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ORIGINAL ARTICLE

Radiologic types of *Mycobacterium xenopi* pulmonary disease: different patients with similar short-term outcomes

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Abstract

Mycobacterium xenopi pulmonary disease (Mxe-PD) is common among nontuberculous mycobacterial infections in Europe and Canada. Associations between radiological pattern and clinical features and outcomes are inadequately studied in Mxe-PD. We sought to investigate clinical characteristics and outcomes according to the dominant radiological pattern among patients with Mxe-PD. We retrospectively studied patients with Mxe-PD seen in our clinic, categorizing their predominant CT pattern as nodular bronchiectasis, fibrocavitary, or unclassifiable, and compared clinical characteristics, treatment, and outcomes between radiologic groups. Of 94 patients with Mxe-PD, CT patterns comprised nodular bronchiectasis (40/94, 42.6%), fibrocavitary (37/94, 39.4%), and unclassifiable (17/94, 18.1%). Compared with fibrocavitation, patients with nodular bronchiectasis were female dominant, less often had COPD, less often had AFB smear-positive sputum, and more frequently had co-isolation of *Pseudomonas*. Patients with nodular bronchiectasis were less often treated (65% versus 91.9%) and when treated, they received fewer anti-mycobacterial drugs (on average 3 versus 4). Outcomes did not differ significantly by radiological pattern. Nodular bronchiectasis was common among Mxe-PD patients in our clinic. Compared with fibrocavitary disease, patients with nodular bronchiectasis had features suggestive of milder disease and were less often treated. Among treated patients, outcomes did not differ by radiologic pattern.

Keywords *Mycobacterium xenopi* · Nontuberculous mycobacteria · Chest CT · Nodular bronchiectasis

Introduction

Pulmonary disease (PD) due to nontuberculous mycobacteria (NTM) is increasing in incidence multi-nationally. Worldwide, *Mycobacterium avium* complex (MAC) is the most common cause of NTM pulmonary disease (NTM-PD) [1]. In Ontario, Canada, MAC is the prevailing cause of NTM-PD, followed by *Mycobacterium xenopi* (Mxe) [2]. Although uncommon in most regions, Mxe is reported to be among the leading causes of NTM-PD in Europe and Canada [3–5]. Since the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines were issued [6], numerous studies of NTM-PD were conducted based on the dominant radiological patterns of nodular bronchiectasis (NB) and fibrocavitary (FC) [7–9]. However, some patients cannot be so classified, because other radiological features (random nodules or consolidations) may predominate, leading to the description of radiological patterns in some patients as "unclassifiable" (UC) [9, 10]. The dominant radiological pattern among NTM-PD patients, especially in MAC, has been shown to be important in predicting outcomes [7, 8, 11]. The

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prognostic role of the dominant radiological pattern in Mxe-PD is less well studied. We sought to retrospectively study clinical characteristics and outcomes according to the dominant radiological pattern among patients with Mxe-PD.

Material and methods

All adults with Mxe-PD seen in our clinic between July 2003 and December 2017 were considered for inclusion in this retrospective cohort study. The study protocol was approved by the University Health Network Research Ethics Board (Research Ethics Board number 18-5104). Given the retrospective design, the requirement of informed consent was waived. Mxe-PD was diagnosed based on the ATS/IDSA criteria [6]. For patients diagnosed with sputum, ≥ 2 positive cultures within 2 years were required. We recorded results of respiratory cultures growing other *Mycobacterium* species, *Pseudomonas* species, and *Aspergillus* species within 2 years after initial isolation of Mxe. We included exclusively patients in whom Mxe was the most common NTM species isolated within 2 years from the initial Mxe isolation. Included patients with another NTM species isolated > 1 (but fewer than the number of Mxe isolations) were designated as having "concurrent" infection. We excluded patients who had other NTM species isolated equally or more frequently than Mxe ("dominant other" infection). Secondary analyses, limited to patients with "exclusive Mxe-PD," excluded patients with concurrent NTM.

The radiologic pattern was categorized as NB, FC, or UC based on thoracic computed tomography (CT) scan: NB required predominant feature of bronchiectasis and centrilobular nodules, FC required cavitation as the predominant finding, and UC was defined when radiological features did not meet NB or FC. In addition, the presence or absence of cavitation, bronchiectasis, centrilobular nodules, random nodules (neither centrilobular nor peribronchovascular nor pleural/perifissural), consolidation/grand-glass opacity (GGO), emphysema, fibrosis, mass, pleural thickening and effusion, pulmonary hypertension (pulmonary trunk enlargement at pulmonary artery bifurcation), mediastinal lymphadenopathy, and hiatus hernia was sought. Determination of the dominant CT pattern was achieved by independent review of the images by two of the authors, with disagreements assessed by the third author.

