

## MAJOR ARTICLE

# Clinical Management of Rapidly Growing Mycobacterial Cutaneous Infections in Patients after Mesotherapy

Stéphanie Regnier,<sup>1</sup> Emmanuelle Cambau,<sup>3</sup> Jean-Paul Meningaud,<sup>4</sup> Amelie Guihot,<sup>1</sup> Lionel Deforges,<sup>3</sup> Anne Carbonne,<sup>2</sup> François Bricaire,<sup>1</sup> and Eric Caumes<sup>1</sup>

<sup>1</sup>Infectious Diseases Unit, Pitié Salpêtrière Hospital, <sup>2</sup>Regional Centre for Nosocomial Infection Control, <sup>3</sup>Bacteriology Laboratory, Henri Mondor Hospital, and <sup>4</sup>Plastic Surgery Unit, Henri Mondor Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France

(See the editorial commentary by van Dissel and Kuijper, on pages 1365–8.)

**Background.** Increasing numbers of patients are expressing an interest in mesotherapy as a method of reducing body fat. Cutaneous infections due to rapidly growing mycobacteria are a common complication of such procedures.

**Methods.** We followed up patients who had developed cutaneous infections after undergoing mesotherapy during the period October 2006–January 2007.

**Results.** Sixteen patients were infected after mesotherapy injections performed by the same physician. All patients presented with painful, erythematous, draining subcutaneous nodules at the injection sites. All patients were treated with surgical drainage. Microbiological examination was performed on specimens that were obtained before and during the surgical procedure. Direct examination of skin smears demonstrated acid-fast bacilli in 25% of the specimens that were obtained before the procedure and 37% of the specimens obtained during the procedure; culture results were positive in 75% of the patients. *Mycobacterium chelonae* was identified in 11 patients, and *Mycobacterium frederiksbergense* was identified in 2 patients. Fourteen patients were treated with antibiotics, 6 received triple therapy as first-line treatment (tigecycline, tobramycin, and clarithromycin), and 8 received dual therapy (clarithromycin and ciprofloxacin). The mean duration of treatment was 14 weeks (range, 1–24 weeks). All of the patients except 1 were fully recovered 2 years after the onset of infection, with the mean time to healing estimated at 6.2 months (range, 1–15 months).

**Conclusions.** This series of rapidly growing mycobacterial cutaneous infections highlights the difficulties in treating such infections and suggests that in vitro susceptibility to antibiotics does not accurately predict their clinical efficacy.

Patients appear to have an ever-increasing interest in cosmetic procedures, particularly in those procedures that are minimally invasive. Despite a lack of valid scientific data, mesotherapy has been widely used in Europe and South America for body contouring and reducing body fat and, more recently, has been intro-

duced in the United States [1]. Mesotherapy is a technique that involves microinjections of conventional medications into the dermis to promote corrective treatment to a specific area of the body [1]. Cutaneous infections are the most commonly cited complication of mesotherapy and are mainly related to rapidly growing mycobacteria (RGM). There are increasing reports of cutaneous infections due to RGM (eg, *Mycobacterium fortuitum* and *Mycobacterium abscessus*). Such infections are most commonly iatrogenic, occurring after a medical or surgical procedure. Cases or outbreaks are therefore reported after plastic surgery procedures (eg, liposuction [2] and breast augmentation [3]) and after insulin injections [4], acupuncture [5], or mesotherapy [6]. Our series describes an outbreak of 16 cases of

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Reprints or correspondence: Dr Stéphanie Regnier, Service de Dermatologie, Hôpital Saint Louis, 1 Avenue Claude Vellefaux, 75010 Paris, France (stephanie.regnier@sls.aphp.fr).

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RGM-related cutaneous infection complicating mesotherapy. We discuss the clinical management of these patients, their long-term follow-up, and the difficulties in treating such infections.

