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Short Communication

Post-surgical atypical mycobacteriosis in 125 patients in Rio de Janeiro

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Abstract

Introduction: The growing incidence of post-surgical atypical mycobacteriosis (PSAM) may be related to the increased use of low- and medium-complexity video-assisted surgery. **Methods:** Between April 2007 and June 2009, 125 patients were referred from the State Health Department of Rio de Janeiro for the treatment of confirmed, probable, or suspected PSAM. **Results:** Laparoscopic cholecystectomy was the most frequent surgical procedure (48.8%) among patients. Clarithromycin, ethambutol, and terizidone were used to treat 113 patients for a mean duration of 226 days. **Conclusions:** Despite the need for multidrug therapy and long treatment duration, most included patients adhered to treatment and experienced cure without relapse.

Keywords: Post-surgical wound infection. Mycobacterium infection. Multidrug therapy.

Atypical mycobacteria are widely distributed in nature and have been isolated from water sources like tap water, and from soil as environmental saprophytes[1], These organisms are opportunistic pathogens in outbreaks of post-surgical atypical mycobacteriosis (PSAM)[2], a healthcare-associated infection that has recently emerged in Brazil and elsewhere. The growing incidence of PSAM may be related to the increased use of low- and medium-complexity video-assisted surgery[3].

From January 2003 to February 2009, 2128 PSAM cases were reported in Brazil. with most occurring in private hospitals. Since 2006, 1107 PSAM cases have been reported to the Health Surveillance Secretary of Rio de Janeiro state. From January 2010 to September 2014, 216 additional cases were reported to the Brazil National Agency of Sanitary Surveillance (ANVISA), 12 of which were in Rio de Janeiro state[4,5].

Medical literature regarding PSAM is limited to case reports or small case series emphasizing laboratory diagnosis. Our objective was to describe the clinical course of patients treated by providers in an infectious disease service during the ongoing PSAM epidemic.

This study included 125 patients referred to the Infectology Service of the Hospital Universitário Antonio Pedro, Universidade Federal Fluminense (UFF) in Niteroi, Rio de Janeiro from April 2007 to June 2009. Patients were referred for evaluation of PSAM by the Health Secretary of Rio de Janeiro state following operations in 10 private hospitals of Rio de Janeiro and neighboring municipalities.

Patients were classified as having suspected, probable, or confirmed PSAM, according to criteria proposed by ANVISA[4,6]. Suspected cases occurred in patients with two or more signs or symptoms of PSAM following video surgery but for whom cultures for fast-growing mycobacteria were not performed or negative. PSAM signs and symptoms were local redness, swelling, and fever lasting >1 week; nodules with or without fistulous tracts; ulcerations with persistent serous, purulent, or bloody purulent discharge; impaired wound healing, unresponsive to conventional treatment; and lesions along the cannula or trocar path, with or without spread to adjacent areas. Probable PSAM referred to patients meeting the criteria for suspected PSAM plus the presence of granulomas in surgical wound or adjacent tissue biopsies or the presence of acid-fast bacilli but negative mycobacterial cultures. Confirmed cases

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had positive mycobacterial cultures from surgical wound or adjacent tissue material.

The antimicrobial regimen initially indicated by the Brazilian Ministry of Health (BMH) was a combination treatment with clarithromycin, terizidone, and ethambutol. As the epidemic evolved, *Mycobacterium massiliense* was identified as the etiologic agent. Based on the antimicrobial sensitivity of this strain, both terizidone and ethambutol were withdrawn from the regimen. Clarithromycin was then used singly or in combination with amikacin for patients with multiple lesions or infections affecting deeper tissue planes beyond the skin and subcutaneous tissue[7].

In compliance with Resolution 196/96 of the National Health Council, this study was approved by the Research Ethics Committee of the School of Medicine of UFF (number 202665 13.1.0000.5243). All data were obtained from medical records and stored in a database compatible with SPSS 17 (SPSS Inc., Chicago, IL, USA). Epi Info 2015 version 7.1.5.2 (Centers for Diseases Control and Prevention, Atlanta, GA, USA) was also used for some statistical analyses. Differences between proportions were evaluated using chi-square tests, and statistical significance was set at P value <0.05.

The 125 patients were grouped by case type: 24 confirmed (19.2%), 38 probable (30.4%), and 63 suspected (50.4%). Most patients (109) underwent surgery between October 2006 and January 2007. The incubation period ranged from 1 to 170 (mean, 41±33.3) days. Most patients (89; 71.2%) showed clinical signs or symptoms of illness on post-surgical days 8–60; however, 17 patients (13.6%) did not show clinical evidence of the disease until post-surgical days 61–90.

Patients were aged 19–81 (mean, 43.7; median, 41.5) years and most were women (97; 77.6%). Comorbidities were present in 27 patients (21.6%), with systemic arterial hypertension the most frequent (21/27 patients; 77.8%; **Table 1**). Most patients (117; 93.6%) had video-assisted surgery (cholecystectomy, 48.8%; gynecologic procedure, 15.2%; **Table 2**). Lesions were single and superficial in 28 patients (22.4%), multiple and superficial in 56 (44.8%), and deep in 26 (20.8%).

