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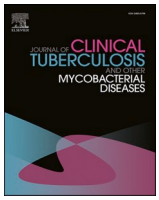

Case Report

Mycobacterium abscessus skin and soft tissue infection following autologous fat grafting in Kurdistan treated with an antibiotic combination including Imipenem-Relebactam and Rifabutin

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ABSTRACT

Medical tourism is becoming increasingly popular. The most popularly sought operations are cosmetic procedures. With the increase in cosmetic tourism, it is unsurprising that there has also been a rise in skin and soft tissue infections caused by nontuberculous mycobacteria (NTM); in particular by the rapidly growing mycobacteria species.

Here we provide a case of a 35 year-old woman who presented after autologous fat grafting with multiple painful, violaceous, and purulent nodules on her arms, legs, and breasts. Infection was found to be due to *Mycobacterium abscessus*. She was successfully treated with azithromycin, clofazimine, rifabutin, amikacin, imipenem-cilastatin-relebactam (Recarbrio™) and imipenem-cilastatin. This is the first described case of a *M. abscessus* infection successfully treated using this combination.

1. Introduction

Medical tourism is becoming increasingly popular, with an estimated 21–26 million cross-border patients worldwide, and increasing 15–25% annually [12]. The most common procedures include breast and gluteal augmentation, abdominoplasty, liposuction, eyelid surgery, and rhinoplasty [15,18,19]. With the increase in cosmetic tourism it is unsurprising that there has also been a rise in skin and soft tissue infections caused by nontuberculous mycobacteria (NTM); in particular by the rapidly growing mycobacteria (RGM) species *Mycobacterium abscessus*, *Mycobacterium chelonae* and *Mycobacterium fortuitum* [9].

Cutaneous *M.abscessus* infections are uncommon, often manifesting as painful, violaceous nodules, recurrent abscesses, or chronic sinus tracts [7]. *M.abscessus complex* is subclassified into *M.abscessus subspecies abscessus.*, *M.massillense,* and *M.bollettii* on the basis of *rpoB* sequences, and the presence and function, or lack of function, of the *erm*(41) gene [4]. These species are differentiated by specific tests that are required to isolate and identify them from culture, which can result in a delay in diagnosis and treatment [8]. Extensive multi-drug resistance is common in *M.abscessus* isolates, which further complicates treatment and results in low cure rates.

2. Case report

A 35-year-old woman with a background of hypothyroidism and asthma presented to our hospital with a 2-week history of six painful, erythematous, ulcerated, and purulent nodules on her arms, legs and breasts bilaterally (Fig. 1). Four weeks previously, she had travelled to a private clinic in Sulaymaniyah, Kurdistan, for autologous fat grafting to her hands, feet and breasts, using fat harvested from her abdomen (Fig. 2). She received no immediate post-operative antibiotics and described no immediate complications. The swelling in her legs began 10 days post-operatively, followed by swelling in her arms and the development of discrete painful nodules. She was prescribed moxifloxacin and linezolid by her surgeon following the appearance of the lesions, with no clinical benefit.

The patient was afebrile without systemic symptoms. Blood tests were unremarkable with a C-reactive protein of 17 mg/L (reference range 0–5 mg/L) and a normal white blood cell count (6.5×10^9/L). Screening for HIV, hepatitis B and C were negative. She underwent

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incision and drainage of the nodules that were left to heal by secondary intention. The intraoperative impression was of infected fat necrosis. She was discharged with amoxicillin/clavulanic acid while awaiting bacterial culture.

Histological examination showed mixed suppurative and granulomatous necrotising inflammation with occasional Langhan's type multinucleate giant cells. No acid-fast bacilli (AFB) were seen on Ziehl-Neelsen (ZN) and auramine staining. Mycobacterial culture of biopsied tissue on Mycobacteria Growth Indicator Tube (MGIT™) grew *M. abscessus* after seven days of incubation. The identification was obtained by Hain GenoType Mycobacterium CM assay in our laboratory. It was later confirmed by whole genome sequencing in the local mycobacterial reference laboratory where the sample was sent for phenotypic susceptibility testing (PST). We were unable to obtain the subspecies identification, but mutations known to confer resistance to macrolides, including mutations affecting the *rrl* and *erm* genes were not detected. Based on the identification of *M.abscessus* from culture and whilst PST results were awaited, we prescribed oral azithromycin 500 mg once daily, clofazimine 100 mg once daily, IV amikacin 20 mg/kg three times a week, and tigecycline 50 mg twice daily administered as outpatient parenteral antibiotic therapy. At this time, she also developed discrete nodules in both breasts. After one month of treatment, the patient developed acute pancreatitis likely caused by tigecycline. All antibiotics were stopped for one week to allow for resolution of the pancreatitis, and tigecycline was discontinued.