Radiological improvement was defined by our global impression based on a combination of the radiologists' reports and our review of images. Culture conversion was defined as three consecutive negative sputum cultures each 4 weeks or more apart [12], or the inability to produce sputum and an absence of otherwise available positive cultures. Microbiological recurrence was defined by the presence of at least two specimens that yielded Mxe after prior culture conversion. Microbiologically refractory (treatment failure [12]) was defined by persistently positive cultures despite ≥ 12 months of antimicrobial therapy. In defining overall outcomes (treatment success and clinical success), we included radiology in addition to microbiology and symptoms and thus diverged somewhat from recently proposed outcomes definitions. "Treatment success" was defined as culture conversion with symptomatic and radiologic control, and "clinical success" was defined as symptomatic and radiologic control regardless of adequate specimens to determine culture conversion. In a sensitivity analysis, we also studied the recently proposed definition of "cure" [12], a combined outcome of sustained microbiological conversion while on treatment and symptomatic improvement. Clinical and radiological assessment at the time of culture conversion (or 12 months posttreatment initiation in patients who could not produce sputum) was used to classify patients as improved, stable (no significant change), or deteriorated.

We reported the proportion of each radiologic pattern (NB, FC, and UC) and other categoric variables as percentages, and continuous variables as medians (quartiles). Differences in clinical characteristics between groups of patients with each dominant radiologic pattern were assessed with chi-square or Fisher's exact tests for categoric variables and one-way ANOVA, Mann-Whitney test, or Kruskal-Wallis test as appropriate for continuous variables. Statistical analyses and graph generation were performed with GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA).

Results

Patient characteristics

Ninety-four patients with Mxe-PD were included in the main analysis (Fig. 1). The dominant CT patterns were NB ($n = 40$, 42.6%), FC ($n = 37$, 39.4%), and UC ($n = 17$, 18.1%) (Fig. 2, Table 1). Females comprised a large majority of NB patients (31/40 [77.5%]), a small majority of FC patients (19/39 [51.4%]), and a minority of UC patients (5/17 [29.4%]) ($p = 0.002$ for sex distribution). Smoking history was less common in NB patients (20/40 [50.0%]) than that in FC and UC patients (30/40 [81.1%] and 14/17 [82.4%]) ($p = 0.007$). Nearly one fourth of NB and UC patients had previously experienced MAC-PD, but this was uncommon among patients with FC Mxe-PD. COPD was more prevalent with FC (17/37 [45.9%]) and UC (7/17 [41.2%]) than with NB (4/40 [10.0%]) ($p = 0.001$). Twenty-nine percent of UC patients were found to have interstitial lung disease (ILD), versus very few among patients with other radiologic patterns ($p = 0.001$). In secondary analyses, restricted to patients with exclusive Mxe-PD, the proportions of dominant radiological types were similar (NB ($n = 29$, 38.2%), FC ($n = 32$, 42.1%), UC ($n = 15$, 19.7%),

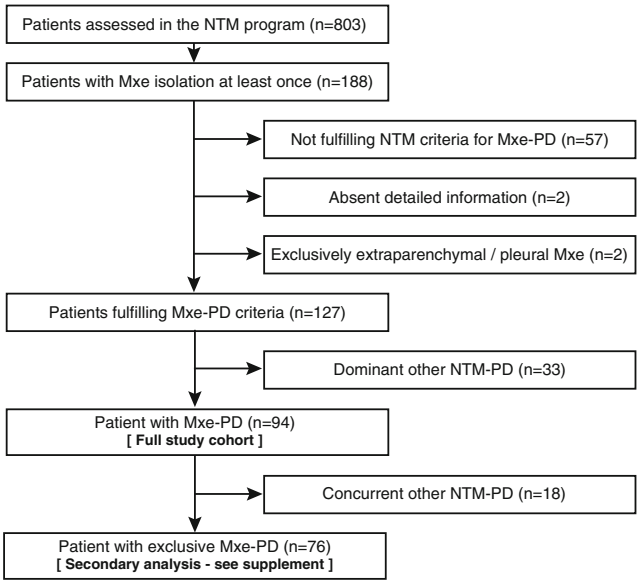

Fig. 1 Study population. Dominant other NTM-PD was defined by the isolation of another NTM species at least as frequently as Mxe during the 2 years following the initial isolation of Mxe (e.g., Mxe × 6 and MAC × 8). Concurrent other NTM-PD was defined by the repeated (> 1) isolation of other NTM species, but less frequently than the isolation of Mxe (e.g., Mxe × 6 and MAC × 4). NTM, nontuberculous mycobacteria; Mxe, *Mycobacterium xenopi*; PD, pulmonary disease

Supplemental Table 1), as were most patient characteristics, with the exception that the excess of GERD among patients with NB disease was statistically significant with "exclusive Mxe-PD."

Obstructive lung disease was common in all groups, but mean FEV1 (percent of predicted) varied, with best values among NB patients (79.0%), followed by FC (67.0%) and UC (48.0%) ($p = 0.002$, Table 1). Restriction was most common in UC patients (5/17 [29.4%]) compared to NB (2/40 [5.0%]) and FC (3/37 [8.1%]) patients ($p = 0.019$). Low diffusion capacity was significantly more common with FC (25/40 [62.5%]) and UC (12/21 [57.1%]) than with NB (12/47 [25.5%]) ($p = 0.004$). The distribution of pulmonary function test findings between radiological groups did not markedly differ in secondary analyses restricted to exclusive Mxe-PD patients (Supplemental Table 1).