## PATIENTS AND METHODS

**Outbreak recognition.** In December 2006, a patient presented to our the Infectious Diseases Unit of Pitié-Salpêtrière Hospital with a dozen nodular cutaneous lesions and abscesses that had appeared within the previous month and were resistant to conventional antibiotics efficacious against streptococcal and staphylococcal cutaneous infections. The lesions were located at various cutaneous sites, all of which were areas where earlier mesotherapy injections had been performed. We therefore suspected that the abscesses were attributable to RGM. After contacting the practicing mesotherapy physician and performing further epidemiologic inquiries, we identified 15 other patients who had also developed abscesses after having undergone injections by the same physician during the at-risk period of 1 October 2006 through 15 January 2007 (the opening and closure dates of the clinic) [7]. All of the patients were referred to the same physician (E.C.).

**Definition of cases.** Confirmed cases were those in which the patient had a typical soft-tissue infection (ie, single or multiple subcutaneous nodules or abscesses localized at cutaneous sites where mesotherapy injections had been performed) from which RGM were cultured. Probable cases were those in which the patient had a typical soft-tissue infection from which no RGM were cultured.

**Procedures.** We evaluated the following variables: demographic characteristics (age, sex, and country of origin), medical history (underlying immunodeficiency, such as human immunodeficiency virus [HIV] infection or use of corticosteroids), date of symptom onset, and number and site of cutaneous lesions. The incubation period could not be clearly determined, because the precise date of contamination was unidentifiable as a result of the fact that most patients had undergone multiple courses of mesotherapy. We therefore estimated the maximum possible incubation period for each patient (ie, the time between the first course of mesotherapy during the at-risk period and the appearance of the first lesion). In addition, we also estimated the minimum possible incubation period (ie, the time between the last mesotherapy session before symptoms appeared and the appearance of the first cutaneous lesion). The duration of the disease was defined as the lag time between the appearance of the first lesion and the appearance of the last lesion.

**Laboratory tests.** Specimens for culture were obtained by needle aspiration of the abscesses before surgical drainage and during surgery by local drainage of abscesses and subcutaneous nodule excision. Bacteriologic diagnosis was established by

acid-fast staining with Ziehl-Neelsen coloration and was confirmed by culture in Lowenstein-Jensen medium. The RGM strains were identified by means of conventional biochemical tests and molecular characterization [8]. Susceptibility testing was performed by Etest and broth microdilution, and the minimum inhibitory concentrations (MICs) of the drugs that were active against RGM were measured [8].

**Treatment.** Surgical treatment, consisting of resection of nodules and drainage of abscesses, was performed for every patient at least once. An antibiotic therapy regimen was proposed according to the number of initial lesions. Patients with only a single lesion were not treated unless they specifically requested to be treated. Patients with multiple lesions were treated systematically unless they refused or failed to comply with treatment. The treatment consisted initially of double- or triple-drug combinations of antibiotics followed by oral monotherapy or dual therapy, respectively. Patients with particularly aggressive disease (ie, >1 lesion appearing within 1 week after onset) were initially treated with triple therapy, whereas patients with less aggressive forms of the disease received dual therapy. Only antibiotics that demonstrated in vitro activity (ie, MICs below resistance breakpoints) were prescribed. The duration of antibiotic therapy varied according to clinical response and antibiotic tolerance.

**Follow-up.** Patients were followed up until healing was complete, which was defined as the absence of new cutaneous lesions for a minimum of 6 months. Patients were initially followed up weekly and then monthly until cure was established. A full physical examination was performed at each visit, and patients were specifically asked about any adverse effects associated with the medications. The number of cutaneous lesions, red blood cell and white blood cell counts, and biochemical, renal, and liver function test results were noted at each visit. All patients were also followed up by means of a telephone interview in December 2008, ~2 years after the estimated date of infection.

