and treatment of these iatrogenic infections is necessary, which requires a high index of clinical suspicion.

RGM are a type of non-tuberculous mycobacteria (NTM) characterized by their growth within 7 days when subcultured in the laboratory, differing from other mycobacteria, which may take several weeks to grow (De Groot, 2006). RGM are ubiquitous in the environment and are a recognized cause of skin and soft tissue infections associated with surgical site infections, typically due to contaminated water sources (Phillips, 2001; Zosso, 2015). There have been a number of recent RGM outbreaks identified in patients who have undergone cosmetic procedures abroad, including breast augmentation, abdominoplasty, liposuction, and buttock lift procedures (Singh, 2016; Furuya, 2008; Schnabel, 2014). Recent reports of invasive Mycobacterium infections associated with contaminated heater cooler units in cardiovascular surgery have also been described (Stewardson, 2017).

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Three clinically relevant species frequently associated with cosmetic surgery infections are *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum* (Zhang, 2015). RGM, particularly *M. abscessus*, can form biofilms and they tend to be resistant to disinfectants. Thus, inadequate sterilization techniques are thought to be largely responsible for these surgical infections (Zosso, 2015; Furuya, 2008; Esteban, 2008; Chadha, 1998). RGM infections are uniquely challenging as they are difficult to diagnose and treat, with disease recurrence being a common morbidity of this disease process. The treatment of these infections often requires medical as well as surgical interventions to achieve clinical cure.

The authors' clinical experience with four cases of RGM infections acquired through cosmetic surgery procedures performed in the Dominican Republic is described in this report. These patients first presented to the Montefiore Medical Center (MMC), a multi-site academic medical center, between August 2015 and June 2016.

Case reports

Case 1

A 31-year-old female presented in May 2016 with diffuse burning in her abdomen and fever. Two months prior to presentation she had undergone a bilateral revision mastopexy, abdominoplasty, and liposuction in the Dominican Republic. She reported an increase in drainage from her umbilical and abdominal surgical sites and dehiscence of her lower abdominal wound. Radiographic and clinical evaluation revealed multiple anterior abdominal wall abscesses. She was started on empiric therapy with ampicillin–sulbactam and vancomycin. She later underwent percutaneous drainage with removal of 30 ml of bloody turbid fluid, which was sent for culture.

The culture stained positive for acid-fast bacilli (AFB), and growth was later identified as *M. abscessus* using RNA polymerase β -subunit (*rpoB*) gene sequencing, a laboratory method used by National Jewish Health, Denver, Colorado, USA, and validated according to the Clinical Laboratory Improvement Amendment (CLIA) (Adékambi, 2003). Ampicillin–sulbactam and vancomycin were discontinued, and intravenous imipenem–cilastatin, intravenous amikacin, and oral clarithromycin were initiated while awaiting sensitivity results. A repeat computed tomography (CT) scan showed interval resolution of the abscesses and she was discharged 9 days after presentation on this regimen.

In June 2016, within 2 weeks of commencing this antimicrobial regimen, the patient returned to the hospital with fever despite compliance with the antibiotic treatment. CT showed residual phlegmon in the abdomen, with extensive inflammatory changes of the rectus sheath but no drainable collections. Her *M. abscessus* isolate was later found to be susceptible to amikacin, tigecycline, cefoxitin, clarithromycin, azithromycin, clofazimine, and tobramycin, but was intermediately susceptible to imipenem–cilastatin (based on broth microdilution minimum inhibitory concentration (MIC) method). Her regimen was optimized by increasing the dose of amikacin to 12.5 mg/kg and switching to cefoxitin and azithromycin for better tolerability. Her clinical course was complicated by the development of severe leukopenia with a white blood cell count of $0.9 \times 10^9/l$ and absolute neutrophil count of $0 \times 10^9/l$ attributed to 4 weeks of cefoxitin. As a result, cefoxitin was switched to tigecycline, which was poorly tolerated due to significant gastrointestinal adverse effects. Tigecycline was discontinued; imipenem–cilastatin was then restarted and amikacin and azithromycin were continued.

