some symptoms, including cough ($n$ = 20), haemoptysis ($n$ = 21), sputum ($n$ = 18), dyspnoea ($n$ = 3), subfever ($n$ = 2) and body weight loss ($n$ = 1). The majority of the patients were thin, elderly women. One patient had an underlying respiratory condition with mild bronchial asthma. Thirty patients had underlying non-respiratory conditions: 17 had a history of major surgery, 5 had chronic hepatitis, 3 had diabetes mellitus, 2 had rheumatoid arthritis and 3 had hypertension. Seven patients had previously received treatment for MAC-PD.

Upon diagnosis of MAC, *M. avium* was the most frequently detected species. Resistance to a macrolide was assessed in cultures from 31 patients at the initial visit, three (9.7%) of whom were resistant to a macrolide (minimum inhibitory concentration > 32 μg/ml). Forty-four patients received multidrug treatment, including a macrolide for >6 months according to the standard guidelines.[8] The macrolide dosage was as follows: clarithromycin ($n$ = 42) 495.2 ± 126.8 mg/day, azithromycin ($n$ = 2) 250 mg/day. The remaining 28 patients did not receive standard chemotherapy: 11 were observed without any antimycobacterial medication, 8 were treated with macrolide-containing therapies that were not tolerated and therefore discontinued, and 9 were treated with regimens that were not in accordance with the standard guidelines. Treatment decisions (timing and drug choice) were made by individual physicians. Sputum culture conversion was achieved in 30 (68.2%) of the 44 patients who received treatment; 23 (76.7%) of these relapsed. Treatment after initial antimycobacterial chemotherapy varied among the patients. Macrolide susceptibility at initial visit was examined in 19 patients who received standard chemotherapy. The sputum culture conversion rate was 70.6% (12/17) in macrolide-susceptible and 0% (0/2) in macrolide-resistant patients.

### *Long-term radiographic outcome of MAC-PD*

The Figure illustrates MAC-PD progression at 1, 5 and 10 years. Only 1 (1.4%) of the 72 patients showed progressive or remarkably progressive disease at 1 year. However, the rate of progressive or remarkably progressive disease increased to 22.2% at 5 years. Among the 30 patients followed up at 10 years, none showed progressive or remarkably progressive disease at 1 year, while the rate of progressive or remarkably progressive disease increased to 10.0% at 5 years, and to 53.3% at 10 years. Patients who showed deterioration of at least 1 grade (as assessed by CXR) compared to the initial visit accounted for 15.3% at 1 year, 51.4% at 5 years and 70.0% at 10 years.