Regardless of radiologic pattern, cough was the most common symptom (> 75%), followed by sputum production (> 50%) without significant differences among 3 groups (Table 2). Dyspnea was very common with UC (13/17 [76.5%]), less so with FC (22/37 [59.5%]), and in the minority with NB (15/40 [37.5%]) ($p < 0.016$). Weight loss was more common with FC (18/37 [48.6%]) than with NB (5/40 [12.5%]) and UC (3/17 [17.6%]) ($p = 0.001$). The distribution of symptoms between radiological groups did not markedly differ in the secondary analysis restricted to exclusive Mxe-PD patients (Supplemental Table 2).

Approximately three quarters of all patients were microbiologically diagnosed via sputum, whereas approximately one quarter were diagnosed bronchoscopically, without major differences between groups (Table 2). During the study period, AFB smear-positive sputum was most common with FC (23/

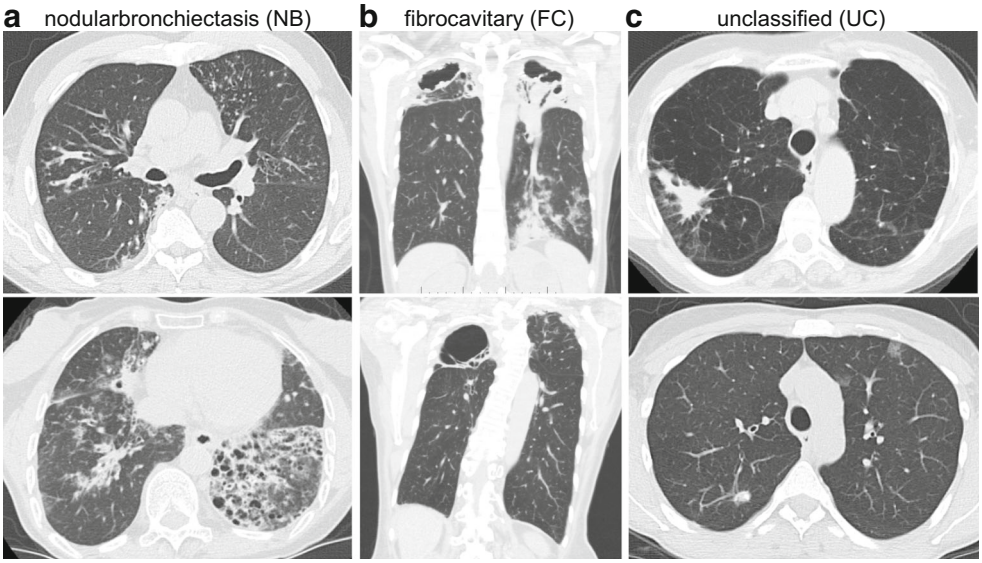

Fig. 2 Representative chest CT scan images in patients with Mxe-PD enrolled in the study. **a** (upper) Depicts NB with bronchiectasis and mucus plugging in the right upper lobe and multiple centrilobular nodules in the left upper lobe. **a** (lower) Depicts NB with peribronchial inflammatory changes in the right lower lobe and extensive cylindrical and varicose bronchiectasis involving segmental and sub-segmental airways and scattered airway secretions in the left lower lobe. **b** (upper) Depicts FC with bilateral apical cavitary lesions. The cavity in the left lung contained debris and had adjacent consolidation. Consolidation and opacification along bronchovascular bundles were seen in the left lower lobe. **b** (lower) Depicts FC illustrating the cavitary lesion and accompanying volume loss within the right upper lobe. **c** (upper) Was UC with focal consolidation in the upper lobe in the context of severe centrilobular emphysema. **c** (lower) Was UC showing randomly distributed nodules and ground-glass opacity.

Table 1 Characteristics of patients with Mxe-PD ($n = 94$)

