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Respiratory infections associated with nontuberculous mycobacteria in non-HIV patients

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ABSTRACT: The incidence of nontuberculous mycobacteria (NTM) pulmonary diseases in HIV-negative patients was studied prospectively from January 1, 2001 to December 31, 2003 by 32 sentinel sites distributed throughout France.

In total, 262 patients who yielded NTM isolates from respiratory clinical specimens, met the bacteriological, radiological and clinical criteria established by the American Thoracic Society for NTM respiratory disease. Among the 262 NTM isolates, 234 were slow-growing mycobacteria (125 *Mycobacterium avium-intracellulare* complex (MAC), 66 *M. xenopi*, 34 *M. kansasii*) and 28 were rapidly growing mycobacteria (25 *M. abscessus* complex). In the Paris area, *M. xenopi* was the most frequently isolated species, followed by MAC.

Most patients (>50%), except those with *M. kansasii*, had underlying predisposing factors such as pre-existing pulmonary disease or immune deficiency. Asthenia, weight loss, chronic cough and dyspnoea were the most common clinical symptoms. The classical radiological appearance of NTM infections was indistinguishable from that observed in patients with pulmonary tuberculosis.

In summary, the incidence of nontuberculous mycobacteria pulmonary infections in HIV-negative patients was estimated at 0.74, 0.73 and 0.72 cases per 100,000 inhabitants in 2001, 2002 and 2003, respectively.

KEYWORDS: HIV-negative patients, nontuberculous mycobacteria, pulmonary diseases

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As nontuberculous mycobacteria (NTM) are common in the environment, infection and colonisation by NTM are not easily distinguishable [1]. For this reason, the minimal criteria required for the diagnosis of pulmonary infection have been established [2, 3]. NTM cause clinically significant infections in both immunosuppressed and immunocompetent patients [4, 5]. However, it has recently been shown that NTM infections are increasing in patients with chronic respiratory diseases [6]. Moreover, increased rates of NTM infections have been reported in areas in which the bacille Calmette–Guerin vaccination has been stopped due to the prevalence of tuberculosis [6, 7]. In contrast to tuberculosis, which is a disease of obligatory declaration in France and for which the annual incidence is therefore well known, the incidence of NTM infections in France is unknown due to a lack of systematic reporting. To determine the occurrence of NTM infections in France and to compare it with that of tuberculosis, data collected by a voluntary-based laboratory network, the French Mycobacteria Study Group (FMSG), was used. The present authors have previously published a study on *Mycobacterium avium* and *M. intracellulare* [8], and the aim of the current study was to extend this work to include all pulmonary infections caused by opportunistic mycobacteria. For this purpose, demographic, epidemiological, clinical and radiological data obtained over a 3-yr period, in 262 HIV-negative patients with NTM pulmonary infections, were prospectively analysed. Further, the incidence of NTM disease was determined taking into consideration the incidence of tuberculosis in France.

MATERIALS AND METHODS

The FMSG constitutes 32 sentinel sites distributed all over France; 21 in regional cities and 11 in the Paris area. This group was formed to provide a systematic surveillance of *M. tuberculosis* drug resistance and covers ~25 % of tuberculosis cases in France [8, 9]. Between January 1, 2001 and

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December 31, 2003, the number of tuberculosis and NTM infections was recorded annually by the FMSG network covering the same population, therefore limiting the risk of differential reporting. For mycobacterial investigations, smears of respiratory secretions were stained and examined for the presence of acid-fast bacilli. Depending on the laboratories, samples of specimens were inoculated onto Löwenstein-Jensen medium (BioRad, Marnes La coquette, or bioMérieux, Marcy l'Etoile, France) and/or in Middlebrook broth medium (Becton Dickinson, NJ, USA or bioMérieux), and incubated, according to underlying conditions, at 30°C and 37°C or 40°C for >2 months. The identification of isolates was performed using approved methods, including biochemical tests and/or molecular tests such as DNA probes or genomic typing [10].

The laboratory records of the 32 sentinel sites were prospectively reviewed to identify patients in whom NTM were isolated from pulmonary specimens obtained during the study period. The bacteriological criteria defined by the American Thoracic Society (ATS) were used to select the patient records.

The data collected were: age, sex and underlying disorders such as pre-existing pulmonary disease, cystic fibrosis (CF), previous infection with *M. tuberculosis* or NTM, leukaemia and/or carcinoma, and immunosuppressive therapy and/or transplantation. Pulmonary (presence of cough, dyspnoea, haemoptysis) and systemic (presence of fever, night sweats, weight loss and asthenia) clinical manifestations, as well as radiographic data (presence of nodules, infiltrates, cavitations) were collected at the time of diagnosis. Patients with active tuberculosis and/or HIV-positive patients were excluded from this study.

