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Original Article

Comparing *Mycobacterium massiliense* and *Mycobacterium abscessus* lung infections in cystic fibrosis patients

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Abstract

Background: Mycobacterium massiliense is closely related to *Mycobacterium abscessus* and is also a frequent cause of mycobacterial lung disease in patients with cystic fibrosis (CF). There has been no previous investigation of possible differences between *M. massiliense* and *M. abscessus* infections in the setting of CF.
Methods: We studied a prospective cohort of 16 *M. massiliense* and 27 *M. abscessus* lung infection cases with CF, with a mean follow-up of 6 years.
Results: M. massiliense cases were younger than *M. abscessus* cases (mean age: 12.8 *vs* 17.1 years; $p = 0.02$) at the time of the first mycobacterial isolation and also had lower body mass index values (mean: 16.4 *vs* 19.3 kg/m^2, $p = 0.002$). All *M. massiliense* cases, except one, had negative BMI Z-score values at the time of the first mycobacterial isolation (11/12 *vs* 16/23 *M. abscessus* cases, $p = 0.04$). Clarithromycin-based combination therapies led to mycobacterial eradication in 100% of *M. massiliense* cases but only in 27% of *M. abscessus* cases ($p = 0.009$).

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Conclusion: Our data show a particular link between *M. massiliense* and malnutrition specifically in CF patients. Unlike *M. abscessus*, the bacteriological response of *M. massiliense* to combination antibiotic therapies containing clarithromycin was excellent. Distinguishing between *M. massiliense* and *M. abscessus* has major clinical implications for CF patients.

Keywords: Mycobacterium abscessus complex; Malnutrition; Nontuberculous mycobacteria; Cystic fibrosis

1. Introduction

Mycobacterium abscessus complex (MABSC) is in fact a complex of three closely related "species" of rapidly growing mycobacterium (taxonomically, they are a single species [1]): *M. abscessus sensu stricto*, hereafter referred to as *M. abscessus*, *Mycobacterium massiliense*, and *Mycobacterium bolletii* [2]. MABSC causes a wide spectrum of diseases in humans, including chronic lung disease, skin disease and disseminated disease [3]. Since the early 2000s, it has increasingly been isolated from the respiratory tract of patients with cystic fibrosis [4–6]. MABSC may infect CF patients at all ages, including the very young [4,7,8]. Infection is mostly indolent and generally progresses slowly. However, a serious, life-threatening lung disease may develop in some patients and fatal disseminated infections have been reported following lung transplantation [9,10].

MABSC is one of the most antibiotic-resistant RGM: very few drugs are potentially active, and of these, only few can be administered by the oral route [3,11,12]. However, *in vivo* selection of *rrl* mutants resistant to clarithromycin has been reported and inducible resistance to clarithromycin, due to the presence of a functional copy of *erm*(41), affects the majority of *M. abscessus* and *M. bolletii* isolates [13,14].

M. abscessus and *M. massiliense* are responsible for >90% of cases due to MABSC, but the relative proportions of cases caused by the species differ between geographical regions. In the United States and Europe, *M. abscessus* and *M. massiliense* account for 50–60% and 30–35%, respectively, of MABSC pulmonary isolates from both CF and non-CF patients [4,15,16].

Two studies have investigated the clinical significance of distinguishing between the MABSC "species", and especially between *M. abscessus* and *M. massiliense* [16,17]. No clinical differences were found between patients with *M. abscessus* lung disease and those with *M. massiliense* lung disease, but few patients were included and most were non-CF subjects. More recently, two large-scale retrospective studies including non-CF adults compared the clinical characteristics and treatment outcomes between patients with *M. abscessus* lung disease and those with *M. massiliense* lung disease [18,19]. Consistent with the other studies, the clinical presentations of disease caused by the two species were similar, but the rate of response to combination antibiotic therapy including clarithromycin was much higher for *M. massiliense* than for *M. abscessus*.

Our main objectives were to compare *M. massiliense* and *M. abscessus* lung diseases in CF patients and to evaluate the benefit of distinguishing *M. massiliense* from *M. abscessus*. We show that *M. massiliense* targets young CF patients with severe malnutrition and is associated with a better bacteriological response than *M. abscessus* to combination antibiotic therapies containing clarithromycin.