Despite continuing maximal antibiotic therapy, she developed recurrence of the abdominal abscesses with extension to the right

labia majora in late July 2016. She required multiple rounds of incision and drainage for re-accumulation of abdominal wall abscesses. A decision was made at this point to pursue clofazimine as an alternative treatment given her complicated course with multiple recurrences, limited antibiotic choices based on susceptibility data, and intolerance to several antibiotics due to significant adverse effects. Clofazimine was obtained under a single patient investigational new drug (IND) application from the US Food and Drug Administration (FDA), which she began in September 2016; intravenous antibiotics were stopped. She was continued on the combination regimen of oral azithromycin and clofazimine for a total of 5 months, with transient clofazimine-induced hyperpigmentation of the skin. She has not developed further recurrences to date.

Case 2

A 52-year-old female presented in late August 2015 with bilateral breast pain and right breast drainage. She had undergone two prior bilateral breast augmentations performed in the Dominican Republic, in 2002 and 2015, the latter only 6 weeks prior to presentation. Four weeks postoperatively, she reported fever, chills, and copious purulent discharge from the right breast incision site. She was admitted, evaluated by plastic surgery, and underwent removal of the bilateral breast implants. Gram staining of cultures showed Gram-positive cocci and she was discharged home with a 2-week course of oral trimethoprim–sulfamethoxazole.

Culture growth was noted within 10 days and the isolate identification was confirmed 3 weeks later, in September 2015, as *Mycobacterium chelonae/abscessus* complex (identified using high-performance liquid chromatography (HPLC) by the Mycobacteriology Laboratory at New York City Department of Health) (Butler, 1991). She was started on clarithromycin based on the localized infection. Two weeks later the patient developed increased bilateral breast drainage with fistula formation and wound dehiscence. An ultrasound showed a 1.2-cm loculated fluid collection in the right breast. She underwent incision and drainage of the bilateral breasts and 5 ml of serous fluid was removed and sent for culture. Cefoxitin and amikacin were added to her clarithromycin regimen.

Antibiotic susceptibility testing showed sensitivity to amikacin, kanamycin, tobramycin, cefoxitin, imipenem–cilastatin, clarithromycin, azithromycin, clofazimine, and tigecycline, and intermediate susceptibility to linezolid. Cefoxitin was switched to imipenem–cilastatin for convenience of administration (four times daily vs. three times daily dosing), while amikacin 12.5 mg/kg/daily and oral clarithromycin were continued. Intravenous antibiotics (imipenem–cilastatin and amikacin) were continued for a total of 1 month and clarithromycin alone was continued subsequently.

The patient did relatively well, with two mild recurrences at 3 months and 7 months later. Both episodes were treated with the addition of oral linezolid to clarithromycin with a good clinical response. In both instances, she developed localized fluctuance over the left breast with purulent drainage. In March 2016, she was re-evaluated by plastic surgery and underwent debridement with excision of breast tissue revealing deep retained nylon sutures that were visibly the source of the chronic draining sinuses. These nylon sutures were removed and cultures obtained during the procedure were negative.

A few days after completion of a 2-month course of linezolid and clarithromycin, her right breast abscess recurred. Intravenous antibiotic therapy with imipenem–cilastatin, tigecycline, and clarithromycin was initiated. Tigecycline and clarithromycin were later switched to amikacin 12.5 mg/kg/daily and azithromycin due to persistent nausea. In an effort to prevent recurrence, the patient

underwent further debridement with removal of all scar tissue and retained sutures in July 2016. She completed a 6-week course of intravenous antibiotic therapy in July 2016. Since then, no recurrence has developed.

Case 3

A 48-year-old female presented with intermittent abdominal pain 4 weeks after an abdominoplasty procedure performed in the Dominican Republic in January 2016. Starting in March 2016, she presented almost monthly to different hospitals for recurring abdominal abscesses that were treated with incision and drainage.