Pulmonary disease was established in patients when ATS-defined bacteriological criteria were associated with radiographic and clinical criteria suggesting mycobacterial infections and/or when a treatment was decided by a clinician.

Moreover, each laboratory provided the number of culture-positive tuberculosis cases observed during the study period. The data were compared using the Chi squared or t-test. A p-value of <0.05 was considered significant.

RESULTS

Over the study period, 262 HIV-negative patients with lung disease due to NTM were identified (table 1). Among these lung diseases, 234 (89%) were due to slow-growing mycobacteria (SGM): the most common species was *M. avium-intracellulare* complex (MAC; 125 isolates) followed by *M. xenopi* (66 isolates) and *M. kansasii* (34 isolates), while *M. malmoense*, *M. simiae*, *M. szulgai*, *M. scrofulaceum* and *M. triplex* were rarely isolated (nine isolates). Among the 28 infections (10.6%) caused by rapidly growing mycobacteria (RGM), 25 were due to *M. abscessus* complex, 12 of which were isolated in patients with CF. The other RGM species (*M. fortuitum*, *M. smegmatis*, *M. peregrinum*) were only isolated once. The low number of NTM cases reported by each sentinel site does not allow analysis of distribution according to the regional cities; however, the Paris area was examined individually from all the other French regions. As reported in table 2, the rate of patients with *M. xenopi* diseases was significantly higher ($p<0.001$) in the Paris area (40.5%) than in regional cities (18%), while the proportion of MAC was lower in the Paris area ($p<0.01$). For *M. kansasii* and *M. abscessus* infections, similar rates were observed in the Paris area and in all regional cities combined (table 2).

Assuming that the incidence of tuberculosis cases in France for 2001 is 10.8 per 100,000 inhabitants [11, 12, 13], the annual population studied by the FMSG was evaluated to be 11.3 million ($1,225/10.8 \times 100,000 = 11.3 \times 10^6$). Thus, overall national rates of NTM pulmonary disease were estimated at 0.74, 0.73 and 0.72 cases per 100,000 inhabitants in 2001, 2002 and 2003, respectively (table 3).

The main characteristics of patients with mycobacterial infections are listed in table 4. Male patients were more frequently infected by *M. xenopi* or *M. kansasii* (77.3 and 79.4%, respectively; $p=0.001$) whereas female patients were more frequently infected with MAC or RGM (62.4 and 68%, respectively; $p=0.001$). The mean age was >60 yrs, except for patients infected by *M. kansasii* (54 yrs). Predisposing factors for developing lung disease were frequently found among patients with NTM infections, with pre-existing pulmonary diseases being the most frequent. However, such factors were significantly less frequent in patients infected with *M. kansasii* than in those infected with other species ($p<0.0001$).

Interstital infiltrates and/or nodules were the predominant radiological patterns, with no significant difference between patients infected by different species. A higher rate of cavitations (38%) was observed in patients infected by *M. kansasii.* Constitutional symptoms, including asthenia and weight loss, were common; most patients presented cough and dyspnoea. Haemoptysis occurred in <26% of patients.

DISCUSSION

In the present study, the mean number of respiratory infections due to NTM in HIV-negative patients was $87 \cdot yr^{-1}$ and was stable over the 3-yr study period. MAC was preponderantly isolated, followed by *M. xenopi*, *M. kansasii* and *M. abscessus*. During the study period, no significant changes in the incidence rates of NTM pulmonary infections in HIV-negative patients (0.74, 0.73 and 0.72 cases per 100,000 inhabitants in 2001, 2002 and 2003, respectively) were observed. These rates are similar to those observed in Europe but lower than those reported in the USA [6].

TABLE 1 Number of nontuberculous mycobacteria infections by species in HIV-negative patients

	Slow growing				Rapidly growing		Total
	MAC	*M. xenopi*	*M. kansasii*	Others	CF	Non-CF	
2001	42	25	6	2	5	4	84
2002	44	17	16	4	4	6	91
2003	39	24	12	3	7	2	87
Total	125 (47.7)	66 (25.2)	34 (12.9)	9 (3.4)	16 (6.1)	12 (4.6)	262

Data are presented as n or n (%), unless otherwise stated. MAC; *Mycobacterium avium-intracellulare* complex; *M. xenopi*: *Mycobacterium xenopi*; *M. kansasii*: *Mycobacterium kansasii*; CF: cystic fibrosis.

TABLE 2 Number of patients with nontuberculous mycobacteria (NTM) infections (total number and distribution according to species) or with tuberculosis according to geographical area

	Total n	Paris area	Regional cities	p-value
NTM infections n	263	84	179	
MAC	125	32.1	54.7	<0.01
M. xenopi	66	40.5	18.4	<0.001
M. kansasii	34	16.7	11.2	>0.05
M. abscessus	24	7.1	10.1	>0.05
Other NTM	13	3.6	5.6	>0.05
Tuberculosis n	3787	1250	2537	

Data are presented as %, unless otherwise stated. MAC: *M. avium-intracellulare* complex; *M. xenopi*: *Mycobacterium xenopi*; *M. kansasii*: *Mycobacterium kansasii*; *M. abscessus*: *Mycobacterium abscessus*.

