This case is highlighted by its rarity and severity, with the occurrence of multiple adverse reactions to the antituberculous drugs in an immunocompromised patient with miliary tuberculosis. The WHO recently published the initial results of a pilot study about the surveillance of antituberculous agents' adverse events, named aDSM (active tuberculosis Drug Safety Monitoring and management), which demonstrates monitoring is feasible.[2] The authors also wish to emphasize that, although uncommon, the occurrence of rifampicin-induced thrombocytopenia is a potentially serious and fatal ADR, which imposes its suspension and contraindicates its reintroduction.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical disclosures

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.
Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received enough information and gave their written informed consent to participate in the study.
Right to privacy and informed consent: The authors declare that no patient data appear in this article.

Conflict of interest

None.

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27 June 2019

https://doi.org/10.1016/j.pulmoe.2019.09.005
2531-0437/

The effect of alcohol consumption in the treatment of nontuberculous mycobacteria

To the editor:

Nontuberculous mycobacteria (NTM) are considered opportunistic pathogens. They are widely distributed in the environment, and several species are associated with a wide range of infections, most commonly affecting the lung.[1–3] The increasing number of immunocompromised patients and predisposing diseases – such as chronic obstructive pulmonary disease (COPD), silicosis and bronchiectasis—as well as the increasing life expectancy of patients with cystic fibrosis, are factors contributing to a rising incidence of NTM disease.[2–4] However, patients can develop NTM disease without any apparent underlying cause. This suggests that NTM disease is a multifaceted disease, and the genetic background or environmental exposures could, also, increase susceptibility to infection.[1–3] Population-based studies across Europe report a steady increase in NTM isolation and related lung disease over time. In Portugal, epidemiological studies are scarce but are in line with

Table 1 Baseline characteristics of the study population - data are presented as n (%) or median (min-max); HIV: human immunodeficiency virus; COPD: chronic obstructive pulmonary disease.

Baseline characteristics	Total
Male	369 (60.5)
Age (years)	58 (19-97)
Alcohol consumption	65 (11.5)
Underlying diseases	
HIV infection	133 (21.8)
COPD	63 (10.3)
Diabetes mellitus	27 (4.4)
Lung cancer	10 (1.6)
Other neoplasms	19 (3.1)
Drug abuse	51 (8.9)
Imprisonment/Homelessness/Community shelter	21 (3.6)
NTM lung disease	540 (89)
Sputum	355 (64.8)
Bronchoalveolar lavage	157 (28.6)
Pleural fluid	9 (1.6)
Lung biopsy	1 (0.2)
Missing data	18
NTM extra-pulmonary disease	70 (11.5)
Blood culture	13 (2.4)
Urine	5 (0.9)
Lymph node aspirate	5 (0.9)
Missing data	47
Species of nontuberculous mycobacteria	
Mycobacterium avium/intracellulare	340 (55.7%)
M. kansasii	78 (12.8%)
M. gordonae	39 (6.4%)
M. xenopi	34 (5.6%)
M. chelonae	23 (3.8%)
M. fortuitum	23 (3.8%)
M. abscessus	10 (1.6%)
Other	63 (10.3%)

these reports. Two studies, conducted in Lisbon Area, found NTM to account for approximately 12% of all mycobacterial isolates,[5,6] and hospital-based research[7] showed a definite rise in the number of NTM isolates each year of the study, and 89% of those were found to be clinically significant, fulfilling the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) criteria.[2]

NTM disease is complex to manage and a significant cause of morbidity and mortality.[4] Treatment is long and requires multiple drugs, which can be challenging due to side effects and different resistance profiles.[2] Therefore, the treatment success rate remains unsatisfactory.[4] Host factors and comorbidities can influence the outcome, and this is rarely covered by studies reported to date or in the current guidelines.

The present study aimed to identify the effect of alcohol consumption on the treatment outcome of NTM disease.

This study collected information from the structured questionnaire filled in by clinicians who initiate treatment for NTM disease and which is stored in the Portuguese National Epidemiological Surveillance Commission for Tuberculosis. We retrospectively reviewed the data from patients with NTM disease from January 2003 to December 2016. All patients met the diagnostic criteria for NTM disease from the ATS/IDSA guidelines. Clinical and socio-demographic data were collected. Alcohol consumption was self-reported in the questionnaire at time of diagnosis and was defined as the presence or absence of consumption. Excluded from the main outcome analysis were patients still in treatment, those who had discontinued the therapy, those lost to follow-up or transferred out.

Treatment outcome of NTM disease was binarily evaluated as a good or bad outcome. Good outcome was defined as culture conversion after initiation of treatment and maintenance of a negative culture for $\geqslant$12 months on treatment. Bad outcome was defined as no culture conversion or as death while being treated for NTM disease. Simple logistic regression models evaluated univariate effects, and multiple logistic regression models identified the simultaneous effects of potential risk factors for a bad outcome. Selection of the final model was based on the backwards algorithm combined with the results from the univariate analysis. The statistical analysis was performed with the R language and software environment for statistical computation [The R Project for Statistical Computing, https://www.r-project.org/, version 3.4.3]. The significance level was set to $\leq$0.05.