Wound drainage (86.4%) and peri-surgical nodules (65.6%) were the most common clinical signs. Redness (24.8%), induration (23.0%), and suture dehiscence (18.4%) were also noted.

Clinical specimens were collected from 98 patients (78.4%) for direct examination, culture, or histopathology. Of the 98 specimens, 57 were collected prior to treatment initiation. Of the 44 specimens subjected to histologic examination before treatment initiation, 21 (47.7%) had evidence of granulomas. Cultures were positive for 20 of 46 specimens (43.5%) obtained prior to treatment initiation.

TABLE 1: Demographic characteristics of 125 patients with post-surgical mycobacteriosis.

Characteristics	Confirmed n=24 (%)	Probable n=38 (%)	Suspected n=63 (%)	All n=125
Age, years				
<20	0 (0.0)	1 (100.0)	0 (0.0)	1
20–29	7 (26.9)	6 (23.1)	113 (50.0)	26
21–39	5 (17.8)	8 (28.6)	15 (53.6)	28
40–49	3 (10.7)	11 (39.3)	14 (50.0)	28
50–59	6 (24.0)	8 (32.0)	11 (44.0)	25
>60	3 (17.6)	4 (23.5)	10 (58.9)	17
Sex				
Female	21(21.6)	31 (32.0)	45(46.4)	97
Male	3 (10.7)	7 (25.0)	18 (64.3)	28
Residential municipality				
Rio de Janeiro	16 (21.6)	27 (36.5)	31 (41.9)	74
Duque de Caxias	3 (11.5)	4 (15.4)	19 (73.1)	26
Other	5 (20.0)	7 (28.0)	13 (52.0)	25
Comorbidities				
Yes	5 (18.6)	10 (37.0)	12 (44.4)	27
No	19 (19.4)	28 (28. 6)	51 (52.0)	98

TABLE 2: Surgical procedures related to post-surgical mycobacteriosis, by case type.

Surgical procedures	Confirmed n=24 (%)	Probable n=38 (%)	Suspect n=63 (%)	All n=125
Cholecystectomy	11(18.0)	16 (26.2)	34 (55.8)	61
Gynecologic	3 (15.8)	9 (47.3)	7 (36.9)	19
Gastroplasty	2 (14.2)	8 (57.2)	4 (28.6)	14
Appendectomy	2 (18.1)	1 (9.0)	8 (72.7)	11
Arthroscopy	1 (10.0)	2 (10.0)	7 (80.0)	10
Mammoplasty	4 (80.0)	0 (0.0)	1 (20.0)	5
Urologic	1 (33.3)	2 (66.7)	0 (0.0)	3
Liposuction	0 (0.0)	0 (0.0)	1 (100.0)	1
Video-laparoscopy	0 (0.0)	0 (0.0)	1 (100.0)	1

Of the 41 specimens collected following treatment initiation, 39 (95.1%) were tissue fragments for histopathologic examination and culture, and 2 (4.8%) were tissue fragments and swabs. Tissue fragments were cultured for 31 cases; of the 24 cultures with known results, 4 were positive (16.7%). Histopathologic examination of 41 tissue fragments collected after treatment initiation showed that 26 (63.4%) had granulomas.

Frequencies of positive cultures for specimens obtained before and after treatment initiation were compared, regardless of specimen type. The likelihood of obtaining a positive culture was much higher for specimens collected prior to treatment initiation than for those collected after treatment initiation (odds ratio, 3.84; 95% confidence interval, 1.36–13.05).

The most frequently isolated mycobacterial species was *M. massiliense* (22 cases). *M. mageritense* and *M. fortuitum* were each present in two patients who underwent augmentation mammoplasty. *M. neoarum* and *M. massiliense* were both present in a single patient.

Combination treatment with clarithromycin (500 mg PO every 12 hours), ethambutol (1.2 g PO daily), and terizidone (500–750 mg PO daily) was initially used to treat 113 patients (90.4%). Of these, 69 patients (61%) completed their treatment course in 105–342 (mean, 226±52.5; median, 229) days, without modification. Seventeen (15%) patients discontinued treatment, most often secondary to nonadherence (16 patients).

Fourteen of the 29 patients (48.2%) with single and superficial lesions, 44 of the 56 (78.6%) with multiple superficial lesions, and 25 of the 26 (96.0%) with deep lesions underwent one or more surgeries to treat to surgical site infection. All nine patients with metal shoulder anchors and all five with breast implants had these devices removed.

Adverse effects were reported by 78 patients (62.4%), with bitter taste (37.6%), somnolence (11.2%), dizziness (10.4%), memory impairment (8.8%), and epigastric pain (8%) occurring most commonly. Other side effects affected 44 patients, with frequencies <8%.