She presented to MMC in June 2016 with another recurrence. CT of the abdomen showed several subcutaneous peripherally enhancing small abscesses in the anterior abdominal wall. The largest was drained with removal of 13 ml of serosanguineous fluid. No organisms were seen on Gram or AFB staining, but cultures later grew *M. abscessus* (identified using *rpoB* sequence analysis at National Jewish Health, Denver, Colorado). She was started on clarithromycin, amikacin, and cefoxitin.

Despite compliance with antibiotics, she presented in late July with progressive worsening of the abdominal wall abscesses and new circular subcutaneous tender nodules. Extensive incision and drainage of the lesions was performed by plastic surgery at this time, and cultures were positive for mycobacteria. The isolate was susceptible to amikacin, clarithromycin, clofazimine, and tigecycline, with intermediate susceptibility to cefoxitin, imipenem–cilastatin, and linezolid (method used as described above). Her antibiotic regimen was adjusted to clarithromycin, amikacin, and tigecycline based on antibiotic susceptibility results. The patient's course was complicated by amikacin-related ototoxicity after 4 weeks of 10 mg/kg/daily amikacin, which led to amikacin discontinuation.

With limited treatment options, meropenem was added to the tigecycline–clarithromycin regimen in October, as imaging showed improving but persistent collections. Her intravenous antibiotics were abruptly discontinued due to refusal of insurance coverage for her regimen in December 2016. She was continued on clarithromycin alone until January 2017 and has had no recurrence since completion of antibiotic therapy.

Case 4

A 50-year-old female presented in March 2016 with 3 weeks of abdominal pain and abdominal discharge after abdominoplasty in the Dominican Republic in January 2016. Her wounds had been healing well until 3 weeks prior to presentation. A CT scan revealed multiple abdominal abscesses, which were subsequently aspirated by interventional radiology. Initial empiric treatment was started with piperacillin–tazobactam and vancomycin while awaiting culture results. Despite antibiotic therapy the patient continued to experience fever spikes with increasing leukocytosis. Six days later cultures grew *M. abscessus* (identified using *rpoB* sequencing at National Jewish Health, Denver, Colorado). At this point, antibiotics were changed to cefoxitin, clarithromycin, and amikacin. The isolate was susceptible to tigecycline, clarithromycin, amikacin, kanamycin, and clofazimine (performed as described above). After the results returned, the antibiotic regimen was adjusted to tigecycline, clarithromycin, and amikacin.

The patient's course was complicated by the development of vestibular toxicity after 1 month of amikacin dosed at 10 mg/kg/daily. Amikacin was discontinued and tigecycline and clarithromycin were continued. A repeat CT showed interval worsening of numerous thick-walled abscesses and additional foci of gas in the anterior subcutaneous fat tissue of the abdominal wall. Tigecycline

was changed to imipenem–cilastatin due to a shortage of tigecycline in June 2016.

Shortly after, clofazimine was obtained under a single patient IND from the FDA and was added to the imipenem–cilastatin and clarithromycin regimen in late June. Despite compliance with this regimen, the patient experienced recurrent abdominal abscesses of the subcutaneous tissues and in August 2016 required extensive incision and drainage of abscesses and wound granulomas. Cultures remained negative and the patient remained on a triple regimen of clofazimine, clarithromycin, and imipenem–cilastatin until October 2016, when imipenem–cilastatin was discontinued. She continued oral therapy until January 2017. After 5 months of the 6-month clofazimine regimen, the patient developed hyperpigmentation of the skin without any rashes. Cultures from a repeat surgical resection of abscess cavities and debridement of the fascia in January 2017 grew methicillin-sensitive *Staphylococcus aureus* (MSSA) and she was treated with 4 weeks of oral cephalixin. She has been recurrence-free since (Tables 1 and 2).