## RESULTS

**Description of patients.** Sixteen patients with soft-tissue infections due to RGM were identified. Of these, 12 met the definition for confirmed cases, and 4 met the probable case definition. Individual patient characteristics are presented in Table 1. All patients underwent mesotherapy to reduce body fat. All of the patients except 1 were female, with a mean age of 40 years (range, 24–58 years). No major disease comorbidities or causes of immunosuppression (eg, HIV infection) were identified among the patients. Five patients had received various antibiotic regimens before their first visit to our unit, as follows: amoxicillin (1 patient); tetracycline (1 patient); spiram-

**Table 1. Demographic, Clinical, and Bacteriologic Characteristics of 16 Patients with *Mycobacterium chelonae* and *Mycobacterium frederiksbergense* after Mesotherapy**

Variable	Patient						
	1	2	3	4	5	6	7
Age, years	51	40	46	58	24	29	34
Period from first injection to first lesion, weeks	4	3	1	3	10	5	11
No. of lesions at first consultation	6	12	30	10	15	12	4
Direct examination result (Ziehl-Nielsen coloration)							
Specimen obtained before surgical procedure	ND	Neg	Neg	Neg	Neg	Neg	Pos
Specimen obtained during surgical procedure	Pos	Neg	Neg	Pos	Neg	Neg	Pos
Culture							
Specimen obtained before surgical procedure	ND	Pos	Pos	Pos	Neg	Neg	Pos
Specimen obtained during surgical procedure	Pos for <i>M. chelonae</i> and <i>M. frederiksbergense</i>	Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Neg	Pos for <i>M. frederiksbergense</i>	Pos for <i>M. chelonae</i>

**NOTE.** ND, not done; Neg, negative; Pos, positive.

cin and metronidazole (1 patient); netilmicin, pristinamycin, and ofloxacin (1 patient); and an unknown drug (1 patient).

**Clinical characteristics.** The mean maximum possible incubation period was 9.5 weeks (range, 1–29 weeks), and the minimum possible incubation period was 9 days (range, 7–152 days). One patient who had undergone 2 sessions of mesotherapy within 1 week had an incubation period of only 1 week after the first mesotherapy procedure. No patient reported any systemic symptoms of feeling unwell, but all patients presented with similar cutaneous lesions that started as painful nodules that gradually increased in size to 2–5 cm in diameter. The nodule would fistulize, open on the skin, and drain pus for 7–14 days. The cutaneous scar would then take ~1 month to form completely. All lesions occurred in areas of previous injection (eg, abdomen, thighs, buttocks, and arms). At first presentation, the patients had a mean of 7 lesions each (range, 1–30 lesions).

**Microbiological data.** Specimens were obtained for bacteriologic examination from 12 patients before the surgical procedure was performed. Three patients (25%) had results positive for acid-fast bacilli, and 8 patients (75%) had cultures positive for *Mycobacterium chelonae*. During the surgical procedure, additional specimens were collected from all 16 patients. Of these patients, 6 (37.5%) had results positive for acid-fast bacilli, and 12 (75%) had cultures positive for RGM, with *M. chelonae* being identified in specimens from 11 patients and *Mycobacterium frederiksbergense* being identified in specimens from 2 patients (1 patient had test results that were positive for both species). Of the 4 patients with negative culture results, 3 had received antibiotics previously, but 2 of these antibiotic regimens had no efficacy against *M. chelonae*. The 11 *M. chelonae* isolates showed similar susceptibility patterns (Table 2). The *M. frederiksbergense* isolates were susceptible to clarithromycin (MIC, 0.06–0.25 µg/mL), tigecycline (MIC, 0.09–0.12 µg/mL), tobramycin (MIC, 4–6 µg/mL), ciprofloxacin (MIC, 0.03 µg/mL), and various other drugs (eg, imipenem, tetracycline, linezolid, and ceftioxin).

**Treatment.** All patients initially underwent surgical pro-

cedures to drain existing abscesses and resect any immature nodules. Of the 16 patients, 14 received antimicrobial therapy (Table 3) of a mean duration of 14 weeks (range, 1–24 weeks). All therapies included clarithromycin. Six patients initially received intravenous therapy, 6 initially received triple therapy, and 8 patients received dual therapy. Overall, 14 patients received clarithromycin (1–2 g per day, varying according to weight), 6 patients received tobramycin (3 mg/kg per day administered intravenously), 14 received ciprofloxacin (500 mg twice per day administered orally), and 6 received tigecycline (an initial dose of 100 mg followed by 50 mg per day administered intravenously).