Five patients developed allergic urticarial reactions secondary to ethambutol, and 34 developed central nervous system signs and symptoms (e.g., somnolence, dizziness, sadness, depression, headache, tremor, and convulsions) secondary to terizidone. No changes in serum liver enzyme levels occurred during monthly follow-up evaluations. After antibiotic treatment completion, 120 of the 125 patients (96%) had no evidence of relapse during 2 years of follow-up.

The present study spanned 2006 to 2009 in Rio de Janeiro, during which time PSAM incidence peaked and eventually decreased, likely owing to implementation of measures to control the epidemic[4,8].

The *M. massiliense* BRA100 clone is responsible for this epidemic of surgical infections caused by fast-growing mycobacteria[9]. Predominance of a single clone in multiple regions of Brazil suggests a common source, possibly linked to sanitizers and surgical equipment. Processing flaws in cleaning, disinfection, sterilization, and surgical technique, as well as tolerance of *M. massiliense* to glutaraldehyde, are the main hypotheses explaining the outbreak[4,10]. We identified *M. massiliense* in most specimens with positive culture results. Identification of three other species in this study may reflect lack of attention to cleaning and disinfection, supported by findings later in this outbreak that viable mycobacteria were present in disinfectant solutions[9,11].

ANVISA has implemented several safety measures regarding processing and sterilization of materials used in video-assisted surgeries. High-level disinfection is now prohibited for materials expected to penetrate sterile tissues or cavities, as well as sterilization of laparoscopes and other equipment by immersion in chemicals. Moreover, ensuring that disinfectants and sanitizers can eliminate *M.* massiliense is now mandatory[8].

Abdominal surgeries were most frequently associated with PSAM in this study (92.8%) and in the overall epidemic (59.2%)[4], probably because this type of surgery is increasingly performed using video laparoscopy. Most of our patients were women (77.6%) and more than half (50.5%) underwent

cholecystectomy for biliary lithiasis, which is more prevalent among women[12]. Sixty-one patients (48.8%) underwent cholecystectomy.

Positive cultures (43.5%) were more frequent among specimens collected prior to antibiotic treatment initiation. The percentage of patients with negative or no culture results (i.e., suspected cases) was lower in this series (50.4%) than that of the overall epidemic (65.5%)[4]. Treatment initiation for suspected PSAM prior to diagnostic testing is related to widespread knowledge of the outbreak among private health practitioners, which may have contributed to the lower proportion of confirmed cases in our study.

Clinical presentation in this series was similar to that previously described for the PSAM outbreak, with drainage (86.4%), nodules (65.6%), redness (24.8%), induration (23.2%), and wound dehiscence (18.4%) occurring most frequently[1,9,13].

During the epidemic, the first of two guidelines issued by the BMH was implemented in Rio de Janeiro state: surgical debridement followed by triple-drug therapy with clarithromycin, terizidone, and ethambutol. This drug treatment recommendation was based on the concept of polychemotherapy commonly used to treat mycobacterial infections but was not based on systematic studies, which are lacking on this subject[13]. In our study, 92% of patients initially received this drug regimen; however, ethambutol and terizidone were removed once sensitivity profiles for the agent became available. From that point forward, clarithromycin was used for 6 months as monotherapy for single and superficial lesions. Patients with multiple or deep lesions were treated with clarithromycin and amikacin (1 g IV or IM three times/week) for at least 6 months[2,4,7,9]. However, at publication of the second BMH guideline[7], which recommends monotherapy, 113 patients in this study (61%) had already completed triple-drug therapy over an average 7 months.

Although surgery prior to drug treatment, especially to remove foreign bodies and debride infected tissues[13,14], is deemed fundamental for therapeutic success, this was not true in our series. Antimicrobial treatment was initiated prior to surgery in 54.4% of patients and 76.8% underwent at least one subsequent surgical treatment; this was especially common among patients with deep lesions or devices that could be sources of persistent infection. This high rate of follow-up surgery may have contributed to the absence of relapses in our series.

Because fast-growing mycobacteria respond slowly to antimicrobial treatment, patients should be treated for at least 6 months[14]. However, our patients experienced delayed surgical approaches and a high frequency of deep lesions necessitating prolonged therapy, which averaged 226 days.

This clinical–epidemiologic study is limited by challenges inherent in retrieving information from medical records and a lack of laboratory and imaging results. Coordination of patient follow-up with private surgeons and surgery performed only at hospitals with accredited health insurance plans caused difficulties for both health care providers and patients. Because there are few related reports and physicians have little experience in treating PSAM, it is necessary to establish an interim consensus regarding optimal surgical timing, imaging modality and interpretation, and a definition of curative criteria[15].

Abdominal surgeries were most frequently associated with PSAM in this study. Most patients were women, and more than half underwent cholecystectomy for biliary lithiasis. Clinical presentation most often consisted of drainage, nodules, redness, induration, and wound dehiscence. *M. massiliense* was identified in most specimens. Many patients initiated antimicrobial treatment prior to surgery, and 76.8% of patients underwent at least one, albeit later, surgical treatment. Despite the long treatment course and need for multiple drugs, most patients adhered to treatment and experienced cure without relapse.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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