2. Patients and methods

2.1. Patients included and data collection

All *M. massiliense* (16) and *M. abscessus* (27) lung infection cases identified in French CF patients between 2001 and 2004 were included [6]. The French multicenter prevalence study conducted in 2004 involved 41 of 49 French CF Center and included 1582 patients, the overall NTM prevalence was 6.6%. Thus, risks of bias secondary to center effect were minimized. Patients with *M. bolletii* infection were not included for further study because of their small number. All cases fulfilled the American Thoracic Society [20] bacteriological criteria for nontuberculous mycobacteria (NTM) lung infection (*i.e.*, positive culture results from at least two separate expectorated sputum samples) [21]. The mean follow-up was 6 years (extremes, 2 and 9 years). Demographic, clinical and laboratory data were retrieved from the French CF registry, with the permission of an Internal Review Board.

Information about occurrences of "MABSC lung disease" (*i.e.*, clinical and/or radiographic criteria for NTM lung infection [21]), anti-mycobacterial treatments and treatment outcomes were collected by chief medical officers from CF centers. MABSC lung disease was defined by functional deterioration or new infiltrates on thoracic imaging despite antibacterial treatment of the sputum colonization. Constitutional symptoms were not required. Choice of treatment was made according to the treating physician judgment. Response to treatment was defined by the improvement of general symptoms (fever, weight loss) if present, improvement of pulmonary lung function tests and/or thoracic CT scan.

2.2. Bacteriological methods

Sputum smears and mycobacterial cultures were performed using approved techniques as previously described [8]. Identification of "*M. abscessus*" and "*M. massiliense*" was based on *rpoB* and *hsp65* sequencing [22,23]; multilocus sequencing analysis was performed in cases of discrepancy between *rpoB* and *hsp65* sequence data [24].

2.3. Statistical analysis

The chi-square test (or the Fisher exact test if necessary) was used for comparisons of qualitative variables, and Student's t test

for quantitative variables (STATA software Version 9, StataCorp LP). Statistical significance was accepted for $p < 0.05$.

3. Results

3.1. Characteristics of cases at the first mycobacterial isolation

M. massiliense cases (n = 16) were younger than *M. abscessus* cases (n = 27) at the time of the first mycobacterial isolation (mean [SD] age of 12.8 [5.2] *vs* 17.1 [5.8] years, $p = 0.02$) (Table 1). They also had lower BMI values (mean [SD] value of 16.4 [2.3] *vs* 19.3 [3.1] kg/m^2, $p = 0.002$) (Table 1); 56.3% (9/16) had BMI values ≤16 kg/m^2 *vs* only 14.8% (4/27) for *M. abscessus* cases ($p = 0.007$), and a similar difference was found for the subgroup of cases aged 10 to 18 years (64.3% [9/14] *vs* 21.1% [4/19], $p = 0.03$). The *M. massiliense* and the *M. abscessus* groups were otherwise similar with respect to sex ratio, CF genotype, use of pancreatic extracts and colonization with *Pseudomonas aeruginosa* (Table 1). The respiratory function evaluated with FEV1 was also similar between the two groups but we can notice that the mean FEV1 of the two groups was much lower than mean FEV1 of the CF population at the same age (French CF registry).

3.2. Analysis of BMI Z-score data

The much lower BMI values found for the *M. massiliense* group at the time of first mycobacterial isolation prompted us to retrieve BMI Z-score data from the French CF registry. The analysis of BMI Z-score values confirmed the previous BMI data (Fig. 1): all *M. massiliense* cases, except one, had negative BMI Z-score values at the time of the first mycobacterial isolation whereas this was the case for only 69% of *M. abscessus* cases (11/12 *vs* 16/23, $p = 0.04$).

Fig. 2 shows evolution of BMI Z-score in the *M. massiliense* and *M. abscessus* groups. As clearly shown, the Z-score did not decrease around the time that the mycobacteria was isolated, and did not increase after treatment or its eradication. Thus, malnutrition was clearly not a consequence of infection by

Table 1
Characteristics of cases at first isolation of the mycobacterium.