**Outcomes.** Clarithromycin was well tolerated by 10 patients. Of the remaining patients, 4 reported a metallic taste, and 1 developed abnormal liver function test results secondary to unusually high dosages of the antibiotic that resolved after readjustment of the daily dosage. One patient developed moderate (2 times the upper limit of normal) hepatic cytolysis that appeared after 4 weeks of treatment and was attributed to tigecycline, the use of which was therefore suspended. Four patients reported feeling nauseated after intravenous infusion of tigecycline, but this did not lead to treatment suspension. Eight patients reported the following ciprofloxacin-related adverse events that occurred from 2 days through 3 months after treatment initiation: myalgia (3 patients), tendinopathy (3 patients), and nausea (2 patients). Treatment with fluoroquinolones was discontinued for the patients with myalgia and tendinopathy.

No recurrent abscess occurred in 3 patients (2 of whom had only undergone surgical treatment and 1 of whom had undergone surgical treatment combined with antibiotic therapy). In the remaining 13 treated patients, disease initially progressed despite an effective in vitro susceptibility to 2–3 antibiotics. The mean maximal number of lesions per patient reached 22 (range, 1–120), with 2 patients each having >100 lesions. Antibiotic therapy was finally discontinued in 6 patients after no additional abscesses appeared. Of these 6 patients, 1 experienced relapse within 1 month after interruption of an-

**Table 1. (Continued.)**

Patient								
8	9	10	11	12	13	14	15	16
52	52	54	46	26	50	29	25	27
10	9	11	9	8	8	24	8	29
1	2	4	2	3	1	1	1	1
Pos	Neg	Pos	Neg	Neg	ND	ND	Neg	ND
Pos	Neg	Pos	Neg	Neg	Neg	Pos	Neg	
Pos	Pos	Pos	Neg	Pos	ND	ND	Neg	ND
Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Neg	Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Pos for <i>M. chelonae</i>	Neg	Neg

tibiotic therapy. In the remaining 7 patients, use of the antibiotics was stopped because of either adverse effects (1 patient) or compliance issues resulting from patient exhaustion while lesions were still appearing (6 patients).

Fifteen months after contamination, 3 patients still had persistent, recurrent cutaneous lesions. They each refused further treatment. Two years after the contamination, 1 of these 3 patients still had 1 persistent cutaneous lesion that had appeared during the previous month, but no additional cutaneous abscesses had appeared during the 3 subsequent months. None of the remaining 15 patients had experienced relapse. The mean duration of the disease in the 15 patients who experienced cure was therefore estimated to be 6.2 months (range, 1–15 months). Postsurgical scars developed in all patients, as well as scars relating to spontaneous drainage of the lesions. With the exception of 1 patient, all patients refused to undergo additional surgical procedures.

**DISCUSSION**

This is, to our knowledge, the largest series of *M. chelonae* subcutaneous infections after mesotherapy. To the best of our knowledge, this is also the first report of cutaneous infection due to *M. frederiksborgense*. This series confirms the difficulties in diagnosing these infections and illustrates the therapeutic challenge of such infections. Indeed, the most striking result of this study is the lack of efficiency of the antibiotics used, despite their in vitro susceptibility.

*M. chelonae* is a ubiquitous saprophyte RGM that has been isolated in a wide variety of environments, including water, soil, and dust [9]. Cases of infection caused by RGM have been reported worldwide, particularly in developed countries and often after surgical or other invasive procedures. To date, *M. chelonae* has been involved in 5 outbreaks (defined as >2 cases related to a single source of contamination) involving 4–35 patients each [2, 10–13]. The source of the infection identified in 3 of the 5 outbreaks of *M. chelonae* infection was tap water, injected solution, or rinse water for surgical instruments [2, 11,

12]. In our study, an *M. chelonae* strain was identified in the tap water system of the treating physician’s office that was used to clean the injector for mesotherapy, making it the most likely source of contamination [7].