	NB ($n = 40$)	FC ($n = 37$)	UC ($n = 17$)	p value	
Age, year-median (quartiles)	63 (55–73)	61 (50–77)	68 (59–76)	0.527	
Gender (female)	31 (77.5)	19 (51.4)	5 (29.4)	*0.002*	§
Underweight (BMI < 18.5)	5 (12.5)	7 (18.9)	2 (11.8)	0.675	
Smoking history				*0.007*	§
Current/previous smoker	20 (50.0)	30 (81.1)	14 (82.4)		
Non-smoker	17 (42.5)	5 (13.5)	3 (17.6)		
Underlying thoracic disease					
Asthma	10 (25.0)	5 (13.5)	2 (11.8)	0.321	
Bronchiectasis	13 (32.5)	1 (2.7)	0 (0.0)	*0.002*	§
COPD	4 (10.0)	17 (45.9)	7 (41.2)	*0.001*	§
History of lung malignancy	1 (2.5)	4 (10.8)	2 (11.8)	0.288	
History of MAC-PD	9 (22.5)	2 (5.4)	4 (23.5)	0.079	§
Treatment for MAC-PD	4 (10.0)	1 (2.7)	2 (11.8)	0.359	
Interstitial pneumonia	0 (0.0)	2 (5.4)	5 (29.4)	*0.001*	
Old healed tuberculosis	7 (17.5)	3 (8.1)	1 (5.9)	0.313	
Non-pulmonary comorbidities					
Active cancer	1 (2.5)	4 (10.8)	1 (5.9)	0.328	
Diabetes	4 (10.0)	3 (8.1)	1 (5.9)	0.873	
Gastroesophageal reflux disease	9 (22.5)	4 (10.8)	1 (5.9)	0.183	
Oral steroid use	5 (12.5)	1 (2.7)	3 (17.6)	0.158	
Rheumatoid arthritis	1 (2.5)	0 (0.0)	0 (0.0)	N/A	
Pulmonary function					
%Predicted FEV1-median (quartiles)	79.0 (66.0–93.0)	67.0 (41.5–83.5)	48.0 (34.5–74.5)	*0.002*	§
Obstruction	19 (47.5)	24 (64.9)	10 (58.8)	0.300	
Restriction	2 (5.0)	3 (8.1)	5 (29.4)	*0.019*	
Gas trapping	15 (37.5)	19 (51.4)	9 (52.9)	0.383	
Low diffusion capacity	11 (27.5)	24 (64.9)	9 (52.9)	*0.004*	§

Numbers in parentheses indicate the percentage of patients in each radiologic pattern. Bronchiectasis as an underlying thoracic disease indicates a pre-existing symptomatic and radiologically identified entity. Obstruction was defined by a ratio of FEV1 to FVC less than 70%, restriction by TLC less than 80% of predicted value, gas trapping by a ratio of RV to TLC greater than 120% of predicted value, and low diffusion capacity by a diffusing capacity of the lung for carbon monoxide less than 75% of predicted value. p values are presented for differences among all three groups, while additional statistical tests were performed comparing NB versus FC groups, with § indicating significance ($p < 0.05$) between these two groups; the significance ($p<0.05$) was shown as the italic

BMI, body mass index; *COPD*, chronic obstructive pulmonary disease; *FEV1*, forced expiratory volume in 1 s

37 [62.2%]), followed by UC (6/17 [35.3%]) and NB (2/40 [5.0%]) ($p < 0.001$). Although the median number of sputum cultures that yielded Mxe (within 2 years of the initial isolate) did not greatly differ between groups, the number of positive cultures was statistically greater in FC patients than that in NB patients. MAC was the only other NTM species repeatedly isolated among the studied patients within 2 years of the initial Mxe isolate, observed in 11/40 (27.5%) patients with NB, 5/37 (13.5%) patients with FC, and 2/17 (11.8%) patients with UC, without significant difference among groups. *Aspergillus* was identified in 13/94 (13.8%) overall, without statistical difference in isolation frequency among groups. *Pseudomonas* species were isolated predominantly in patients with NB (7/40 [17.5%]) and UC (2/17 [11.8%]), compared with FC (0 [0%]) ($p = 0.032$). In the secondary analysis restricted to patients with exclusive Mxe-PD, the main observed difference was that a smaller proportion of patients with NB had isolation of *Aspergillus* (Supplemental Table 2).

Radiologic features are presented in Table 2 and Supplemental Table 2. Despite the dominant CT pattern, some FC patients had bronchiectasis (18/37 [48.6%]) and centrilobular nodules (19/37 [51.4%]), as did some UC patients (2/17 [11.8%] and 7/17 [41.2%], respectively). Likewise, cavitation was seen in some patients with NB (3/40 [7.5%]) and UC (3/17 [17.6%]). Random nodules were most commonly seen with FC (16/37 [43.2%]), followed by

Table 2 Clinical, microbiological, and radiological assessment for diagnosis of Mxe-PD