Characteristics	*M. massiliense* (n = 16)	*M. abscessus* (n = 27)	*p*-Value
M/F (sex ratio)	7/9 (0.78)	13/14 (0.93)	1
Mean [SD] age, years	12.8 [5.2]	17.1 [5.8]	0.02
F508del/F508del [a]	10/16 (62.5)	12/27 (44.4)	0.35
Mean [SD] BMI, kg/m^2	16.4 [2.3]	19.3 [3.1]	0.002
Mean [SD] FEV1, % predicted [b]	64.8 [18.1] (n = 14)	64.5 [23.7] (n = 26)	0.96
Use of pancreatic extracts [a]	15/15 (100)	26/26 (100)	1
P. aeruginosa [a,c]	8/16 (50)	20/27 (74.1)	0.18

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in one second.
[a] No./total no. evaluated (%).
[b] No. evaluated.
[c] At least one positive sample within the previous year.

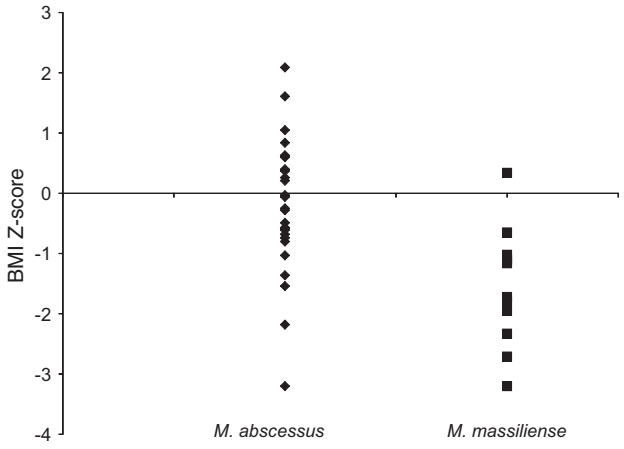

Fig. 1. BMI Z-score in the *M. massiliense* and *M. abscessus* groups.

MABSC. We can also notice that *M. massiliense*, unlike *M. abscessus*, affects CF patients with more severe malnutrition.

We studied the frequency of long-term enteral feeding and parenteral feeding at the time of the first mycobacterial isolation. The percentage of cases receiving long-term enteral feeding was similarly low in the *M. massiliense* and *M. abscessus* groups (2/12 [16.7%] *vs* 4/22 [18.2%], $p = 0{,}91$) and there was no case of parenteral feeding in either group.

3.3. Number of culture-positive samples, acid-fast bacilli (AFB) smear positivity and occurrence of NTM lung disease

Overall, 39/43 (90%) of cases had ≥3 positive sputum samples. The 4 cases found positive only twice were in the *M. massiliense* group (4/16 *vs* 0/27, $p = 0.01$) and displayed negative AFB smears (Fig. 3). During follow-up, 18 patients presented symptoms of MABSC lung disease: 8 patients presented functional deterioration (fever, asthenia, emaciation), 8 presented deterioration of their respiratory function and 9 patients presented with new pulmonary infiltrates on thoracic imaging. *M. massiliense* cases tended to have less frequent reported MABSC lung disease, but the difference between the two groups was not significant (5/16 [31.2%] *vs* 13/27 [48.1%], $p = 0.35$).

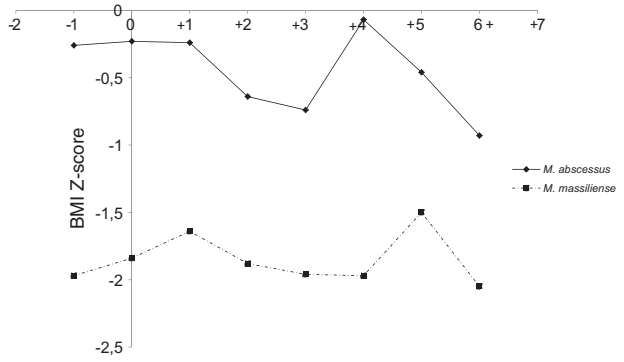

Fig. 2. Kinetics of mean BMI Z-score in the *M. massiliense* and *M. abscessus* groups. 0 is the year of the first mycobacterial isolation.