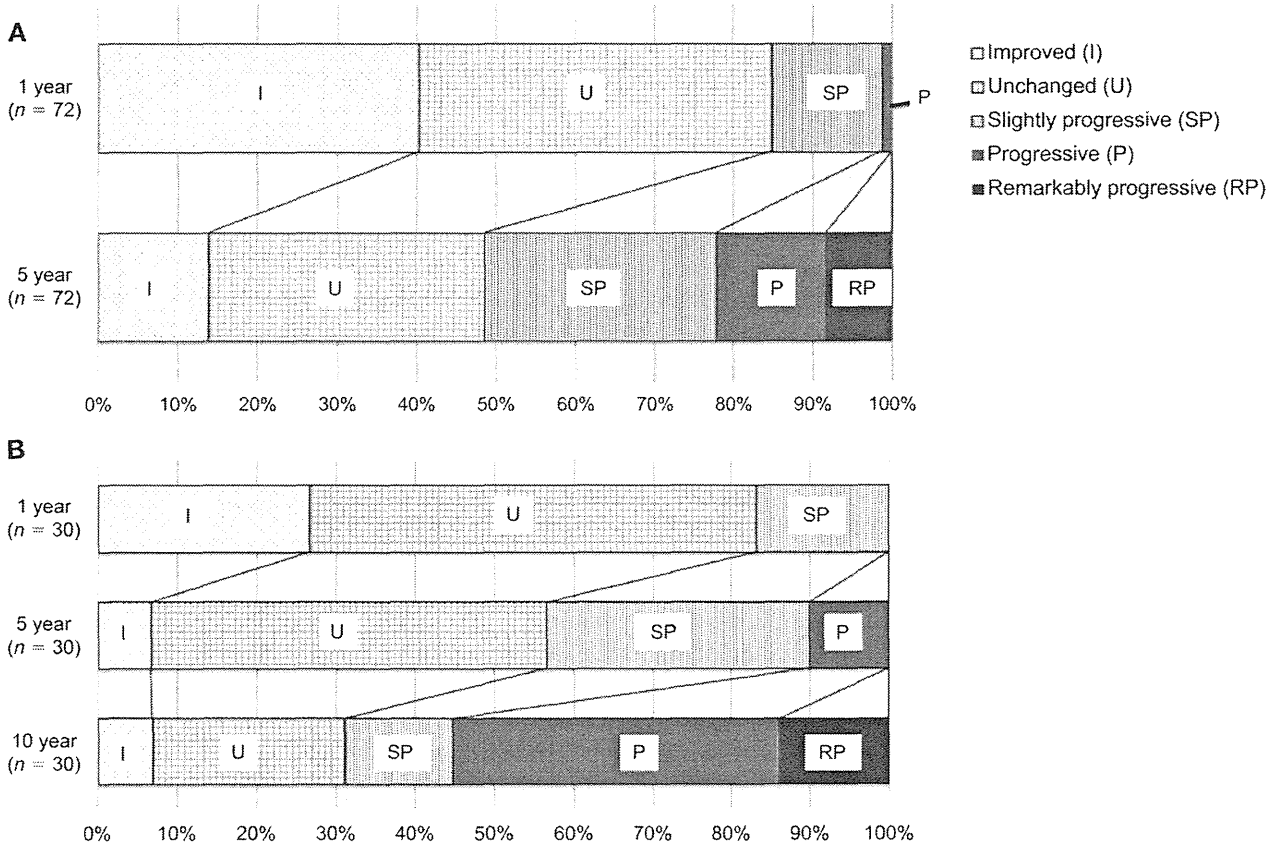


**Figure** Progression of *Mycobacterium avium* complex pulmonary disease assessed by comparing plain chest radiographs at 1, 5 and 10 years with those from the initial visit for patients who were followed up at **A**) 5 years and **B**) 10 years.

**Table 2** Comparison of baseline characteristics between the stable and deteriorated groups at 5 years

| Parameter | Stable ($n$ = 56) $n$ (%) or mean ± SD | Deteriorated ($n$ = 16) $n$ (%) or mean ± SD | $P$ value |
|---|---|---|---|
| Age, years | 60.9 ± 9.7 | 65.9 ± 12.5 | 0.06 |
| Female patients | 45 (80.4) | 15 (93.8) | 0.21 |
| BMI, kg/m$^2$ | 20.3 ± 2.9 | 17.8 ± 2.3 | <0.01 |
| Sputum smear >1+ | 5 (8.9) | 1 (6.3) | 0.73 |
| ESR, mm/h | 35.5 ± 22.3 | 36.6 ± 23.9 | 0.84 |
| Cavitary disease | 3 (5.4) | 7 (43.8) | <0.0001 |
| Resistance to a macrolide* | 0 | 3 | <0.05 |

*Macrolide resistance (MIC > 32 μg/ml) was determined in 31 patients at the initial visit.
SD = standard deviation; BMI = body mass index; ESR = erythrocyte sedimentation rate; MIC = minimum inhibitory concentration.