Minimum inhibitory concentrations (MIC) were calculated using the broth microdilution method. There are no CLSI and EUCAST breakpoints for NTM. PST results that became available showed borderline resistance to clarithromycin (minimum inhibitory concentration, MIC, of 8mcg/mL); resistance to tobramycin (MIC 16mcg/ml), co-trimoxazole (MIC $>$ 8/152 mcg/ml), linezolid (MIC 32 mcg/ml), ciprofloxacin (MIC $>$ 4 mcg/ml), moxifloxacin (MIC $>$ 8 mcg/ml) and doxycycline (MIC $>$ 16mcg/ml); intermediate to cefoxitin (MIC 64mcg/ml); and sensitivity to amikacin (16mcg/ml). Imipenem sensitivities were not interpreted. There is no availability for MIC testing of clofazimine and rifabutin for NTM, as a result, testing for resistance to these antibiotics was not conducted. Treatment was restarted with oral azithromycin, clofazimine, rifabutin 300 mg once daily, IV amikacin and imipenem-cilastatin-relebactam (Recarbrio™) 500 mg/500 mg/250 mg twice daily plus imipenem-cilastatin 500 mg/500 mg twice daily following results of the PST and discussion with the UK NTM Network. To achieve a total daily dose of imipenem 1 g twice daily, along with 250 mg twice daily of relebactam protection, we administered Recarbrio (imipenem-cilastatin-relebactam) at a dose of 500 mg/500 mg/250 mg twice a day, as per its licensed dosage, in addition to imipenem-cilastin 500 mg/500 mg twice a day as a supplement.

After 12 weeks of this regimen, imipenem-cilastatin-relebactam and imipenem-cilastatin were stopped. Two weeks later amikacin was stopped due to concerns regarding ototoxicity, and the patient was continued on triple oral therapy with azithromycin, clofazimine, and rifabutin to complete nine months total of antibiotic therapy. Although the specific treatment of *M.abscessus* skin infection can vary, a review of