Among patients infected by SGM, MAC pulmonary disease was found to be more frequent in elderly females (62%). This is in accordance with the observations of HAN *et al.* [14], who recently reported a higher isolation rate of MAC in females, in whom an age trend for the isolation of *M. intracellulare* was observed. The predominance of females among these patients may be related to specific immune deficiencies and/or the habit of voluntary suppression of cough, particularly in older females, such as those suffering from Lady Windermere syndrome [14, 15]. FIELD *et al.* [16] noted that until 1980 patients with MAC pulmonary infections were predominantly male, and this disease has now become more prevalent in elderly females over the last decade. In the present study, in line with findings of previous studies [17, 18], *M. kansasii* and *M. xenopi* were mostly isolated in males and the mean age of patients infected by *M. kansasii* (54 yrs) was lower than that of patients infected by *M. xenopi* (60 yrs). Excluding CF patients, the mean age of patients infected by RGM was 62 yrs and the sex ratio was 2.5 female/male. This is in concordance with previous reports that showed a female predominance for RGM diseases [19]. It has been shown that the prevalence of NTM infections is higher in CF adults than in CF children [20, 21]. In the current study, no NTM infection was observed in CF patients aged >30 yrs.

NTM infections usually occurred in patients with predisposing host factors such as impairment of local pulmonary defences or generalised immune defects [6, 8, 22, 23]. However, HENRY *et al.* [4] reported that among patients who developed significant NTM pulmonary infections, 37% had no underlying lung disease. In the present study, 44% of *M. kansasii* infections occurred in patients without risk factors. Similar results were reported by BLOCH *et al.* [24]. This may be explained by the fact that some subtypes of *M. kansasii*, such as subtype 1, possess virulence factors that enable them to cause disease in immunocompetent individuals [25, 17]. In the current study, this remains to be characterised as no genotyping was performed. A higher rate of predisposing factors (~85%) was observed among patients infected by species other than *M. kansasii*. Among these patients with predisposing conditions, ~50% had pre-existing chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), and 25% had been previously diagnosed with tuberculosis. Immunosuppressive therapies, haematopoietic malignancies or extra-pulmonary neoplasms, which are also major risk factors for the development of NTM disease, were found in ~20% of the current patients. These findings are similar to those previously published by AKSAMIT [22] who related the importance of pre-existing lung disease (COPD, bronchectasis, prior tuberculosis *etc.*) to the development of a MAC infection in non-immunocompromised patients. Similar observations were made for *M. xenopi*-infected patients by JENKINS *et al.* [18], who reported that a pre-existing lung disease or an impaired immune response was observed in two-thirds and one-quarter of these patients, respectively. Several studies found that CF may have an impact on the development of NTM infections [20]. In the present study, of the 14 CF patients, 12 had an infection caused by *M. abscessus* and two had an infection due to MAC.

TABLE 3 Number of tuberculosis and nontuberculous mycobacteria (NTM) lung infections observed by the French Mycobacteria Group

	Tuberculosis	NTM infections	Tuberculosis incidence[#]	NTM incidence[#]
2001	1225	84	10.8	0.74
2002	1319	91	10.5	0.73
2003	1244	87	10.2	0.72

[#]: per 100,000 inhabitants.

Available clinical investigations indicate that systemic and pulmonary symptoms are associated with NTM infections, although it is often difficult to distinguish them from those related to the underlying lung diseases [5]. In the current study, the most frequent systemic symptoms were asthenia or weight loss. The most frequent pulmonary symptoms were chronic cough, followed by dyspnoea and haemoptysis. Haemoptysis was present in 25% of SGM-infected patients and was rarely observed in patients with RGM infections.

Various radiographic features have been associated with NTM lung infections. However, interpretation of chest radiographs is often difficult, as the radiographic appearance of NTM disease is indistinguishable from that seen with pulmonary tuberculosis and because chronic underlying pulmonary disease may interfere. In the present study, the most common abnormality was the presence of infiltrates that were observed in one-third and one-half of patients infected respectively by SGM and RGM. Cavities were also found to be more frequently observed in *M. kansasii* infections (38.2%) than in other infections. JENKINS *et al.* [18] reported cavities as being the most frequent radiological pattern in patients infected by *M. xenopi*. This was not observed in the present study. This discrepancy may be the result of differences in the populations studied and/or in the study designs. It was reported that *M. abscessus* lung diseases radiographically resemble MAC lung diseases and that for this species the nodular infiltrates were the predominant abnormalities [19, 22].