Diagnosis of cutaneous infection due to RGM is difficult when the infection is not suspected. The clinical symptoms of these infections are often nonspecific abscesses or subcutaneous nodules without systemic features, as demonstrated in our cases and as reported elsewhere in the literature [2]. The mean time between the first injection and the appearance of the first symptoms was 9.5 weeks (range, 1–29 weeks) in our series. This finding is similar to 1 previous report of *M. chelonae* cutaneous infection after liposuction, in which the incubation period was 6 weeks (range, 2–20 weeks) [2]. The incubation period may, however, be as short as 1 week, as demonstrated by 1 of our patients who, after 2 courses of mesotherapy within a single week, developed lesions during the subsequent week. Any chronic cutaneous lesion located at any cutaneous site after a medical procedure must therefore evoke the possibility of RGM infection, even up to 6 months after the at-risk procedure.

Regarding diagnosis, our results show that direct examina-

**Table 2. Microbiological Susceptibility Data for *Mycobacterium chelonae* Strains**

Antibiotic	MIC, mg/L	Interpretation
Imipenem	>32	Resistant
Amikacin	16–32	Intermediate
Tobramycin	1–1.5	Susceptible
Tetracycline	64–256	Resistant
Tigecycline	0.06–0.09	Susceptible
Ciprofloxacin	1.5–3	Intermediate
Clarithromycin	0.09–0.12	Susceptible
Linezolid	32–256	Resistant
Cefoxitin	>256	Resistant
Ethambutol	>4	Resistant
Rifabutin	>16	Resistant

**NOTE.** MIC, minimum inhibitory concentration.

**Table 3. Antibiotic Treatment and Outcomes for 16 Patients with *Mycobacterium chelonae* and *Mycobacterium frederiksbergense* Cutaneous Infection after Mesotherapy**

Variable	Patient						
	1	2	3	4	5	6	7
Antibiotics regimen (weeks)	Tig (14), Tm (3), Clm (19), Cpx (3)	Tig (10), Tm (2), Clm (23), Cpx (15)	Tig (6), Tm (3), Clm (20), Cpx (7)	Tig (9), Tm (2), Clm (24), Cpx (6)	Clm (14), Cpx (14)	Clm (5), Cpx (5)	Tig (2), Tm (2), Clm (5), Cpx (1)
Duration of antibiotic treatment, weeks	19	23	20	24	14	5	5
Maximum no. of lesions	>100	>100	50	30	30	25	14
Reason for interruption of antibiotic treatment	E	E	R	E	R	E	E
Clinical status at antibiotic treatment interruption	P	P	R	P	R	P	P
Clinical status 1 month after antibiotic treatment interruption	P	P	R	P	R	P	P
Final outcome	Healed	Not healed	Healed	Healed	Healed	Healed	Healed
Total duration of disease, months	7	25	9	15	4	7	15

**NOTE.** AE, adverse event; Clm, clarithromycin; Cpx, ciprofloxacin; E, exhaustion; P, progression; R, resolution; Rel, relapse; S, surgery only; Tig, tigecycline; Tm, tobramycin.

tion for acid-fast bacilli lacks sensitivity when specimens are collected before (sensitivity, 25%) or during (sensitivity, 37%) surgical procedures. Culture results, however, were identical for samples collected either before or during surgical procedures (sensitivity, 75%). Surgery may therefore not be necessary for the diagnosis of RGM infection but could instead be restricted to patients with negative results of cultures of cutaneous specimens.

Optimal treatment of cutaneous infection due to *M. chelonae* is yet to be established, and to date, there are no randomized controlled trials that have compared different therapeutic regimens. Effective treatment of these infections is therefore difficult, and identification of antimicrobial susceptibility is essential. As demonstrated in our series, however, in vitro susceptibility does not consistently predict treatment effectiveness. Furthermore, *M. chelonae* exhibits greater antibiotic resistance than does *M. fortuitum* or *M. frederiksbergense*. *M. chelonae* is usually susceptible to tobramycin [14], clarithromycin [15], and linezolid [16], whereas imipenem [17], doxycycline [18], and ciprofloxacin [19] are less efficient. In our study, the *M. chelonae* strains were only susceptible to tigecycline, clarithromycin, and tobramycin, with intermediate results for ciprofloxacin.

