



## Case report

## Immunomodulatory effect of macrolides: At what cost?



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## ABSTRACT

We present the case of a 60-year old female patient, with a 10 year history of non-CF bronchiectasis and use of macrolides as maintenance immunomodulatory treatment, who was diagnosed with macrolide-resistant *Mycobacterium avium* complex lung disease. Macrolides' immunomodulatory effect is appealing for non- CF bronchiectasis patients, hiding a high risk for resistance emergence.

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## 1. Clinical record

A 60-year old woman was referred to the tuberculosis (TB) out-patient clinic for *Mycobacterium avium* (MAC) pulmonary disease after having received 1st line antituberculosis treatment (isoniazid, rifampicin, ethambutol, pyrazinamide) for one month. The initial clinical diagnosis was pulmonary TB, based on patient's symptoms, consisting of fever, productive cough and weight loss for the last 2 months, along with compatible to tuberculosis chest x-ray and computed tomography (CT) scan. The CT scan had revealed 3 cavities and tree-in-bud appearance of the right upper lobe (Fig. 1). Acid-fast smears from sputum and bronchial lavage were negative, however cultures from the lavage revealed the presence of MAC.

The patient had a decade-long history of bronchiectasis with her respiratory tract being chronically colonized with *P. aeruginosa*. She reported infectious exacerbations during the last 10 years, which were mostly treated with macrolides or quinolones. Due to increase in the frequency of the exacerbations to 3–4 per year in the last two years, the patient was on maintenance treatment with azithromycin 250 mg three times per week for the last six months, as suggested by her treating physician.

On examination, after one month of anti-TB treatment, the

patient was found to have gained weight and she reported as being afebrile for the last 2 weeks and without cough. Despite this initial response to treatment, positive culture results from one bronchial washing sample, along with the patient's symptoms and radiological findings, fulfilled ATS criteria for MAC pulmonary disease diagnosis. Her treatment was modified to rifampicin, ethambutol, azithromycin and amikacin. One month later, resistance to macrolides was detected, so azithromycin was discontinued and isoniazid and moxifloxacin were added to the regimen. The patient received treatment for 24 months (amikacin for eight months) and showed a significant clinical and radiological improvement. The patient was unable to produce sputum so microbiological follow up could not be performed. Her CT scan at the end of treatment was also significantly improved (Fig. 2). Due to the persisting presence of a cavity in the right upper lobe at the end of the treatment, the option of surgical resection was proposed but the patient refused. At present, six months after the completion of her treatment, she remains clinically stable and does not report any bronchiectasis-related infectious exacerbation.

## 2. Discussion

Two major aspects seem to be of interest in the present case, which—as we speculate—might not be uncommon. First, MAC disease was not suspected despite the patient's typical profile (postmenopausal white female, bronchiectasis, respiratory tract cultures

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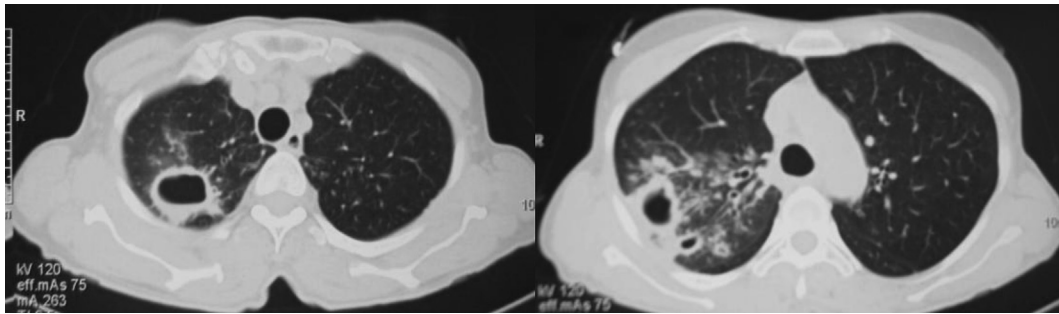


Fig. 1. Chest CT scan on diagnosis.