### *Factors correlating with deterioration of MAC-PD*

Baseline characteristics were compared between the stable and deteriorated groups after defining the two groups on the basis of assessment at 5 years (Table 2). BMI at the initial visit was lower in the deteriorated group than in the stable group ($P < 0.01$). Cavitary disease and resistance to a macrolide were more common in the deteriorated group than in the stable group ($P < 0.0001$, $P < 0.05$). The ratio of patients who received a standard treatment regimen was similar between the stable (62.5%) and the deteriorated (56.3%) groups ($P = 0.65$). The duration of treatment tended to be longer in the deteriorated group (2.5 ± 1.6 years) than in the stable group (1.8 ±1.4 years), although the difference was not statistically significant ($P = 0.06$). Of the 30 patients who achieved culture conversion with treatment, 26 (86.7%) belonged to the stable group at 5 years and none were macrolide-resistant. However, of the 14 patients for whom culture conversion was not achieved, nine (64.3%) were in the stable group at 5 years.

## DISCUSSION

In this study, we investigated the long-term radiographic outcome and factors for the deterioration of MAC-PD. NBE MAC-PD was relatively stable at 1–5 years; however, more than half of the patients showed clearly worsened disease on CXRs taken at 10 years, and 70% of the patients exhibited worse CXRs at 10 years than at the initial visit. Only two patients died due to respiratory failure, suggesting that NBE disease is not usually life-threatening. These data suggest that NBE is a slowly, but substantially progressive disease in the long term. Notably, patients with a lower BMI, cavitary disease and resistance to a macrolide at the initial visit tend to have deteriorated disease at 5 years.

These findings have several implications for disease management. Although more effective antimycobacterial drugs are needed, drug treatment or more aggressive care should be initiated for younger patients or patients with risk factors as identified here, considering that more than half of NBE cases show progression after 10 years. In contrast, elderly patients can be followed up without aggressive medical care. A better understanding of disease progression, as described here, will enable clinicians to tailor treatment strategies for individual patients.

Reports on long-term observations of the clinical course of MAC-PD are limited. A study by the British Thoracic Society (BTS) examined 5-year outcomes in 65 patients with MAC-PD who received standardised treatment.[9,10] Twenty-seven (36%) patients died within 5 years, although only three died from MAC-PD. Increasing age, male sex, involvement of more than one lung zone and low body weight were independent predictors of mortality in this study. Patients in the BTS study were different from those in our study population, making it difficult to compare the studies. In the BTS study, 61% of the patients had co-existing lung disease, mostly healed TB, whereas our study examined NBE disease without underlying lung disease. Yamazaki et al. reported on progression of NBE without any medication over approximately 2 years.[11] They demonstrated that pulmonary disease is more likely to progress in patients with certain characteristics, including older age, lower BMI, increased ESR and increased number of neutrophils in bronchoalveolar lavage fluid. Interestingly, lower BMI is a common predictive factor for deteriorating disease.

In our study population, the response rate to multidrug treatment and the relapse rate were similar to those in previous studies. Tanaka et al. reported that for 28 (71.8%) of 39 patients who received more than 6 months of treatment, sputum culture was negative; however, only 22/39 patients (56.4%) remained culture-negative at 1–6 years after initiation of treatment.[12] Kobashi and Matsushima reported negative sputum conversion in 56.9% of their patients with MAC-PD after antimycobacterial treatment according to ATS guidelines within 6 months after initiation of treatment; however, the condition relapsed in 56.8% of these patients after treatment completion.[13] In the present study, sputum culture conversion was achieved in 30 patients (68.2%) who received treatment, and relapse occurred in 23 (76.7%).

The effect of multidrug treatment on long-term outcome is difficult to determine. Treatment may influence the clinical course of the disease and stabilise the clinical condition in the short term. Indeed, 86.7% of the patients who achieved culture conversion with treatment were in the stable group at 5 years. However, 64.3% of the patients who did not achieve culture conversion were also stable at 5 years. As treatment was initiated according to the decision of the physicians (and was not based on specific criteria), and because treatment regimens after antimycobacterial chemotherapy were not uniform among the

patients, further studies are needed to confirm the long-term effectiveness of multidrug treatment.