Discussion

RGM are emerging pathogens that have become increasingly common in patients who travel internationally for cosmetic procedures, and are also important causes of other nosocomial infections. RGM infections often affect local cutaneous tissue through direct inoculation. Pulmonary infection with RGM generally occurs in patients with underlying lung disease. Disseminated disease can occur in immunocompromised individuals (Zhang, 2015). In the patients reported herein, RGM infections presented with subcutaneous nodules and recurrent abscesses at the incision sites of their surgical procedures. All patients presented with *M. abscessus* infections; this is the most commonly seen pathogen in this clinical setting, but other RGM species have also been associated with similar clinical presentations.

Despite the rising rates of infection in medical tourists presenting with the characteristic manifestations, appropriate and timely diagnosis often remains a challenge (Meyers, 2002; Tiwari, 2003). RGM infections are not reportable diseases in the USA, perhaps contributing to a lack of awareness and underestimation of the prevalence and burden in the population (Griffith, 2007). Maintaining a high index of clinical suspicion is necessary for rapid diagnosis and treatment. Failure to suspect RGM can lead to missed or delayed diagnoses and treatment. Often, only routine bacterial cultures are obtained, which are not designed to identify *Mycobacterium* species. For example, acid-fast (Ziehl–Neelsen) stains are superior to routinely used Gram stain for detecting *Mycobacterium* species. Although RGM grow on conventional bacterial culture media, Lowenstein–Jensen or other mycobacterial culture media should be used when *Mycobacterium* species are suspected (Martin, 1975). Moreover, mycobacteria have a slower replication rate than other typical bacterial pathogens and may not be detected if microbiology culture plates are discarded after failure to observe growth using standard incubation periods. While awaiting culture results, antibiotic treatment is often targeted towards common bacterial pathogens such as streptococci and staphylococci, regimens that are ineffective against RGM infections.

The mainstay of treatment for cutaneous RGM is primarily surgery combined with culture-directed antibiotic therapy (Cai, 2016). Initial aggressive surgical drainage, source control, and removal of infected foreign material, including breast implants, prosthetic devices, sutures, and percutaneous catheters, is imperative for achieving cure (Griffith, 2007). As in cases 1 and 4, patients who initially receive limited drainage often have complex clinical courses, with frequent readmissions for recurrence despite parenteral and oral therapy. The experience with the

Table 1
Demographic and clinical characteristics of patients presenting with RGM infections.

	Patient			
	1	2	3	4
Age (years), sex	31, F	52, F	48, F	50, F
Date and country of procedure	March 2016 Dominican Republic	June 2015 Dominican Republic	January 2016 Dominican Republic	January 2016 Dominican Republic
Surgical procedure	Bilateral revision mastopexy, abdominoplasty, liposuction	Bilateral breast augmentation	Abdominoplasty	Abdominoplasty
Time until initial presentation (weeks) ^a	8	6	12	11
Clinical manifestations	Fever, drainage, multiple subcutaneous abdominal abscesses	Fever, bilateral breast pain, right breast drainage and abscesses	Abdominal pain, subcutaneous abdominal abscesses	Abdominal pain, drainage, multiple subcutaneous abdominal abscesses
Time until diagnosis (weeks) ^b	12	9	27	12
Microscopic findings, culture results, and AFB stain results ^c	<i>M. abscessus</i> Culture + AFB stain +	<i>M. abscessus/chelonae</i> complex Culture + AFB stain –	<i>M. abscessus</i> Culture + AFB stain –	<i>M. abscessus</i> Culture + AFB stain –
Surgical interventions (deep/superficial, bedside/OR) ^d	Abscess drainage (superficial, bedside), abscess drainage (deep, OR)	Removal of breast implants (OR), bilateral breast abscess drainage (superficial, bedside), excision and debridement of chronic breast wounds (OR), removal of deep sutures (OR)	Abscess drainage (superficial, bedside), abscess drainage and debridement (deep, OR)	Abscess drainage (superficial, bedside), abscess drainage and excision with debridement of wound granulomas (deep, OR)
Time on oral antibiotic therapy (weeks)	29	32	28	51
Time on parenteral antibiotic therapy (weeks)	10	10	24	32
Total duration of antibiotic therapy (oral or parenteral) (weeks)	30	38	28	52

AFB, acid-fast bacillus; F, female; OR, operating room; RGM, rapidly growing mycobacteria.