	NB ($n = 40$)	FC ($n = 37$)	UC ($n = 17$)	p value	
Clinical assessment					
Chest discomfort	7 (17.5)	5 (13.5)	1 (5.9)	0.508	
Cough	35 (87.5)	31 (83.8)	13 (76.5)	0.581	
Dyspnea	15 (37.5)	22 (59.5)	13 (76.5)	*0.016*	
Fatigue	8 (20.0)	15 (40.5)	3 (17.6)	0.078	
Hemoptysis	7 (17.5)	7 (18.9)	3 (17.6)	0.986	
Night sweating	3 (7.5)	9 (24.3)	1 (5.9)	0.059	
Fever	4 (10.0)	9 (24.3)	3 (17.6)	0.247	
Sputum production	28 (70.0)	20 (54.1)	11 (64.7)	0.346	
Weight loss	5 (12.5)	18 (48.6)	3 (17.6)	*0.001*	§
Microbiological assessment					
Diagnostic specimen				0.135	
Sputum	29 (72.5)	22 (59.5)	13 (76.5)		
Bronchoalveolar lavage	11 (27.5)	11 (29.7)	4 (23.5)		
Tissue	0 (0.0)	4 (10.8)	0 (0.0)		
AFB positive smear in sputum	2 (5.0)	23 (62.2)	6 (35.3)	*< 0.001*	§
# positive culture - median (IQR) (quartiles)	3 (2–5)	5 (3–7)	3 (2–6)	0.089	§
Isolation of MAC (≥ 2 times)	11 (27.5)	5 (13.5)	2 (11.8)	0.206	
Isolation of *Aspergillus*	6 (15.0)	4 (10.8)	3 (17.6)	0.765	
Isolation of *Pseudomonas*	7 (17.5)	0 (0.0)	2 (11.8)	*0.032*	§
Radiological assessment					
Cavity	3 (7.5)	37 (100.0)	3 (17.6)	*< 0.001*	§
Radiological bronchiectasis	39 (97.5)	18 (48.6)	2 (11.8)	*< 0.001*	§
Centrilobular nodules/tree-in-bud	34 (85.0)	19 (51.4)	7 (41.2)	*0.001*	§
Random nodules	6 (15.0)	16 (43.2)	5 (29.4)	*0.024*	§
Consolidation/ground glass opacity	4 (10.0)	4 (10.8)	6 (35.3)	*0.033*	
Emphysema	5 (12.5)	22 (59.5)	9 (52.9)	*< 0.001*	§
Fibrosis	2 (5.0)	2 (5.4)	2 (11.8)	0.603	
Masses	0 (0.0)	2 (5.4)	1 (5.9)	0.316	
Pleural effusion	2 (5.0)	8 (21.6)	3 (17.6)	0.095	§
Pleural thickening	1 (2.5)	5 (13.5)	0 (0.0)	0.070	
Pulmonary hypertension	2 (5.0)	1 (2.7)	2 (11.8)	0.384	
Mediastinal lymphadenopathy	1 (2.5)	2 (5.4)	0 (0.0)	0.546	
Hiatus hernia	20 (50.0)	25 (67.6)	8 (47.1)	0.207	
Treatment implementation					
Anti-mycobacterial drugs	26 (65.0)	34 (91.9)	12 (70.6)	0.115	§

Numbers in parentheses indicate the percentage of patients in each radiologic pattern. AFB positive smear in sputum observed on at least one occasion during the study period. Isolation of MAC (concurrent MAC-PD) was defined when MAC was isolated twice or more (but less than Mxe). Radiological bronchiectasis was defined by bronchus visualized within 10 mm of pleural surface or with bronchoarterial ratio greater than 1.0, random nodules by neither centrilobular nor peribronchovascular nor pleural/perifissural, fibrosis by honeycombing change together with traction bronchiectasis, masses by solid opacification with a diameter more than 30 mm, pulmonary hypertension by pulmonary trunk enlargement > 29 mm at pulmonary artery bifurcation, mediastinal lymphadenopathy by > 10 mm in short-axis, and hiatus hernia by herniation above the esophageal hiatus in a sagittal view: concentric contour enlargement, rugal folds, and focal irregular lobulation. p values are presented for differences among all three groups, while additional statistical tests were performed comparing NB versus FC groups, with § indicating significance ($p < 0.05$) between these two groups; the significance ($p<0.05$) was shown as the italic

AFB, acid-fast bacilli; #, number

UC (5/17 [29.4%]), and NB (6/40 [15.0%]), ($p = 0.024$). As expected, emphysema was more frequently seen with FC (22/37 [59.5%]) and UC (9/17 [52.9%]), compared with NB (5/40 [12.5%]) ($p < 0.001$), and atypical changes of consolidation or GGO were most often present with UC (6/17 [35.3%], $p = 0.033$). Pleural effusions were present in a substantial minority of patients with FC (8/37 [21.6%]) and UC (3/17 [17.6%]), but uncommon with NB (2/40 [5.0%]). Though there was not a statistically significant difference among all groups, pleural effusions were statistically more common in FC than NB patients ($p = 0.042$). Hiatus hernia was found in almost half of patients overall, but honeycombing with traction bronchiectasis, masses, pleural thickening, pulmonary hypertension, and mediastinal lymphadenopathy was uncommon. No striking differences emerged in the secondary analysis restricted to patients with exclusive Mxe-PD (Supplemental Table 2).

Treatment and outcomes

Most patients were treated with anti-mycobacterial drugs (Table 2), including the large majority of patients with FC (34/37 [91.9%]) and a somewhat lower proportion of others

(NB 26/40 [65.0%], UC 12/17 [70.6%]). Although there was no significant difference among the three groups overall ($p = 0.115$), a statistically greater proportion of patients with FC than patients with NB were treated ($p = 0.010$). Results were generally similar in the secondary analysis restricted to patients with exclusive Mxe-PD, although a somewhat smaller proportion of NB patients were treated in this analysis (Supplemental Table 2).