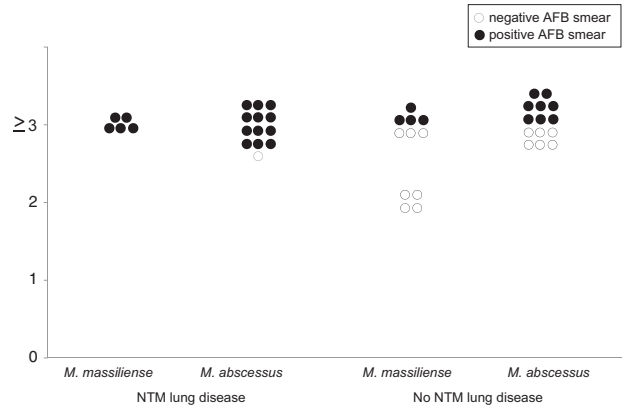

Fig. 3. Number of positive MABSC cultures and AFB smear positivity in cases with or without MABSC lung disease. AFB smear-positive cases were all cases with at least one positive AFB smear. Samples were obtained for a minimum period of 18 months. Patients with a positive NTM sample had to submit three more sputum samples at monthly interval and then every 3 months.

All cases with clinical MABSC lung disease (18/18) had ≥3 positive sputum samples and all but one (17/18 [94.4%]) had positive AFB smears (Fig. 3). However, most cases with no evidence of MABSC lung disease also had ≥3 positive sputum samples (21/25, 84%) with half having positive AFB smears (12/25, 48%). Thus, indicators based on ≥3 positive samples and positive AFB smears showed excellent negative predictive values (100% and 92.9%, respectively), but poor positive predictive values for MABSC lung disease (46.1% and 58.6%, respectively).

3.4. Response to antimycobacterial treatment

Twenty-two cases, 8 in the *M. massiliense* group (47.1%) and 14 in the *M. abscessus* group (46.7%), received specific treatment with anti-MABSC combination therapies during the follow-up period. Four patients were treated for persistent MABSC "colonization" without any evidence of lung disease (3 in the *M. massiliense* group and 1 in the *M. abscessus* group). Clarithromycin-based therapies were used in all cases but two (one in each group), both of which received tigecycline and amikacin. The antimicrobial agents associated with clarithromycin were mostly amikacin (88.2%), imipenem (64.7%) and ethambutol (47.1%), and more rarely trimethoprim-sulfamethoxazole (1.2%), tobramycin, tigecyclin and linezolid (0.6% each).

Response to treatment was known for 19/22 cases (*M. massiliense*, 7 cases; *M. abscessus*, 12 cases). MABSC was successfully eradicated in 6/7 of *M. massiliense* cases but only in 3/12 of *M. abscessus* cases ($p = 0.02$) (Table 2). Moreover, among the cases treated with clarithromycin-based combination therapies, MABSC was eradicated in 6/6 of *M. massiliense* cases but only in 3/11 of *M. abscessus* cases ($p = 0.009$). As clearly shown in the Fig. 4, the treatment and the eradication of the mycobacteria have no obvious impact on FEV1. There is a progressive deterioration of the respiratory function in eradicated and noneradicated CF patients over time in the *M. massiliense* group and in the *M. abscessus* group. This progressive deterioration of the respiratory function is also observed in non-treated patients (data not shown).

Table 2
Microbiological characteristics and treatment responses for patients with *M. abscessus* or *M. massiliense* lung disease.

	M. massiliense	*M. abscessus*	*p*-Value
Transient colonization	4/16	0/27	0.01
Chronic colonization [a]	8/16	13/27	0.9
Clinical lung disease	4/16	14/27	0.08
– Antimycobacterial treatment	8/16	14/27	0.9
– Spontaneous eradication	2/7	4/12	0.8
– Eradication after treatment	6/7	3/12	0.02

[a] Chronic colonization is defined as more than two positive sputum with MABSC with no clinical or radiological criteria of mycobacterial lung disease.

3.5. Mortality

Three patients died, one in the *M. massiliense* group and two in the *M. abscessus* group. The patient in the *M. massiliense* group was a girl with a severe form of CF; she died when she was ten years old in the context of *Burkholderia cepacia* syndrome several years after her sole asymptomatic episode of transient colonization with *M. massiliense*. One of the two deceased patients from the *M. abscessus* group was a boy with repeated positive sputum samples, but with no NTM lung disease. He died at the age of 18 years following a lung transplant rejection 1 year post-transplantation, with no clinical or radiological criteria of mycobacterial lung disease. The other patient was a girl positive for *M. abscessus* since the age of 20 years; lung transplantation was not possible (contraindicated for repeated *M. abscessus* positive cultures under antimycobacterial treatment) and she died when she was 27 years old.