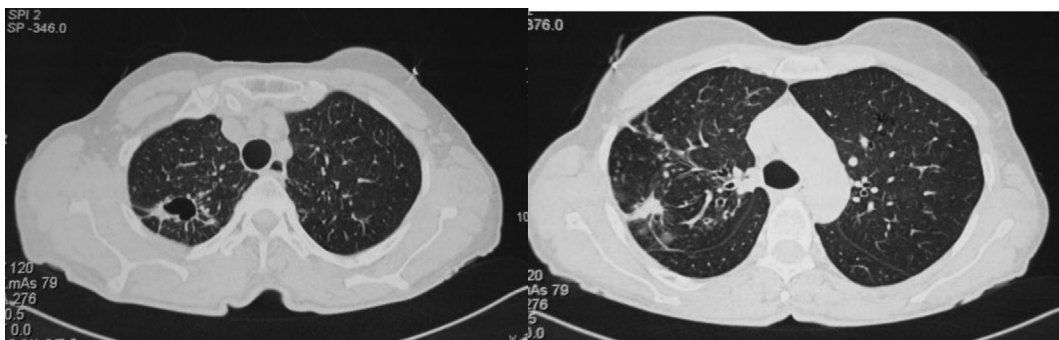


Fig. 2. Chest CT scan after 24 months of treatment.

positive for *P. aeruginosa*) [1,2] and frequent bronchiectasis exacerbations. Secondly, and perhaps more crucial, immunomodulatory treatment with azithromycin was initiated without previous exclusion of MAC disease (neither when she initially presented with bronchiectasis 10 years ago nor while frequent exacerbations occurred during the last two years) and thus, this is probably associated with the emergence of macrolide resistance.

The incidence of non-tuberculous mycobacteria (NTM) seems to be on the rise, and this cannot be attributed solely on laboratory methods improvement [3]. According to recent evidence from Canada, NTM disease occurs several fold more frequently than tuberculosis, in persons over 50 years old [3], whereas, NTM frequency was estimated to be as high as 37% among non-CF bronchiectasis patients, with 30% of these also meeting ATS criteria for NTM disease [4]. MAC lung disease represents the great majority of NTM pulmonary disease and also seems to be more common than previously thought [1,3,4].

Interestingly, in the present case, MAC disease was never suspected during the history of patient's frequent bronchiectasis exacerbations, and the initial diagnosis after the lung cavitation appearance was pulmonary TB. This is actually not so unusual, since 1 out of 10 of patients considered as having chronic tuberculosis, are finally found suffering from lung disease due to NTM [5]. The delay in diagnosis is mainly attributed to the low level of suspicion for NTM disease, especially in countries like ours, where tuberculosis is significantly more prevalent, and where many respiratory physicians seem to consider NTM disease as a clinical entity affecting exclusively immunocompromised patients. That is definitely not the case, since only 25% of patients with confirmed NTM infection are under immunosuppressive treatment, with no co-existing condition being a prerequisite for the disease [1,3,6].

Macrolides stand as the most important element in the multi-drug treatment regimen of MAC lung disease, being the only drug in this regimen for which *in vitro* susceptibility corresponds with

clinical efficacy [1]. Introduction of newer macrolides represents a major therapeutic advance for MAC lung disease [1,7], whereas optimal treatment for macrolide-resistant MAC has not been determined yet [1].

Macrolide-resistant MAC lung disease is linked to poor treatment outcome, requiring skilled management, analogous to that of multi-drug resistant tuberculosis [1]. In a series of 51 HIV negative patients with resistant MAC, culture conversion was achieved in 79% of those treated with both surgery and an injectable agent containing regimen for at least 6 months, whereas conversion rate was only 5% for those treated with either one of them [8]. Previous macrolide monotherapy is considered the major risk factor for the development of resistance, and as a result, prevention of resistance is the main reason why combination therapy including ethambutol, rifabutin and an aminoglycoside is recommended for the treatment of MAC lung cavitory disease [1]. In this setting, it seems sensible to attribute the macrolide-resistant MAC, in the presented case, to the previous macrolide use, as maintenance therapy for bronchiectasis.

Macrolides are currently increasingly appreciated for their anti-inflammatory and immunomodulatory effect and, on that basis they are considered part of evidence-based treatment in diffuse panbronchiolitis and CF-related chronic respiratory infection [9,10]. As far as non-CF bronchiectasis are concerned, recent research supports that chronic administration of macrolides is related to lower rates of infectious exacerbations and, perhaps, a better quality of life, especially in patients with 2 or more infectious exacerbations during the past year [11,12]. Although these results seem to favor the chronic medication with macrolides in patients with non-CF bronchiectasis, prior presence of NTM lung disease and possible emergence of resistance was not evaluated among the patients studied [11,12].

Emergence of macrolide-resistant MAC seems to follow the pattern of common pathogens. Significant rise in macrolide resistance among pharyngeal streptococci was observed even after

short course of treatment, in healthy volunteers [13]. In the same setting, due to the extensive macrolide prescription in Greece, resistance of *S. pneumoniae* is as high as 25%, rendering monotherapy with macrolides a suboptimal option for the treatment of community-acquired pneumonia [14,15].