Treatment details are presented in Table 3. Patients with NB and UC were usually treated with three antibiotics (19/26 [73.1%] and 9/12 [75.0%], respectively), whereas patients with FC were usually treated with four or more drugs (21/34 [61.8%]). The median (quartiles) duration of therapy tended to be longer with NB (21 (12–60) months) and FC (22 (12–36) months) than that with UC (12 (3–29) months), though there was not a statistical difference among the three groups ($p = 0.126$). Specific drugs typically used were macrolides (71/72 [98.6%]), ethambutol (67/72 [93.1%]), rifamycins (46/72 [63.9%]), and fluoroquinolones (48/72 [66.7%]) without important differences by radiologic pattern. In FC patients, both rifamycins and fluoroquinolones tended to be used more often than in the other groups, but the differences were not statistically significant. Adjuvant lung resection was used almost exclusively in patients with FC (11/34 [32.4%], $p < 0.05$) compared with NB (1/26 [3.8%]) and UC (1/12 [8.3%]). Treatment details did not differ significantly in the secondary analysis restricted to patients with exclusive Mxe-PD (Supplemental Table 3).

Table 3 Treatment details and outcomes for patients with Mxe-PD

	NB ($n = 26$)	FC ($n = 34$)	UC ($n = 12$)	p value	
The number of antibiotics used				*0.010*	§
3 or less antibiotics	19 (73.1)	13 (38.2)	9 (75.0)		
4 or more antibiotics	7 (26.9)	21 (61.8)	3 (25.0)		
Antibiotics among treated patients					
Total treatment duration - median months (quartiles)	21.0 (12.0–60.0)	22.0 (11.5–36.0)	11.5 (3.0–29.0)	0.126	
Macrolide	26 (100.0)	33 (97.1)	12 (100.0)	0.567	
Median months (quartiles)	21.0 (12.0–60.0)	22.0 (12.0–34.5)	11.5 (3.0–29.0)	0.132	
Azithromycin	24 (92.3)	24 (70.6)	10 (83.3)		
Clarithromycin	2 (7.7)	9 (26.5)	2 (16.7)		
Ethambutol	22 (84.6)	33 (97.1)	12 (100.0)	0.100	
Median months (quartiles)	18.5 (13.5–69.0)	16.5 (8.5–26.3)	11.5 (3.0–28.3)	0.100	
Rifamycin	14 (53.8)	25 (73.5)	7 (58.3)	0.264	
Median months (quartiles)	20.0 (12.0–51.0)	16.5 (6.0–29.8)	3.0 (1.0–11.0)	*0.017*	
Rifampicin	13 (50.0)	24 (70.6)	7 (58.3)		
Rifabutin	1 (3.8)	1 (2.9)	0 (0.0)		
Fluoroquinolone	14 (53.8)	26 (76.5)	8 (66.7)	0.476	
Median months (quartiles)	25.5 (9.8–72.0)	16.5 (7.5–24.8)	15.5 (3.0–31.0)	0.386	
Moxifloxacin	2 (7.7)	16 (47.1)	4 (33.3)		
Levofloxacin	5 (19.2)	5 (14.7)	4 (33.3)		
Ciprofloxacin	7 (26.9)	5 (14.7)	0 (0.0)		
Amikacin	4 (15.4)	8 (23.5)	1 (8.3)	0.454	
Median months (quartiles)	14.5 (3.8–23.8)	8.0 (6.3–16.0)	1	N/A	
Intravenous	2 (7.7)	8 (23.5)	1 (8.3)		
Inhaled	1 (3.8)	0 (0.0)	0 (0.0)		
Intravenous, followed by inhaled	1 (3.8)	0 (0.0)	0 (0.0)		
Other medication	3 (11.5)	6 (17.6)	0 (0.0)		
Surgical intervention	1 (3.8)	11 (32.4)	1 (8.3)	*0.011*	§
Outcome among treated patients					
Clinical stability or improvement	23 (88.5)	24 (70.6)	11 (91.7)	0.126	
Radiological stability or improvement	20 (76.9)	25 (73.5)	10 (83.3)	0.787	
Culture conversion	21 (80.8)	23 (67.6)	8 (66.7)	0.476	
Microbiological recurrence	5 (19.2)	4 (11.8)	3 (25.0)	0.519	
Microbiological refractory	6 (23.1)	7 (20.6)	2 (16.7)	0.902	
Treatment success	13 (50.0)	15 (44.1)	6 (50.0)	0.883	
Clinical success	16 (61.5)	20 (58.8)	7 (58.3)	0.972	
Mortality	4 (15.4)	12 (35.3)	2 (16.7)	0.078	