3.6. Lung transplantation

Five of the 43 patients included in the study (11.6%) received lung transplants (*M. abscessus*, 3; *M. massiliense*, 2). One of these patients, infected with *M. abscessus*, died from transplant rejection 1 year post-transplantation, with no evidence of mycobacterial disease (see above). The other four cases were still alive 1 to 3 years after transplantation, with MABSC eradication in two, both *M. massiliense*, cases.

Lung transplantation was not proposed to three patients because sputum was culture-positive for *M. massiliense* (n = 1) or *M. abscessus* (n = 2); these three cases included the deceased patient described above.

4. Discussion

We here emphasize the importance of nutritional status in *M. massiliense* lung disease in CF patients. Importance of nutritional status in NTM lung disease has been previously highlighted by several studies outside the CF context. Pulmonary NTM lung disease in patients without predisposing condition predominantly affects thin postmenopausal women. Mean BMI values in North American studies ranged from 21.1 to 22.1 kg/m^2

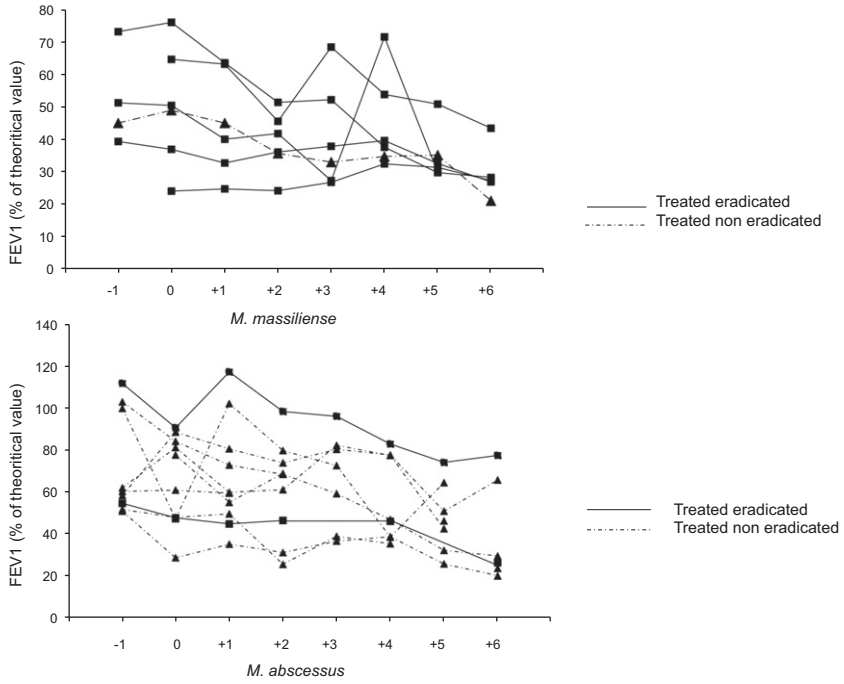

Fig. 4. Evolution of FEV1 in treated eradicated patients and treated non-eradicated patients in the *M. massiliense* and *M. abscessus* groups. Graphs are represented with individual curves. 0 is the year of first mycobacterial isolation.

vs 28.2 kg/m^2 in the USA control population (National Bureau of Weights and Standards, Hyattsville, MD) [25]. Adiponectin, an immunosuppressive adipokine, is inappropriately secreted in these patients [25–27]. There are several reports of NTM lung disease in patients suffering from anorexia nervosa [28,29], in whom impaired cellular immune response has been demonstrated [30].

Unexpectedly, we show that *M. massiliense*, unlike *M. abscessus*, affects young CF patients with severe malnutrition. Recent studies did not find such difference in BMI values of patients with *M. massiliense* or *M. abscessus* lung infection, which ranged from 18.8 to 20.8 kg/m^2 in Asian studies and from 22.5 to 24.4 kg/m^2 in the North American study [16,18,19,31]. However, these studies were performed in non-CF adult patients or mostly non-CF patients, suggesting that the relationship between *M. massiliense* and low BMI values is specific to the context of CF and/or to children and teenagers.

These BMI data were confirmed by the analysis of the BMI Z-score value, a measure better adapted for evaluating malnutrition, particularly in children [32]. The reason why malnutrition is a major susceptibility factor in CF for *M. massiliense*, but not for *M. abscessus*, remains unknown. Possibly, this may be due to *M. massiliense* being less able to establish in the upper respiratory tract. This is supported by the observation that cases of "transient colonization" (only two positive samples with repeated subsequent negative cultures) were only observed within the *M. massiliense* group. Also, the study of Zelazny et al. performed in non-CF adult patients found an underlying lung disease prior to the diagnosis of MABSC pulmonary infection in all *M. massiliense* cases but only in one third of *M. abscessus* cases [16].