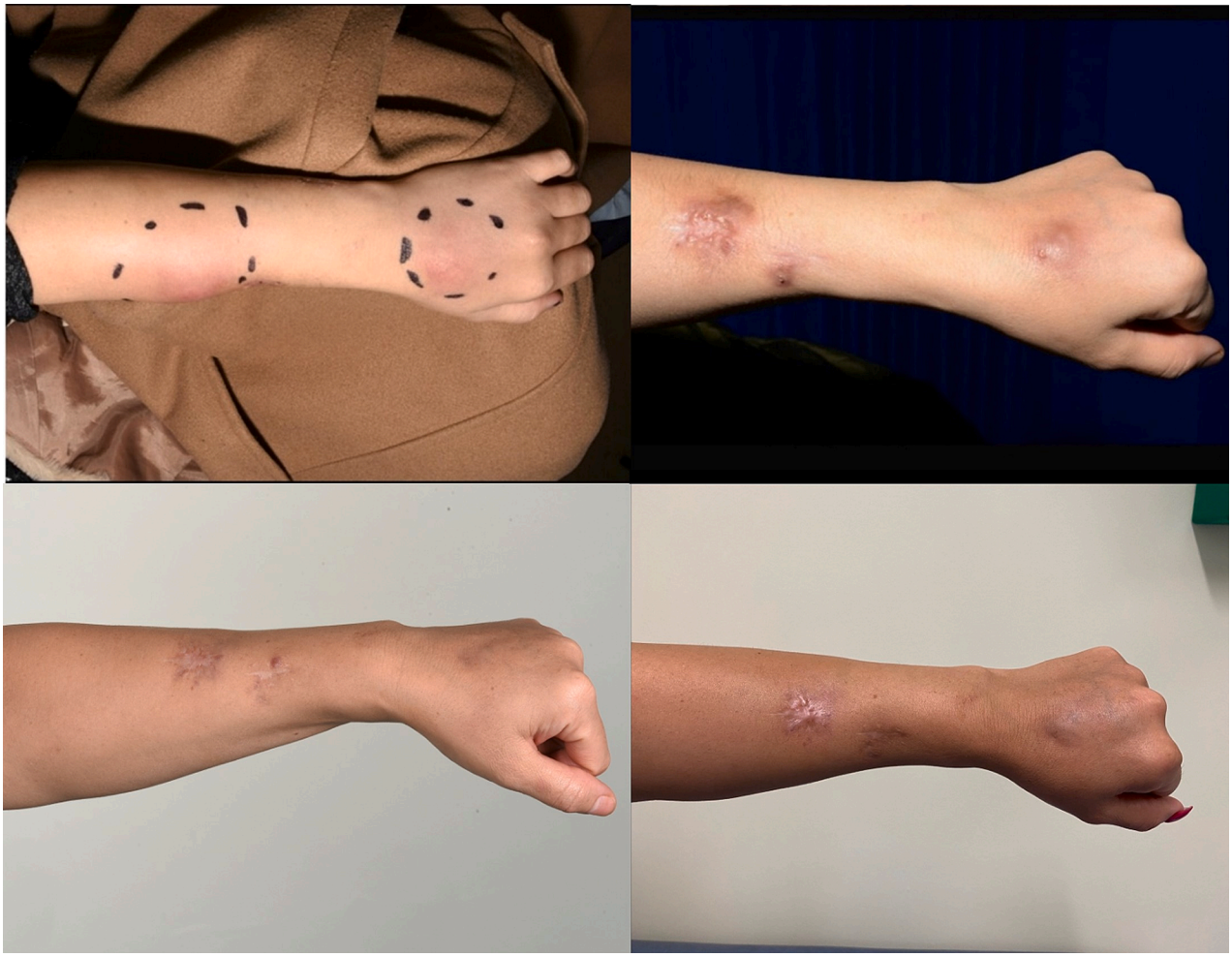

Fig. 1. The appearance of the lesions (in a clockwise direction, from top left): initial presentation (top left); 3 months after initial incision and drainage and 1 month after commencement of M.Abscessus antimicrobial treatment (top right); the date of treatment cessation (bottom right); 2 months after treatment cessation (bottom left).

the literature suggests that it typically falls within the range of six to twelve months [18]. For this reason we opted for a 9-month treatment course, which is comparable to the treatment course typically recommended for pulmonary disease caused by *M.abscessus*. New nodules appeared on the legs and breasts (surgical sites) throughout the first five months of therapy and were subsequently biopsied, revealing suppurative inflammation with poorly defined granulomas, histiocytes, and scattered Langhans giant cells on histological examination. AFBs were not seen on auramine staining and viable mycobacteria did not grow from culture. The nodules arising during the treatment course were considered paradoxical reactions and improved without any additional treatment. At no point during her treatment did she develop nodules at the site of fat harvesting. The appearance of the lesions improved throughout the treatment course. At completion of the nine months of treatment some nodules on the left breast and right hand were present but had reduced in size and were no longer inflamed therefore, deemed inactive. These nodules resolved five months after treatment cessation. The patient was left with significant scarring, and she remains under follow up.

3. Discussion

Outbreaks of RGM surgical site infections are increasingly reported in the literature [8]. Their abundance in the environment and resistance to common methods of sterilisation such as chlorine, heat, ammonia and 2% formaldehyde makes them a difficult pathogen to eradicate [10]. RGM possess a hydrophobic and lipid rich cell wall that characteristically enables biofilm formation on solid surfaces such as water pipes and medical implants [14].

Delay in diagnosis is common due to a low index of suspicion from clinicians and to disease latency. Features in the history and examination that raise suspicion include invasive procedures undertaken in recent weeks, and presentation with painful, erythematous nodules, abscesses, or areas of induration [7]. Prompt diagnosis is essential as prolonged infection may cause significant tissue destruction and poor cosmetic outcomes.

As was the case in our patient, limited response to first-line antibiotics used to treat the common bacterial skin pathogens and lack of growth from routine bacterial culture should raise suspicion of RGM infection [13]. Although direct microscopic examination may elicit AFB on ZN or auramine staining, the sensitivity of this has been reported as around 50% [20]. Culture on specific growth media remains the gold standard, with *M.abscessus* often growing within 7 days [21]. Molecular diagnostic tests can be used to differentiate between rapidly growing NTMs, which is necessary as different treatment regimens are required. Species specific 16S and 23S rRNA encoded with the rpoB or hsp65 genes can allow for rapid speciation [10]. Given the long duration of therapy, complex multi-drug treatment regimens, risk of drug toxicity, and vastly different antimicrobial susceptibility profiles of RGM, ensuring the correct treatment regimen early is imperative [1].