Numbers in parentheses indicate the percentage of patients in each radiologic pattern. Culture conversion: three consecutive negative sputum cultures each 4 weeks or more apart or the inability to produce sputum and an absence of ongoing positive cultures. Microbiological recurrence: at least two specimens that yielded Mxe after successful treatment. Microbiological refractory: persistently positive cultures despite $\geq$ 12 months' antimicrobial therapy. Treatment success: culture conversion with symptomatic and radiologic control. Clinical success: defined as symptomatic and radiologic control regardless of adequate specimens to determine culture conversion. p values are presented for differences among all three groups, while additional statistical tests were performed comparing NB versus FC groups, with § indicating significance ($p < 0.05$) between these two groups; the significance ($p<0.05$) was shown as the italic

Employing the recently proposed outcome of cure (sustained culture conversion and symptom improvement [12]) yielded outcome rates of 18/26 (69.2%) in NB, 16/34 (47.1%) in FC, and 7/12 (58.3%) in UC achieved "cure" without significance among three groups ($p = 0.227$)

Twelve-month treatment outcome data were available for all patients. With multi-drug antimicrobial therapy, most patients in each category showed clinical and radiological stability or improvement and culture conversion, without statistical difference by radiologic pattern (Table 3). FC patients had numerically lower rates of clinical stability/improvement (24/34 [70.6%] vs NB 23/26 [88.5%] and UC 11/12 [91.7%]), while NB patients had the highest rates of culture conversion (21/26 [80.8%] vs FC 23/34 [67.6%] and UC 8/12 [66.7%]), but differences among groups were not statistically significant. Overall, treatment success (culture conversion with symptomatic and radiologic control) occurred in 50.0% with NB, 44.1% with FC, and 50.0% with UC, while clinical success (symptomatic and radiologic control regardless of adequate specimens to determine culture conversion) occurred in 61.5%, 58.8%, and 58.3%, respectively, without significant differences among the three groups. A numerically higher proportion of patients with FC died during the observation period (FC 12/34 [35.3%] vs NB 4/26 [15.4%] and UC 2/12 [16.7%], $p = 0.078$). Treatment outcome by radiological disease type did not differ significantly in the secondary analysis restricted to patients with exclusive Mxe-PD (Supplemental Table 3). In sensitivity analysis studying the recently proposed outcome of "cure" [12] based on sustained culture conversion and symptom improvement, we found 18/26 (69.2%) in NB, 16/34 (47.1%) in FC, and 7/12 (58.3%) in UC achieved "cure" without significance among the three groups ($p = 0.227$).

To explore the relative effectiveness of fluoroquinolones and rifamycins, patients treated with the rifamycin-free regimen ($n = 26$) and fluoroquinolone-free regimen ($n = 24$) were compared (data not shown). Overall, the clinical improvement (22/26 [84.6%] vs 20/24 [83.3%]), radiological improvement (22/26 [84.6%] vs 20/24 [83.3%]), and culture conversion (18/26 [69.2%] vs 17/24 [70.8%]) with rifamycin-free and fluoroquinolone-free regimens were similar.

Discussion

In our experience with 94 Mxe-PD patients, we observed nearly equivalent proportions of patients with FC and NB disease and a substantial minority with UC disease comprising largely patients with COPD with random nodules or ILD with peripheral opacities. Treatment outcomes did not differ substantially between groups, although numbers were small. Mortality during the observation period tended to be higher with FC disease.

Nodular bronchiectasis was most often seen in female never-smokers with AFB smear-negative sputum and not infrequently, prior MAC-PD. Additionally, they frequently had co-isolation of *Pseudomonas* or concurrent MAC-PD, suggesting a strong underlying predisposition of lung infection with environmental organisms. Fibrocavitation was seen more often in males with emphysema, obstructive physiology, AFB smear-positive sputum, and more constitutional symptoms who were more likely to be initiated on therapy. Patients with FC were treated more intensively, including much more frequent adjuvant surgical resection. Our patients with UC disease, comprising largely patients with COPD or ILD, have similarities to some previously described cohorts. The random nodules in COPD patients with UC are a previously described pattern [13, 14] and may be similar to the nodular form in a multi-center French series [5]. The predominantly peripheral consolidation in ILD patients with UC is similar to prior NTM-PD cohorts with IPF [15, 16].

Our finding of similar proportions of NB and FC is surprising given that the typical description of Mxe-PD is FC in the presence of emphysema. A systematic review including many cases without CT scans comprised mostly cavitary upper lobe disease [17]. In a more recent series of 136 well-characterized Mxe-PD patients from 13 French centers, patients were divided according to radiological pattern as cavitary (28.7%), nodular (30.1%), or infiltrative (33.1%) [5], although 47.8% lacked CT scans, and so the classification could not be easily translated into FC versus NB versus UC. Only 9% overall had bronchiectasis, suggesting a low frequency of NB, but the frequent absence of CT scans limits the ability to characterize radiologic type.