Malnutrition is a major problem in CF, and is associated with poorer quality of life, more frequent infection and poor prognosis [33]. The maintenance of a good nutritional status is therefore a major goal in CF, and one of the reasons is that it increases the median life expectancy [34]. Despite the general awareness of the importance of nutrition in CF patients, the situation is unsatisfactory: the CF Foundation Patient Registry in the United States indicates that one third of patients are in urgent need of a better nutrition [35]. Our findings are consistent with these data as complementary enteral feeding was given to a very small proportion of patients, especially in the *M. massiliense* group.

We confirm in the CF population that *M. massiliense* infection, in contrast with *M. abscessus* infection, responds remarkably well to combination therapies containing clarithromycin (bacterial eradication in 100% of cases in our study). Similar observations were recently reported for non-CF patients in Korea [19] and in Japan [18]. The good response of *M. massiliense* to clarithromycin-based combination therapies is probably due to this species not having an inducible resistance to clarithromycin [14]: the *erm*(41) gene, which confers inducible macrolide resistance is non-functional in *M. massiliense* [36]. Note, however, that there was clinical improvement in all cases of *M. abscessus* infection in our series treated with clarithromycin, including those with bacteriological failure. This suggests that clarithromycin and/or the associated antibiotics were at least partially effective in our series. A similar discordance between clinical and bacteriological results in non-CF patients has been described by Koh et al: 75% of cases showed clinical improvements although the eradication rate was only 25% [19]. Our data, and the recent findings of Koh et al. [19] and Harada et al. [18] for non-CF patients, indicate that clarithromycin is the cornerstone of treatment of *M. massiliense*

infections. This is consistent with the current recommendations of the ATS, which state that MABSC-positive CF patients should not receive macrolide monotherapy to avoid the development of resistance to clarithromycin [21].

Our findings suggest that the new cut-off of two positive samples, as recommended in the ATS 2007 guidelines [21], is not stringent enough for the detection of mycobacterial disease in CF patients. Our study also confirms the prognostic value of AFB smears. Positive AFB smears were found in 95% of the cases of mycobacterial disease, less than 50% of those without disease, and only 10% of those with spontaneous eradication of mycobacteria. Thus, positive AFB smear results appear to be a marker of the severity of the course of MABSC infections in CF. However, caution is required in the interpretation of any such results, and their practical value is unclear. Indeed, our study involved mostly patients screened as part of systematic monitoring over several years. This is a different context to that of cases of suspected NTM lung infection for which the history of NTM infection is not known.

The issue of lung transplantation in MABSC-positive CF patients has been addressed in numerous case reports and studies [7,37]. The isolation of MABSC pre-transplant is a risk factor for the development of post-transplant NTM disease [7]. Despite the risk of post-transplant complications, which may in some cases be severe, lung transplantation appears to be feasible in CF patients with MABSC infection. Our findings, albeit for a small number of cases, support this view, as there were no cases of post-transplant MABSC lung disease in our series. Previous studies did not differentiate between *M. massiliense* and *M. abscessus*. However, we found that *M. massiliense* cases became negative after transplantation. Thus *M. massiliense* infection should not be considered as a contraindication for transplantation, and should be treated before transplantation with the aim of total eradication.

Our study demonstrates that for prognostic and therapeutic reasons, it is essential in routine practice to distinguish between *M. massiliense* and *M. abscessus* in CF patients. Various appropriate techniques are now available, mostly based on testing one or more genes, for example *rpoB*, *hsp65* and *sodA* [22,23]. However, the analysis of a single gene can lead to errors of identification (for ~10% of strains) due to genetic transfer between the two species. We recommend testing at least two loci in the genome, and using multilocus sequencing to resolve cases of discordant results [38]. In addition to species identification, it is recommended that antibiotic sensitivity profile be tested by broth microdilution techniques [21]. High-level resistance to clarithromycin, due to *rrl* mutations, is easily detected, but inducible clarithromycin resistance associated with the *erm*(41) requires an extended incubation [13,14].