Tigecycline was added to the initial regimen for the patients with the most-severe infections because of the lack of other efficient treatment options. Indeed, all of our strains were susceptible in vitro to tigecycline. Similarly, in a bacteriologic study, 100% of the strains of *M. chelonae* were susceptible to tigecycline in vitro [18]. Moreover, according to one case report, tigecycline was effective in the treatment of *M. chelonae* necrotizing pneumonia [20]. No previous study has reported the use of tigecycline in the treatment of cutaneous infections due

to RGM. Of our 6 patients who were treated with tigecycline, 2 continued to have persistent disease despite the in vitro susceptibility of the infecting strains.

Clarithromycin is the only oral drug to which all *M. chelonae* strains are susceptible, as demonstrated in another study [15]. Unfortunately, clinical efficacy is not obvious. In a clinical trial involving 14 patients treated with clarithromycin for *M. chelonae* cutaneous infection, 6 patients had persistent lesions and new abscesses that appeared during the antibiotic course [21]. Furthermore, 13 of our 14 clarithromycin-treated patients developed recurrent lesions during the antibiotic course. It has been reported previously that acquired resistance to clarithromycin may develop after monotherapy [21, 22], and so, in agreement with the evidence thus far, we do not recommend the use of monotherapy, at least initially, in the treatment of RGM cutaneous infections.

Perhaps the most striking result of our study is the lack of efficacy of even double or triple therapy. Conversely, 2 patients experienced clinical cure without antibiotic therapy. Antibiotics are usually recommended for various durations, depending on disease location and severity [23]. From 2 through 4 months of antibiotic therapy is usually recommended in localized infection, and at least 6 months is usually recommended for the treatment of disseminated cutaneous disease [23]. Nonetheless, despite prolonged therapy, abscesses were still appearing in 7 of our 14 treated patients when treatment was discontinued. Therefore, not only did antibiotics not help to cure these patients, but more surprisingly, antibiotics did not prevent the appearance of new lesions in this group. In addition, 1 patient experienced relapse within 1 month after stopping treatment. Therefore, 8 patients continued to experience disease progres-

**Table 3. (Continued.)**

Patient								
8	9	10	11	12	13	14	15	16
Clm (21), Cpx (19)	Clm (15), Cpx (13)	Tig (4), Tm (2), Clm (19), Cpx (1)	Clm (1), Cpx (1)	Clm (5), Cpx (1)	Clm (14), Cpx (2)	S	S	Clm (12), Cpx (12)
21	15	19	1	5	14	S	S	12
11	8	6	6	5	2	2	1	1
E	R	R	AE	R	R	NA	NA	R
P	R	R	P	R	R	NA	NA	R
P	R	R	P	Rel	R	NA	NA	R
Healed	Healed	Healed	Healed	Healed	Healed	Healed	Healed	Healed
8	4	4	7	6	3	2	1	1

sion despite antibiotic therapy. However, the cultures of specimens obtained from a patient's new lesions were negative for the bacterium.

It is worth remembering that excision and drainage remain the treatment of choice for cutaneous abscesses due to *Staphylococcus aureus* [24]. As a rule, this approach may also apply to cutaneous abscesses due to RGM, and the rationale behind the use of antibiotics to treat *M. chelonae* cutaneous infections should be questioned.

In conclusion, the treatment of cutaneous infections due to RGM is obviously difficult. No efficient strategy has been demonstrated so far. The use of surgery and/or antibiotic therapy needs to be evaluated on a case-by-case basis. On the basis of our experience, we recommend surgical treatment for patients with only a limited number of lesions, with the addition of antibiotic therapy individualized according to disease severity and potentially being indicated only for patients who are either immunocompromised or have multiple lesions. Treatment should then be guided by the in vitro susceptibility results. Patients should be informed of the evidence surrounding the seemingly poor efficacy of the antibiotic regimen, as well as the risks of scarring after surgery and their aesthetic implications.

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