Particularly surprising in the distribution of radiological subtypes in the present study is the contrast from our prior work [13, 14]. We previously reviewed CT scans from small numbers of Mxe-PD patients at our institution, numbering 16–24, and observed NB in only up to 4%, FC in 33–40%, and another/UC pattern in 63–66% [13, 14]. The difference between our prior versus current study is undoubtedly due to biases from different study designs. Our prior work included all patients with positive microbiology who had a CT scan and clinical notes at any of the campuses of our multi-site hospital. Many patients were not being seen specifically for their Mxe-PD, but were assessed for other reasons, and had adequate information in our electronic record to assess Mxe-PD status and type. This contrasts with the current study, including only patients assessed in our NTM clinic, where we observed a very large proportion of NB. Perhaps in following a significant number of patients with bronchiectasis who are predisposed to NTM-PD, we observed the inevitable; a substantial number of such patients become infected with Mxe, the second most commonly isolated NTM species in Ontario. Supporting this, 25% of our NB patients were previously infected with MAC. The combination of a high likelihood of recurrent NTM-PD among patients with NB [18, 19] and studying a dedicated NTM program where patients have lengthy follow-up may overestimate the frequency of NB in Mxe-PD in a region where Mxe is common. Regardless of biases, inherent in all studies to date, we demonstrate that Mxe-PD may present as NB—a very common finding in our setting.

Although a standard anti-mycobacterial drug regimen for Mxe-PD has not been established, a macrolide, ethambutol, and rifamycin combination was proposed by the ATS/IDSA [6], while recently, the British Thoracic Society (BTS) recommended the same combination plus a fluoroquinolone or isoniazid [20]. In our practice, there was less rifamycin and more macrolide use than in either the retrospective French study [5] or the randomized UK trial [21]. In our experience, almost all NB patients received a macrolide and ethambutol plus either rifampin or a fluoroquinolone, in similar proportions. Our FC patients were treated more intensively, similar to recent BTS recommendations [20], and frequently had adjuvant surgical resection of focal destroyed lung tissue, usually while receiving amikacin. Our UC patients tended to be treated more like the NB patients. Although both rifamycins and fluoroquinolones have been recommended as potentially useful in Mxe-PD, in our retrospective review, we were unable to discern a benefit of one agent over the other. In a systematic review, point estimates suggested that both rifamycins and fluoroquinolones were associated with better outcomes [17], while the French series found that rifampin use was associated with survival [5]. We are unaware of data comparing these two agents, which both appear to be useful for Mxe-PD.

Our treatment success, defined by culture conversion and radiological and symptomatic control, was approximately 50%, within the wide range of 8.8–73% reported in a recent meta-analysis of Mxe-PD studies [22]. Using the restricted metric of clinical stability or improvement, perhaps more meaningful to patients, 80.6% (58/72) of patients benefitted from therapy, while 76.4% (55/72) experienced radiological benefit and 72.2% (52/72) achieved microbiological response. Although the proportion of clinical success in each CT pattern appeared to be similar (58–62%), patients with UC CT patterns achieved better clinical and radiological improvement, perhaps due to the lack of significant cavitation or extensive bronchiectasis with co-existing microbes that may complicate management. Despite the fact that cavitation is traditionally considered to be a poor prognostic factor, our FC patients achieved clinical success at a similar rate to other patients and were less often microbiologically refractory or recurrent. The latter differences could be in part related to surgical intervention. Despite the apparently favorable features, mortality in FC was high, although our study is of inadequate size and duration to adequately study survival.

Studying outcomes in NTM-PD is complex. Just as in the diagnosis, researchers may need to consider not only microbiology but also symptoms and radiology. Each of these "outcomes" can be difficult to address. Sputum may become difficult to expectorate or induce after a period of treatment. Sputum microbiology may potentially also be negative despite the presence of viable organisms in areas of lung destruction, which may be apparent upon bronchoscopy or the culture of surgically resected tissue. Radiologic abnormalities and symptoms may be caused or worsened by other pathogens. Because any one of the component abnormalities used in assessing patients with NTM-PD could potentially be misleading, we think it may be useful to consider all components' outcome assessments. For this reason, our combined outcomes included imaging, thus diverging somewhat from some recently proposed outcomes [12]. As described above, rates of "cure," as defined by van Ingen et al. [12], were somewhat higher than "treatment success" as we defined to include imaging. Although there remained no statistically significant difference among groups, using the outcome of van Ingen and colleagues led to a numerically greater separation of rates between NB and FC patients.

In conclusion, 94 patients with Mxe-PD in a single clinic were reviewed and classified into NB, FC, and UC based on the predominant CT pattern. The NB and FC patterns were found to be approximately equally distributed, with a smaller proportion observed to have other CT findings. Despite the clinical differences, patients with different radiological types had similar treatment responses, although it was noted that patients with FC disease were treated more aggressively. Interventional clinical studies, stratified by predominant CT pattern, are needed to improve the management of patients with Mxe-PD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was reviewed by the University Health Network-Research Ethics Board (Research Ethics Board number 18-5104).

Informed consent In light of the retrospective design, the requirement of informed consent was waived.

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