In conclusion, this study found clinically significant differences between *M. abscessus* and *M. massiliense* lung diseases in CF patients. Our data point out the importance of a good nutritional status in CF patients. In our experience, malnutrition seems to be a key factor for *M. massiliense* lung disease in CF. We are aware of the limits of this retrospective study conducted in a limited number of patients. Thus, our results need to be confirmed in further studies.

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Conflict of interest

All authors declare that they have no conflict of interest.

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References

[1] Leao SC, Tortoli E, Euzeby JP, Garcia MJ. Proposal that Mycobacterium massiliense and Mycobacterium bolletii be united and reclassified as Mycobacterium abscessus subsp. bolletii comb. nov., designation of Mycobacterium abscessus subsp. abscessus subsp. nov. and emended description of Mycobacterium abscessus. Int J Syst Evol Microbiol 2011;61:2311–3.

[2] Adekambi T, Reynaud-Gaubert M, Greub G, Gevaudan MJ, La Scola B, Raoult D, et al. Amoebal coculture of "Mycobacterium massiliense" sp. nov. from the sputum of a patient with hemoptoic pneumonia. J Clin Microbiol 2004;42:5493–501.

[3] Jonsson BE, Gilljam M, Lindblad A, Ridell M, Wold AE, Welinder-Olsson C. Molecular Epidemiology of Mycobacterium abscessus, with Focus on Cystic Fibrosis. J Clin Microbiol 2007;45:1497–504.

[4] Esther Jr CR, Henry MM, Molina PL, Leigh MW. Nontuberculous mycobacterial infection in young children with cystic fibrosis. Pediatr Pulmonol 2005;40:39–44.

[5] Olivier KN, Weber DJ, Wallace Jr RJ, Faiz AR, Lee JH, Zhang Y, et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med 2003;167:828–34.

[6] Roux AL, Catherinot E, Rippoll F, Soismier N, Macheras E, Ravilly S, et al. Multicenter French prevalence study of non tuberculous mycobacteria in cystic fibrosis. J Clin Microbiol 2009;47:4124–8.

[7] Chalermskulrat W, Sood N, Neuringer IP, Hecker TM, Chang L, Rivera MP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax 2006;61:507–13.

[8] Pierre-Audigier C, Ferroni A, Sermet-Gaudelus I, Le Bourgeois M, Offredo C, Vu-Thien H, et al. Age-related prevalence and distribution of nontuberculous mycobacterial species among patients with cystic fibrosis. J Clin Microbiol 2005;43:3467–70.

[9] Brown-Elliott BA, Wallace Jr RJ. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. Clin Microbiol Rev 2002;15:716–46.

[10] Sanguinetti M, Ardito F, Fiscarelli E, La Sorda M, D'Argenio P, Ricciotti G, et al. Fatal pulmonary infection due to multidrug-resistant Mycobacterium abscessus in a patient with cystic fibrosis. J Clin Microbiol 2001;39:816–9.

[11] Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. Curr Opin Infect Dis 2012;25:218–27.

[12] Nessar R, Cambau E, Reyrat JM, Murray A, Gicquel B. Mycobacterium abscessus: a new antibiotic nightmare. J Antimicrob Chemother 2012;67:810–8.

[13] Bastian S, Veziris N, Roux AL, Brossier F, Gaillard JL, Jarlier V, et al. Assessment of clarithromycin susceptibility in strains belonging to the Mycobacterium abscessus group by erm(41) and rrl sequencing. Antimicrob Agents Chemother 2011;55:775–81.

[14] Nash KA, Brown-Elliott BA, Wallace Jr RJ. A novel gene, erm(41), confers inducible macrolide resistance to clinical isolates of