^a Time until initial presentation is the duration in weeks between the initial surgical procedure and the first healthcare presentation.

^b Time until diagnosis is the duration in weeks between the initial surgical procedure and diagnosis by culture or pathology.

^c The species for case 2 was identified by high-performance liquid chromatography (HPLC) and the species for cases 1, 3, and 4 were identified by *rpoB* sequencing, which accounts for differences in identification.

^d Surgical interventions included superficial or deep interventions and those occurring by bedside or in an operating room.

patients presented here underscores that aggressive surgical intervention for abscess drainage, debridement, and removal of retained sutures is critical for improvement.

Table 2
Antimicrobial susceptibilities of the Mycobacterium isolates.^a

	Patient			
	1	2	3	4
Amikacin	S	S	S	S
Augmentin	R	R	R	R
Azithromycin	S	S	S	S
Cefoxitin	S	S	I	I
Ciprofloxacin	R	R	R	R
Clarithromycin	S	S	S	S
Clofazimine	S	S	S	S
Doxycycline	R	R	R	R
Imipenem–cilastatin	I	S	I	I
Kanamycin	S	S	S	S
Linezolid	R	I	I	R
Moxifloxacin	R	R	R	R
Tigecycline	S	S	S	S
Tobramycin	S	S	I	I
Trimethoprim–sulfamethoxazole	R	R	R	R

S, susceptible; R, resistant; I, intermediate; MIC, minimum inhibitory concentration.

^a Antimicrobial susceptibility testing of all the isolates was performed using the broth microdilution MIC method by the Mycobacteriology Laboratory at National Jewish Health, Denver, Colorado, USA.

It is known that T-cell-mediated immunity plays a role in the pathogenesis of RGM infections, and disseminated disease has been attributed to systemic defects in the immune system. Inborn errors in the interleukin-12 and interferon-gamma pathways lead to increased susceptibility to disseminated disease with presentation early in life and have been well characterized previously (Wu, 2015). It is believed that the presentation of localized, iatrogenically acquired recurrent disease in the setting of inadequate source control was not likely to be related to underlying immune defects. However none of the patients in this case series were on any immune suppressive treatments or had any history of immunodeficiency. Testing completed to look for underlying immune defects such as HIV infection were normal.

Antibiotic treatment regimens are often personalized based on the extent of disease, RGM species, and adequacy of surgical debridement. Nevertheless, the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines on the treatment of cutaneous RGM infections recommend an oral macrolide backbone with initial parenteral therapy of cefoxitin, amikacin, or imipenem–cilastatin (Griffith, 2007). For serious soft tissue infections caused by *M. abscessus*, the most active parenteral agent is amikacin. However, higher doses of amikacin given at a dose of 10–15 mg/kg daily are recommended for the treatment of RGM infections to provide appropriate peak serum levels of the

drug (Griffith, 2007). The administration of long-term parenteral therapy requires a peripherally inserted central catheter (PICC) or other central line, along with pharmacy resources to arrange infusions. The case patients were enrolled in the outpatient parenteral antimicrobial treatment (OPAT) program with regular laboratory monitoring for adverse effects by an infectious disease physician. Such resources may not be available in all clinical settings. Indwelling central venous catheters carry risks of thromboembolism, malfunction, and infection. Fortunately, none of these adverse events were seen in the patients.

Treatment is often complicated by adverse effects from antibiotic therapy (Brown, 1992; Kasperbauer, 2015). Cefoxitin-associated leukopenia (case 1) and amikacin-related ototoxicity/vestibular toxicity (cases 3 and 4) were two important drug-associated toxicities seen in the patients, requiring adjustment of therapy. Additionally, there were some less serious medication-associated adverse effects, including gastrointestinal intolerance of tigecycline, further exemplifying the complexities encountered in treating RGM infections.