During the study period, 610 patients were eligible. The median age was 58 years (min-max, 19–97 years), and 369 (60%) of the patients were male. The vast majority of patients had NTM lung disease (n = 540, 89%). Alcohol consumption was reported at diagnosis in 65 (11.5%) patients. Table 1 shows the population demographic and clinical characteristics.

A favourable outcome was achieved in 517 (84.8%) patients, and 93 (15.2%) had an unfavourable outcome. The median total antibiotic treatment duration was longer in patients with a good outcome than in those with a bad outcome (376 vs. 167 days; $p < 0.001$). The (crude) odds ratio (OR) for a bad outcome among the individuals who declared alcohol consumption was almost 3.5 times the same odds for those that declared they did not drink (95% CI:1.91–6.21, $p < 0.001$).

The final multiple logistic regression model revealed that alcohol consumption was associated with bad outcome (OR 2.01, 95% CI:1.05–3.87, $p < 0.001$). This effect was adjusted for history of COPD (OR 2.38, 95%CI: 1.22–4.63 $p = 0.011$) and other co-morbidities (OR 3.29, 95%CI: 1.26–8.61 $p = 0.015$), cancer (OR 4.47, 95%CI: 1.86–10.72, $p = 0.001$), having at least one previous treatment (OR 1.86, 95%CI: 1.01–3.43 $p = 0.023$) and HIV-infection (OR 2.09, 95%CI: 1.2–3.97 $p = 0.001$). Female gender was identified as a statistically significant protective factor (OR 0.45, 95%CI: 0.24–0.84 $p = 0.001$). Fig. 1 represents the Crude OR and Adjusted OR for a bad outcome of NTM disease.

Our results showed that alcohol consumption doubled the odds for a bad outcome, after adjustment for COPD and other comorbidities, cancer, at least one previous treatment, HIV-infection and gender. Among all these confounders, only the female gender was significantly identified as a protective factor.

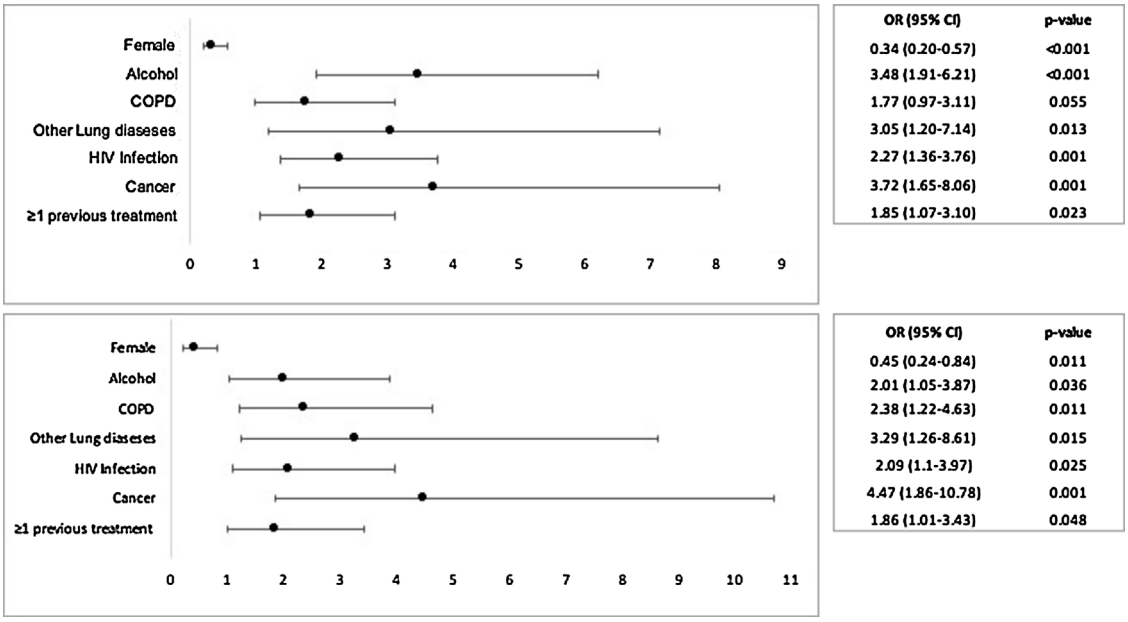

Fig. 1 Forest Plot representation of the crude odds ratios (above) and adjusted odds ratios (below) for a bad outcome of NTM disease.

The ATS/IDSA provides guidelines for the prevention, diagnosis and treatment of NTM infections.[2] In the case of NTM disease—in which immediate symptomatic benefits are not always obvious, and treatments can be long and toxic—compliance with therapy is often low. In every patient, the decision to treat NTM disease involves balancing the benefits and the risks of drug toxicity,[4] and it is essential to manage the patient's underlying diseases, such as alcohol dependence, COPD or cancer.

For this study, we relied on self-reported alcohol consumption at diagnosis, which might be the main limitation, as it may not reflect the drinking pattern over the time of the treatment. Other limitations include its retrospective nature, possible incomplete data from the nationwide forms and overestimation of unfavourable outcomes (older patients, more likely to be male, to have alcohol consumption or several comorbidities).