Mycobacterium abscessus but is absent from Mycobacterium chelonae. Antimicrob Agents Chemother 2009;53:1367–76.
[15] Aitken ML, Limaye A, Pottinger P, Whimbey E, Goss CH, Tonelli MR, et al. Respiratory outbreak of Mycobacterium abscessus subspecies massiliense in a lung transplant and cystic fibrosis center. Am J Respir Crit Care Med 2012;185:231–2.
[16] Zelazny AM, Root JM, Shea YR, Colombo RE, Shamputa IC, Stock F, et al. Cohort study of molecular identification and typing of Mycobacterium abscessus, Mycobacterium massiliense, and Mycobacterium bolletii. J Clin Microbiol 2009;47:1985–95.
[17] van Ingen J, de Zwaan R, Dekhuijzen RP, Boeree MJ, van Soolingen D. Clinical relevance of Mycobacterium chelonae-abscessus group isolation in 95 patients. J Infect 2009;59:324–31.
[18] Harada T, Akiyama Y, Kurashima A, Nagai H, Tsuyuguchi K, Fujii T, et al. Clinical and microbiological differences between Mycobacterium abscessus and Mycobacterium massiliense lung diseases. J Clin Microbiol 2012;50:3556–61.
[19] Koh WJ, Jeon K, Lee NY, Kim BJ, Kook YH, Lee SH, et al. Clinical significance of differentiation of Mycobacterium massiliense from Mycobacterium abscessus. Am J Respir Crit Care Med 2011;183:405–10.
[20] Chopra S, Matsuyama K, Hutson C, Madrid P. Identification of antimicrobial activity among FDA-approved drugs for combating Mycobacterium abscessus and Mycobacterium chelonae. J Antimicrob Chemother 2011;66:1533–6.
[21] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.
[22] Adekambi T, Colson P, Drancourt M. rpoB-based identification of nonpigmented and late-pigmenting rapidly growing mycobacteria. J Clin Microbiol 2003;41:5699–708.
[23] Ringuet H, Akoua-Koffi C, Honore S, Varnerot A, Vincent V, Berche P, et al. hsp65 sequencing for identification of rapidly growing mycobacteria. J Clin Microbiol 1999;37:852–7.
[24] Macheras E, Roux AL, Bastian S, Leão SC, Palaci M, Sivadon-Tardy V, et al. Multilocus sequence analysis and rpoB sequencing of Mycobacterium abscessus (sensu lato) strains. J Clin Microbiol 2011;49:491–9.
[25] Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. Am J Respir Crit Care Med 2013;187:197–205.
[26] Chan ED, Iseman MD. Slender, older women appear to be more susceptible to nontuberculous mycobacterial lung disease. Gend Med 2010;7:5–18.
[27] Tasaka S, Hasegawa N, Nishimura T, Yamasawa W, Kamata H, Shinoda H, et al. Elevated serum adiponectin level in patients with Mycobacterium avium-intracellulare complex pulmonary disease. Respiration 2010;79:383–7.
[28] Brown GR. Anorexia nervosa complicated by Mycobacterium xenopi pulmonary infection. J Nerv Ment Dis 1987;175:629–32.
[29] Cosson MA, Bertrand JB, Martin C, Veziris N, Picard C, Goulvestre C, et al. Temporal interferon-gamma release response to Mycobacterium kansasii infection in an anorexia nervosa patient. J Med Microbiol 2012;61:1617–20.
[30] Nova E, Samartin Gomez S, Morandé G, Marcos A. The adaptive response of the immune system to the particular malnutrition of eating disorders. Eur J Clin Nutr 2002;56(Suppl. 3):S34–7.
[31] Shin SJ, Choi GE, Cho SN, Woo SY, Jeong BH, Jeon K, et al. Mycobacterial genotypes are associated with clinical manifestation and progression of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense. Clin Infect Dis 2013;57:32–9.
[32] Lai HC, Kosorok MR, Sondel SA, Chen ST, FitzSimmons SC, Green CG, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. J Pediatr 1998;132:478–85.
[33] Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax 2002;57:596–601.
[34] Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. Eur Respir J 2007;29:522–6.
[35] U.S. Cystic Fibrosis Foundation. The Cystic Fibrosis Patient Registry: Annual data report 2011. Available from: www.cff.org.
[36] Kim HY, Kim BJ, Kook Y, Yun YJ, Shin JH, Kim BJ, et al. Mycobacterium massiliense is differentiated from Mycobacterium abscessus and Mycobacterium bolletii by erythromycin ribosome methyltransferase gene (erm) and clarithromycin susceptibility patterns. Microbiol Immunol 2010;54:347–53.
[37] Gilljam M, Schersten H, Silverborn M, Jönsson B, Ericsson Hollsing A. Lung transplantation in patients with cystic fibrosis and Mycobacterium abscessus infection. J Cyst Fibros 2010;9:272–6.
[38] Macheras E, Roux AL, Ripoll F, Sivadon-Tardy V, Gutierrez C, Gaillard JL, et al. Inaccuracy of single-target sequencing for discriminating species of the Mycobacterium abscessus group. J Clin Microbiol 2009;47:2596–600.