Macrolide resistance is increasing among *M.abscessus* isolates, either acquired through point mutations in the *rrl* gene [4], or inducible secondary to macrolide exposure through induction of the *erm*(41) gene via the whiB7 transcription factor [2,5]. *M.abscessus* isolates in pulmonary disease have an estimated 40–60% presence of macrolide resistance resulting in low cure rates (25–40%, compared to 88–95% in macrolide susceptible isolates) [4]. Rifabutin has recently been shown to be bactericidal against *M.abscessus* and acts as an inhibitor of transcription, to prevent effective induction of the *whiB7-erm*(41) resistance system, thus potentially restoring macrolide susceptibility [2]. We therefore continued azithromycin after the PST result became available despite a borderline elevated MIC (8 mg/L), along with rifabutin as a synergistic agent, based on in-vitro evidence indicating that rifabutin can help lower the MIC of azithromycin [3,6,16]. Clofazamine was prescribed despite no availability of MIC testing as a synergist to amikacin [1], which reduces MICs to both drugs in rapidly and slow growing mycobacteria [1].

M.abscessus expresses intrinsic resistance to beta-lactam antibiotics through endogenous class A beta-lactamase (BlaMab) [11]. In vitro studies with new beta-lactamase antibiotics have recently demonstrated inhibition of Bla(Mab) beta-lactamase activity, improving the efficacy of imipenem against *M.abscessus* [17]. Le Run et al described a 2-fold decrease in the MICs of imipenem and amoxicillin when a combination of relebactam and beta lactams was used in vitro [17]. Avibactam was similar to relebactam in potentiating the antibacterial activity of beta-lactams however, data showed relebactam inactivated BlaMab 150-fold more [17]. Avibactam is only available in combination with ceftazidime which has no activity against *M.absessus* therefore, we opted to use imipenem-cilastatin-relebactam [17]. Adverse events of antibiotic therapy are often reported in patients undergoing treatment for NTM due to the prolonged treatment course. Our options for therapy were limited due to our patient developing pancreatitis, a rare but potentially life-threatening complication of tigecycline therapy, and ototoxicity secondary to amikacin.

4. Conclusion

This is the first described case of a *M.abscessus* infection successfully treated using a combination of imipenem-cilastatin-relebactam and rifabutin. Multi-drug resistance of *M.abscessus* is common and newer agents such as imipenem-cilastatin-relebactam and rifabutin should be considered as adjuncts to induce susceptibility and increase chances of cure**.** Cost of imipenem-cilastatin-relebactam and of PST may be limitations to treatment in resource-limited countries, where surgical site infections caused by RGM are more likely to occur. A multidisciplinary approach that incorporates primary care providers, pathologists, infectious disease specialists, and plastic surgeons along with increased awareness are necessary to improve patient outcomes.

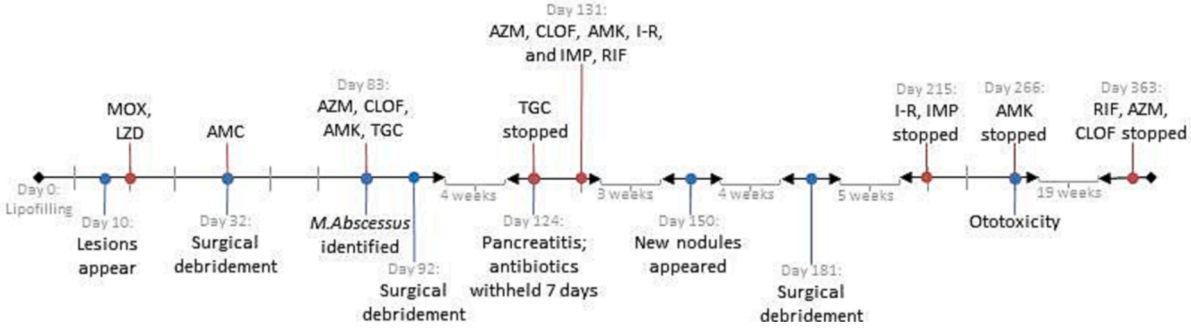

Fig. 2. Timeline of events and antibiotics. AMC: amoxicillin-clavulanic acid; AMK: Amikacin; AZM: azithromycin; CLOF: clofazimine; IMP: Imipenem-cilastatin; I-R: Imipenem-relebactam; LZD: Linezolid; MOX: moxifloxicin; RIF: rifabutin; TGC: tigecycline.

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6. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Alison J. Beech: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Sharon E. Weinberg:** Conceptualization, Investigation, Writing – review & editing, Visualization. **Alice E. Mortimer:** Conceptualization, Investigation, Writing – review & editing. **Fiona Lynch:** Writing – review & editing. **James Bedford:** Writing – review & editing, Supervision. **Giorgio Calisti:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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