Our retrospective study has several limitations. First, we did not investigate the natural history of MAC-PD. As mentioned above, many patients had received chemotherapy, which may affect the clinical course. Second, the progression of MAC-PD was assessed by plain CXR: CT images were not obtained regularly for all patients. We devised a novel method of evaluation of disease progression, as there is currently no standardised procedure for the assessment of the radiographic severity of MAC-PD. In addition, the extent of disease at the initial visit was not determined in the present study, as the extent of disease, especially the extent of small nodules, is difficult to evaluate by CXR. Third, bacteriological findings were not used in evaluating the status of the MAC disease. It was difficult to perform a quantitative assessment, as the timing of sputum examination varied greatly among subjects.

## CONCLUSIONS

The results demonstrate that NBE MAC-PD is a slowly but substantially progressive infection in the long term, although it is not usually life-threatening. Patients with lower BMI, cavitary lesions and resistance to a macrolide at the initial visit are more likely to develop deteriorating disease over 5 years.

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## RÉSUMÉ

CONTEXTE : Bien que les affections pulmonaires dues au complexe *Mycobacterium avium* (MAC-PD) constituent un problème de santé croissant, on a peu de connaissances au sujet des résultats radiologiques à long terme et des facteurs de détérioration chez les patients atteints de MAC-PD.
MÉTHODES : On a revu rétrospectivement les données concernant les patients atteints de MAC-PD nodulaire avec bronchectasie (NBE) qui avaient été régulièrement suivis pendant plus de 5 ans. On a comparé les modifications du cliché thoracique (CXR) standard et les caractéristiques de départ entre les groupes stables et détériorés.
RÉSULTATS : On a pu investiguer 72 patients dont 30 ont été examinés 10 années après la visite initiale. On a observé une maladie progressive ou très progressive au CXR à 1 an chez un patient (1,4%) et à 5 ans dans 22,2%. Le taux a augmenté jusqu'à 53,3% après 10 ans. L'index de masse corporelle (BMI) était plus bas lors de la visite initiale dans le groupe avec détérioration que dans le groupe stable. On a noté également une fréquence plus élevée des maladies cavitaires et de résistance aux macrolides dans le groupe avec détérioration par rapport au groupe stable.
CONCLUSIONS : La NBE MAC-PD est une infection lentement mais nettement progressive à long terme (5–10 ans). Nos données suggèrent que la progression vers une affection avec détérioration est plus fréquente chez les patients qui ont au départ un BMI plus faible, une maladie cavitaire et une résistance aux macrolides.

## RESUMEN

MARCO DE REFERENCIA: Pese a que la enfermedad pulmonar causada por el complejo *Mycobacterium avium* (MAC-PD) constituye un problema sanitario creciente, se conoce poco sobre la evolución radiográfica a largo plazo y los factores que determinan el deterioro en estos pacientes.
MÉTODOS: Se examinaron en forma retrospectiva los datos de los pacientes con bronquiectasias nodulares (NBE) causadas por el complejo *M. avium* que habían acudido al seguimiento periódico durante más de 5 años. Se compararon las anomalías de la radiografía de tórax (CXR) y las características iniciales de los pacientes del grupo estable y del grupo que sufrió deterioro.
RESULTADOS: Se estudiaron 72 pacientes, de los cuales 30 se habían acudido hasta 10 años después de su consulta inicial. En el primer año, un paciente (1,4%) presentó enfermedad progresiva o notoriamente progresiva en la CXR; a los 5 años la proporción fue del 22,2% y aumentó hasta un 53,3% a los 10 años. El índice de masa corporal (BMI) en la consulta inicial fue más bajo en el grupo que se deterioró que en el grupo estable. La presencia de cavernas y la resistencia a los macrólidos fueron más frecuentes en la consulta inicial de los pacientes del grupo con deterioro que en el grupo estable.
CONCLUSIÓN: La NBE MAC-PD es una infección a largo plazo de evolución lenta pero eminentemente progresiva (5 a 10 años). Los resultados del estudio indican que los pacientes que en la consulta inicial presentan un bajo BMI y resistencia a los macrólidos tienen una mayor probabilidad de evolucionar hacia una enfermedad con deterioro notable.