TABLE 4 Characteristics of patients with nontuberculous mycobacteria pulmonary infections

	MAC	*M. xenopi*	*M. kansasii*	RGM/non-CF	p-value
Subjects n	125	66	34	16	
Age yrs	70 (1–95)	60 (19–84)	54 (22–93)	62 (32–81)	<0.0001
Sex male/female	53/80	52/15	27/7	5/11	0.001
Underlying conditions					
Pre-existing pulmonary disease	89 (71.2)	28 (42.4)	7 (20.6)	8 (50)	<0.0001
Previous *M. tuberculosis*	35 (28)	17 (25.8)	9 (26.5)	3 (18.7)	0.88
Immunosupression/transplantation	34 (27.7)	17 (25.8)	5 (14.7)	1 (6.2)	0.15
None/anorexia	14 (11.2)	18 (27.3)	15 (44.1)	4 (25)	0.0002
Radiographic abnormalities					
Infiltrates	46 (36.8)	21 (31.8)	12 (35.3)	8 (50)	0.59
Nodules	28 (22.4)	21 (31.8)	10 (29.4)	3 (18.7)	0.44
Cavitation	13 (10.4)	11 (16.7)	13 (38.2)	1 (6.2)	0.0008
Nonspecific	44 (35.2)	19 (28.8)	4 (11.7)	7 (43.7)	0.04
General clinical symptoms					
Fever, night sweats	34 (27.2)	26 (39.4)	4 (14.7)	7 (43.7)	0.037
Weight loss	60 (49)	28 (42.4)	15 (44.1)	13 (81.3)	0.043
Asthenia	73 (58.4)	31 (47)	17 (50)	13 (81.8)	0.069
No symptoms	35 (28)	22 (33.3)	10 (29.4)	0 (0)	0.065
Pulmonary symptoms					
Cough	97 (77.6)	39 (59.1)	22 (64.7)	12 (75)	0.048
Haemoptysis	18 (14.4)	17 (25.8)	8 (23.5)	2 (12.5)	0.20
Dyspnoea	60 (48)	37 (56.7)	9 (26.5)	6 (37.5)	0.036
No symptoms	12 (9.6)	12 (18.2)	7 (20.5)	0 (0)	0.071

Data are presented as n, mean (range) or n (%), unless otherwise stated. MAC: *Mycobacterium avium-intracellulare* complex; *M. xenopi*: *Mycobacterium xenopi*; *M. kansasii*: *Mycobacterium kansasii*; RGM: rapidly growing mycobacteria; CF: cystic fibrosis.

Recommendations have been established for the treatment of lung infection caused by NTM [2, 3]. Treatment with rifampicin plus ethambutol, with or without isoniazid, is currently recommended for lung disease caused by *M. kansasii* [3, 24, 26, 27]. During the present study, patients infected with *M. kansasii* were predominantly treated with rifampicin, ethambutol and isoniazid for 9 months, and only one relapse occurred. Patients with pulmonary MAC or *M. xenopi* disease are usually treated with multidrug regimens including rifampicin or rifabutin, ethambutol, isoniazid and clarithromycin [4, 28, 29]. In the current study, high mycobacterial clearance rates were observed when patients were treated with this combination plus another antibiotic, such as a fluoroquinolone. However, relapse rates were high for several months or years, even after conversion of sputum culture from positive to negative. Among patients with *M. xenopi* infections, 22.8% had been diagnosed with the same infection a few years earlier. JENKINS *et al.* [18] reported a relapse rate of 12% for patients infected by *M. xenopi,* treated in a randomised trial with rifampicin plus ethambutol, rifampicin, or ethambutol plus isoniazid. Thus, for patients with localised pulmonary lesions persisting after medical treatment, a surgical treatment is recommended [30]. Antimicrobial treatment of lung disease caused by *M. abscessus* is usually unsuccessful; therefore, the ATS recommends the use of antimicrobial drugs, such as clarithromycin plus cefoxitin and/or amikacin. However, acquired resistance to clarithromycin has been reported in *M. abscessus* and may cause eradication failure [19, 31].

In summary, the clinical presentations and radiographic manifestations of pulmonary nontuberculous mycobacteria infections are quite variable and are further modified by underlying comorbidities. To establish the diagnosis of infection it is necessary to combine data obtained from the mycobacterial laboratory with the clinician's assessments. Further, the adherence to published guidelines should improve the diagnosis of these diseases and consequently their survey all over the world. The present study indicates that the French Mycobacteria Study Group could provide an estimation of the frequency of nontuberculous mycobacteria disease in France, particularly now, as the bacille Calmette–Guerin vaccine is less frequently used due to the low risk of tuberculosis.

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