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Â.D. Cunha[a,*], N. Melo[b], S. Guimarães[c], C.S. Moura[c], J.M. Pereira[d], A. Morais[b,e,f]

[a] *Pulmonology Department, Centro Hospitalar Tondela-Viseu, Viseu, Portugal*
[b] *Pulmonology Department, Centro Hospitalar São João, Porto, Portugal*
[c] *Pathology Department, Centro Hospitalar São João, Porto, Portugal*
[d] *Radiology Department, Centro Hospitalar São João, Porto, Portugal*
[e] *Faculdade de Medicina do Porto, University of Porto, Portugal*
[f] *Institute for Research and Innovation in Health (I3S), University of Porto, Portugal*

* Corresponding author.
E-mail address: 6979@hstviseu.min-saude.pt (Â.D. Cunha).

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Miliary tuberculosis in a rheumatoid arthritis patient receiving long-term tumor necrosis factor monoclonal antibody therapy

Dear Editor,

A 51-year-old woman had a diagnosis of seropositive rheumatoid arthritis (RA) with polyarthritis involving bilateral elbow, small joints of hand and knee areas on March 12, 2004. Owing to refractory therapeutic responses with a DAS28 score of 6.16 under methotrexate 15 mg/week, hydroxychloroquine 400 mg/day and prednisolone 10 mg/day, she started to receive regular biweekly 40 mg subcutaneous injection of adalimumab, a tumor necrosis factor (TNF) monoclonal antibody (mAb) since June 17, 2011. She had no history of lung diseases with a clear chest X-ray (Fig. 1A). There was a negative QuantiFERON test before initiating anti-TNF therapy. She had reduced disease activity after treatment without further prescription of hydroxychloroquine and prednisolone. Owing to productive cough with intermittent fever and weight loss for 3 weeks, the use of TNF mAb was discontinued on February 20, 2018, 80 months after initiating such a treatment. However, she did not receive follow-up QuantiFERON test during her long-term anti-TNF therapy. Chest images including X-ray (Fig. 1B) and computed tomography (Fig. 1C) showed bilateral diffuse miliary lesions characterized by innumerable micronodular opacities. She had no exposure to fine mineral or chemical dust, and her malignancy survey and human immunodeficiency virus examination were negative results. Sputum cultures were positive for *Mycobacterium tuberculosis*. There was no recent household tuberculosis (TB) contact history. She received anti-TB medications with daily dosages of rifampicin 480 mg, isoniazid 320 mg, pyrazinamide 1000 mg and ethambutol 800 mg for 9 months from April 12, 2018 (drug-susceptibility testing in TB with resistance to streptomycin and sensitive to others). After antibiotic therapy, there were no more respiratory or constitutional symptoms, negative sputum culture results and resolved pulmonary miliary nodules (Fig. 1 D). For her arthritis flare-up after discontinuing TNF mAb injection, rituximab, a B-cell depleting mAb, under a regimen of 1 g × two fortnightly infusions every 6 months was initiated on February 7, 2020 with improved disease activity (DAS 28 score 5.34 to 2.70) after 4 infusions at the end of 2020.

Miliary TB, a rare fatal presentation of mycobacterial infection, can occur in the presence of impaired host immunity under the prescription of immunosuppressive agents.[1,2] TNF blocker administration has been recognized as a risk for TB reactivation in various autoimmune-mediated inflammatory disorders,[3] especially when anti-TNF treatment is combined with the use of immunosuppressive agents like methotrexate.[4] Greater incidences are found during the first year of treatment than afterwards, while there are higher occurrences with mAb than with recombinant soluble receptor fusion protein therapy. Despite an additional risk of having been born in an area of endemic TB,[5] the reported case raises a potential infection hazard under the long-term TNF mAb treatment.

In conclusion, we reported miliary TB in a RA patient receiving long-period TNF blocker therapy. In addition to the initial QuantiFERON survey, periodic latent TB testing should be carried out in patients receiving the long-term immunosuppressive agents like TNF monoclonal antibodies.