In conclusion, we presented a case of a macrolide-resistant MAC pulmonary disease after administration of macrolides as maintenance therapy for non-CF bronchiectasis. Bronchiectasis and NTM infection, especially MAC, often co-exist and sometimes the question whether bronchiectasis is the predisposing factor for mycobacterial infection or it is a bronchiectatic MAC lung disease from the very beginning, is hard to be answered [1]. Careful evaluation for non-tuberculous mycobacteria is an essential part of follow-up in these patients and should always precede add-on therapy with macrolides, when this is indicated. In any case, chronic administration of macrolides, as immunomodulatory agents in non-CF bronchiectasis, although very appealing, hides the high risk of resistance emergence for those cases where MAC is also present.

## References

- [1] D.E. Griffith, T. Aksamit, B.A. Brown-Elliott, A. Catanzaro, C. Daley, F. Gordin, et al., An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases, *Am. J. Respir. Crit. Care Med.* 175 (4) (2007) 367–416.
- [2] K. Fujita, Y. Ito, T. Hirai, T. Kubo, K. Togashi, S. Ichijima, et al., Prevalence and risk factors for chronic co-infection in pulmonary *Mycobacterium avium* complex disease, *BMJ Open Respir. Res.* 1 (1) (2014) e000050.
- [3] K.L. Winthrop, E. McNelley, B. Kendall, A. Marshall-Olson, C. Morris, M. Cassidy, et al., Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease, *Am. J. Respir. Crit. Care Med.* 182 (7) (2010) 977–982.
- [4] M. Mirsaeidi, W. Hadid, B. Ericsson, D. Rodgers, R.T. Sadikot, Non-tuberculous mycobacterial disease is common in patients with non-cystic fibrosis bronchiectasis, *Int. J. Infect. Dis.* 17 (11) (2013) e1000–e1004.
- [5] M. Maiga, S. Siddiqui, S. Diallo, B. Diarra, B. Traoré, Y.R. Shea, et al., Failure to recognize nontuberculous mycobacteria leads to misdiagnosis of chronic pulmonary tuberculosis, *PLoS one* 7 (5) (2012) e36902.
- [6] D.S. Prince, D.D. Peterson, R.M. Steiner, J.E. Gottlieb, R. Scott, H.L. Israel, et al., Infection with *Mycobacterium avium* complex in patients without predisposing conditions, *N. Engl. J. Med.* 321 (13) (1989) 863–868.
- [7] Y. Kobashi, K. Yoshida, N. Miyashita, Y. Niki, M. Oka, Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates, *J. Infect. Chemother.* 12 (4) (2006) 195–202.
- [8] The Research Committee of the British Thoracic Society, Pulmonary disease caused by *Mycobacterium avium*-intracellulare in HIV-negative patients: five-year follow-up of patients receiving standardised treatment, *Int. J. Tuberc. Lung Dis.* 6 (7) (2002) 628–634.
- [9] P.A. Flume, B.P. O'Sullivan, K.A. Robinson, C.H. Goss, P.J. Mogayzel Jr., D.B. Willey-Courand, et al., Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health, *Am. J. Respir. Crit. Care Med.* 176 (10) (2007) 957–969.
- [10] G. Amsden, Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J. Antimicrob. Chemother.* 55 (1) (2005) 10–21.
- [11] D.J. Serisier, M.L. Martin, M.A. McGuckin, R. Lourie, A.C. Chen, B. Brain, et al., Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non-Cystic Fibrosis Bronchiectasis: The BLESS Randomized Controlled Trial, *Jama* 309 (12) (2013) 1260–1267.
- [12] J. Altenburg, C.S. de Graaff, Y. Stienstra, J.H. Sloos, E.H. van Haren, R.J. Koppers, et al., Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial, *Jama* 309 (12) (2013) 1251.
- [13] S. Malhotra-Kumar, C. Lammens, S. Coenen, K. Van Herck, H. Goossens, Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study, *Lancet* 369 (9560) (2007) 482–490.
- [14] L.A. Mandell, R.G. Wunderink, A. Anzueto, Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults, *Clin. Infect. Dis.* 44 (2) (2007) S27–S72.
- [15] Working Group of Greek Comitee of Infectious Diseases, Greek Chemotherapy Comitee and Greek Comitee of Respiratory Disease. Guidelines for the diagnosis and empirical treatment of community acquired pneumonia. In: Guidelines for Diagnosis and Treatment of Infectious Diseases, Scientific Comitee of Hospital acquired Infectious Diseases.