In conclusion, this study supports the hypothesis that alcoholism influences the prognosis of NTM disease. After adjustment for potential risk factors, alcohol consumption was estimated to double the odds of an unsuccessful outcome, underlining the need for close monitoring among patients with alcohol dependencies to improve treatment outcomes.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgment

Rita Gaio was partially supported by CMUP (UID/MAT/00144/2013), which is funded by FCT (Portugal) with national (MEC) and European structural funds (FEDER), under the partnership agreement PT2020.

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29 June 2019

https://doi.org/10.1016/j.pulmoe.2019.08.005
2531-0437/

Immunotherapy rechallenge in patients with non-small-cell lung cancer

Immunotherapy is an effective treatment option for patients with non-small-cell lung cancer (NSCLC) with advanced disease. Several immune checkpoint inhibitors (ICI) have significantly improved survival of patients with NSCLC.[1] The safety profile of immunotherapy differs from the known safety profile of chemotherapy and includes immune-related adverse events (irAEs) such as fatigue, rash, pruritus, diarrhea and arthralgia, occurring in >20% of patients.[2] A recent meta-analysis reported all-grade immune-related lung toxicity (pneumonitis) in 4.1% of patients with NSCLC treated with ICIs, which was reported as grade $\geq$3 in 1.8% of patients.[3] In daily practice, it is important to know whether it is possible to rechallenge a patient with NSCLC with the same PD-1 inhibitor after resolution of an irAE to be able to continue providing clinical benefit.

Case presentation

We report the case of a 63-year-old female patient diagnosed in December 2014 with NSCLC (cT2N2M0), localized at the right upper lobe. She received neoadjuvant chemoradiotherapy with intravenous cisplatin 75 mg/m^2 plus vinorelbine 25 mg/m^2 on days 1 and 8 in 3-week cycles and 60 Gy (in 2 Gy per fraction) from January 2015 until April 2015. After completing 2 cycles she was not a candidate for surgery due to the persistence of N2 (evaluated by Endobronchial Ultrasonography [EBUS]), so she continued with 2 more cycles of chemoradiotherapy until May 2015. In January 2016, the patient showed disease progression in the lung (Fig. 1A), so she started a second-line of treatment with nivolumab (3 mg/kg intravenously every 14 days) attaining a partial response in March 2016 after 4 treatment cycles. In April 2016, the patient was admitted with grade 3 fever and increased dyspnea that occurred even on minimal exertion. These symptoms had been ongoing for 2 weeks before being admitted to the hospital. An X-ray was performed, showing bilateral dispersed alveolar opacities (Fig. 1B). The main differential diagnoses were infection, immune-related toxicity, radiation-induced pneumonitis, and disease progression. Thoracic computed tomography (CT) (Fig. 2A), bronchoscopy with bronchoalveolar lavage (BAL) and bronchoalveolar aspirate (BAS) were performed to ensure the correct diagnosis. Negative bacterial cultures ruled out the possibility of infection and cytology did not show malignant cells. Although late radiation pneumonitis was difficult to exclude, the time elapsed between the end of the radiotherapy treatment and the beginning of the symptoms suggested an immunerelated pneumonitis. Moreover, irradiated lungs are more susceptible to develop pneumonitis when treated with ICI. The patient was diagnosed with a grade 3 immune-related pneumonitis and the PD-1 inhibitor had to be permanently stopped, despite having attained a partial response. Pneumonitis was treated with high doses of corticosteroids (methylprednisolone 1 mg/kg/day) followed by tapering. Patient symptoms improved after 1 week of corticosteroid treatment, with complete clinical and radiological recovery after 11 weeks of treatment (Fig. 2B). On May 2017, during a follow-up visit, a thoracic CT scan showed disease progression. Considering the patient's previous response to immunotherapy, including 14 months of stable disease after stopping treatment, nivolumab rechallenge was proposed as a treatment option despite the toxicity reported. To avoid new irAEs, nivolumab (3 mg/kg intravenously every 14 days) was reinitiated along with low dose corticosteroids (methylprednisolone 8 mg/day). After four cycles, the patient achieved a partial response in the lung tumor with no further lung toxicity.

Discussion

Immunotherapy-related lung toxicity is rare but can be life-threatening.[2] The clinical presentation of pneumonitis usually consists of non-specific symptoms. However, it is essential to consider pneumonitis among the differential diagnoses in patients receiving treatment with PD-1 or PD-L1 inhibitors, before the respiratory function worsens.[3] To correctly diagnose pneumonitis, a bronchoscopy must be performed to rule out other etiologies, such as infection. The main treatment for the irAE of pneumonia is the administration of high doses of corticosteroids (1–1.5 mg/kg) with subsequent tapering when symptoms and radiological imaging show improvement.[4] Moreover, according to the evidence described in the literature,[4,5] permanent cessation of immunotherapy is the standard procedure in a patient experiencing a grade 3–4 irAE. However, clinicians should always consider the potential loss of clinical benefit for patients