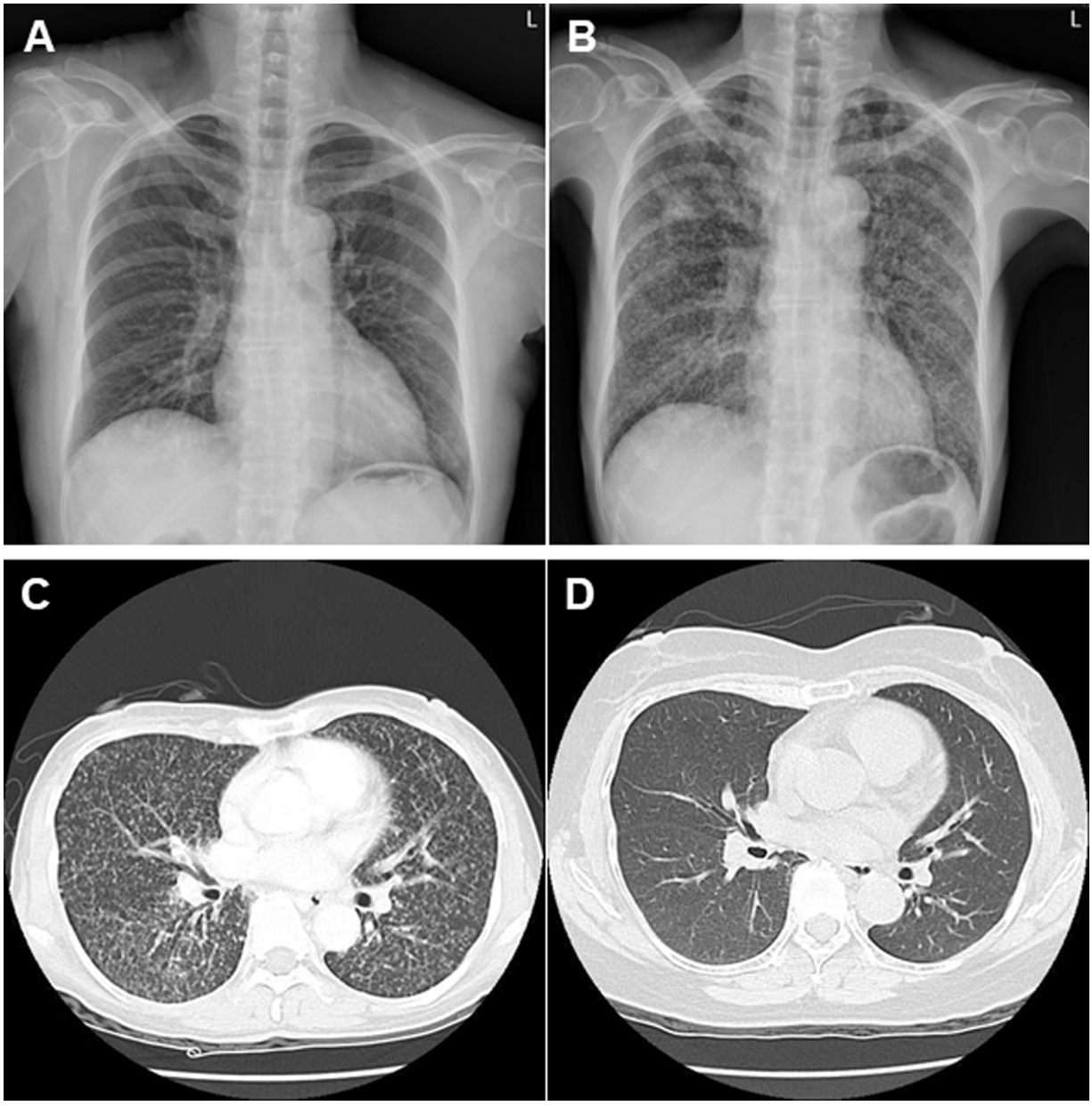

Figure 1 Clinical images of miliary TB in a RA patient receiving TNF mAb therapy. (A). A clear chest X-ray without any lung lesions before starting TNF mAb therapy. (B). Bilateral diffuse military lesions on chest X-ray after TNF mAb therapy. (C). Bilateral innumerable micronodular opacities on chest computed tomography after TNF mAb therapy. (D). Resolved bilateral military nodules on chest computed tomography after anti-TB treatment.