A major limitation of this case series is that the *Mycobacterium* isolate from case 2 was identified by the New York City laboratory using HPLC, which is a practical, rapid, and reliable method. This choice of method, which is determined by the laboratory, does not allow differentiation between *M. abscessus* and *M. chelonae*, hence the isolate was reported as *M. abscessus/chelonae* complex. In contrast, the isolates from the other cases were identified at the National Jewish Health laboratory using partial sequencing of the PCR-amplified *rpoB* gene, which is able to accurately differentiate between the two species with more specific results. However, the susceptibility profiles of all four isolates were assessed at the National Jewish Health laboratory using the broth microdilution MIC method.

In cases 2–4, the newer minocycline derivative, tigecycline, was used as a parenteral option for salvage therapy based on the susceptibility profile and consistent with a report from Taiwan in 2013 showing that tigecycline may have synergistic activity with clarithromycin against *M. abscessus* isolates (Huang, 2013). Carbapenems were administered to all four patients in this series, as there are data showing synergism with other antimicrobial agents in *M. abscessus* infections (Kaushik, 2015). However, the cost of carbapenems often precludes their wider use internationally. Moreover, carbapenems have a broad antimicrobial spectrum, and long-term use carries the risk of increasing antimicrobial resistance.

Resistance to antibiotic therapy is a significant concern in the treatment of RGM, and in vitro susceptibilities do not always correlate to clinical response. Macrolides, namely clarithromycin, have been the cornerstone of antimicrobial therapy. However, both *M. abscessus* and *M. fortuitum* have been found to possess erythromycin ribosomal methyltransferase (*erm*) genes that confer inducible macrolide resistance and result in a poor response to macrolide-based regimens (Griffith, 2007; Nash, 2009). The presence of the *erm* (41) gene has called into question the usefulness of macrolides in treating RGM infections, particularly those with *M. abscessus*. Moreover, there is also evidence of RGM developing mutational resistance with the use of single-drug therapy (Wallace, 1990; Wallace, 1992). As a result, the simultaneous use of multiple antibacterial agents based on susceptibility profiles is recommended for the effective treatment of RGM.

All of the isolates were susceptible to clofazimine. This drug is available in the USA through the FDA under a single-patient treatment IND protocol for mycobacterial disease in patients with isolates sensitive to clofazimine, or those with an inadequate response to first-line therapy. Although developed initially as a treatment for *Mycobacterium tuberculosis*, clofazimine is only approved by the World Health Organization (WHO) and the FDA

for the treatment of leprosy. Clofazimine is more readily available in countries with endemic leprosy and is provided free of charge in those countries by an agreement with Novartis (Hwang, 2014). Clofazimine has been established as safe for long-term use in leprosy patients, with a favorable adverse effect profile (Tyagi, 2015). Three of the patients were treated with clofazimine 100 mg/daily with a good response. Two patients (cases 1 and 4) developed skin hyperpigmentation after a few months of therapy. This series highlights a positive experience with the use of this drug as adjuvant therapy, especially in patients who had completed lengthy courses of parenteral antibiotic therapy. Completion of the treatment course with a combination oral regimen resulted in clinical improvement while avoiding the risks and complications associated with lengthy intravenous therapy. Clofazimine along with macrolides may provide an effective alternative oral regimen.

With rapid diagnoses, aggressive surgical debridement, and effective chemotherapy, this case series highlights both the obstacles in controlling RGM infections and the possibility of successful treatment. Close monitoring for disease recurrence by teams composed of both infectious diseases and surgical services is crucial, because surgical intervention in combination with antimicrobials is needed to achieve cure in these patients. Lastly, awareness of the potential pitfalls of medical tourism may help to abate future RGM infections.

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Conflict of interest

None.

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