Author contributions

Study conception and design: Chrong-Reen Wang.

Data analysis and acquisition: Chrong-Reen Wang, Wei-Chieh Lin, Yi-Shan Tsai.

Drafting of the manuscript: Chrong-Reen Wang.

All authors had access to the data and played a role in writing this manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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C.-R. Wang[a,*], W.-C. Lin[a], Y.-S. Tsai[b]

[a] *Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*
[b] *Department of Medical Imaging, National Cheng Kung University Hospital, Tainan, Taiwan*

* Corresponding author at: Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Road, Tainan 70403, Taiwan.
E-mail address: wangcr@mail.ncku.edu.tw (C.-R. Wang).
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International predictive equations of maximum respiratory mouth pressures: Are they suitable for the Portuguese adult population?

Dear Editor,

Predictive equations of maximum inspiratory (Pimax) and expiratory (Pemax) pressures are important for detecting respiratory muscle weakness. A recent systematic review identified 42 Pimax and 34 Pemax equations as available for healthy adults, but to date no single equation has been recommended.[1] This is problematic as it is known that the presence or absence of respiratory muscle weakness is critically dependent on the equation selected.[1] Predictive equations should be population-specific and none of the identified equations have been developed in Portugal.[2] Portuguese people present specific characteristics, for example they tend to be shorter than people of most other European countries,[3] which may affect how these equations are applied. In the current absence of an equation developed for Portugal, healthcare professionals need short-term guidance on which equations are more appropriate to use. Thus, we explored the suitability of the available predictive equations in a sample of healthy Portuguese adults.

A cross-sectional study, approved by the Ethics Committee of the University of Aveiro (8/2015), was conducted with healthy Portuguese adults recruited from the community. All participants signed an informed consent. Sociodemographic, anthropometric and clinical data were collected to characterise the sample. Respiratory muscle testing followed the European Respiratory Society guidelines[1] (MicroRPM, Carefusion, Basingstoke, UK). Descriptive statistics, Wilcoxon signed-rank tests, Bland-Altman plots and Spearman correlation coefficients were used to characterise the sample, test differences between real and predicted values and ascertain the absolute reliability and concurrent validity, respectively. The lower limit of normality (LLN) was computed as: mean $-$ 1.645 $\times$ standard deviation.[4]

A total of 229 Caucasian individuals (n = 141, 61.6% men) were included. Participants' characteristics are detailed in Table 1.

Thirty-six Pimax and 29 Pemax equations were tested (Fig. 1). Nine equations could not be tested either because some variables were not collected (e.g., waist circumference and vital capacity) or due to lack of information provided by authors (e.g., constant of the equation).

The Pimax predicted values were significantly different from the real values obtained ($p < 0.05$), except for the equations for men developed by Enright et al. (1995),[5] Hautmann et al. (2000)[6] and Sachs et al. (2009),[7] and for women developed by Neder et al. (1999).[8] Values obtained with these equations were amongst the ones with higher correlations (r_s = 0.32–0.47) and lower bias (0.19–4.06) with the actual data (Fig. 1 and supplementary material – Appendix A).

Twelve equations underestimated the real values and 4 equations overestimated the real values for men. The same pattern was found for women, with 15 equations underestimating and 3 equations overestimating the real values.

Regarding Pemax, all equations showed significant differences between real and predicted values ($p < 0.001$), with most equations (n = 10) underestimating the real values for both genders (Fig. 1).

LLN of Pimax resulted in a cut-off of 43.7 cmH_2O for women and 50 cmH_2O for men. The predicted values from all equations were above the LLN, hence not detecting inspiratory muscle weakness according to the LLN.

This study showed that all equations performed poorly, with none of the equations being suitable for detecting people below the LLN.

Nevertheless, of all equations for Pimax, 4 showed no significant differences between predicted and real values: 3 for men[5–7] and 1 for women.[8] Regarding men, the best agreement was found for the equation developed by Sachs et al.[7] This might be explained by the similar equipment and protocol used (e.g., handling of subjects). In fact, almost half of the equations were developed with a lack of compliance with the guidelines,[2] which might explain the disagreement with the real values in this study. Additionally, intrinsic fac-