Tuberculosis after a borderline QuantiFERON result during screening before infliximab

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Key Words:	Monoclonal Antibodies, Infliximab, Latent Tuberculosis, Tuberculosis, Interferon-gamma Release Tests

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our reference ERJ-00913-2018
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subject Resubmission original manuscript

to The Editors of
European Respiratory Journal

Dear Prof. G.B. Migliori, Prof. M. Kolb and Prof. J. Chalmers,

Thank you very much for your email of May 30 with the invitation to revise manuscript ERJ-00913-2018. We also thank the reviewers for the critical and useful comments and suggestions, which we have used for the revision as indicated point by point.

We hereby submit the revised versions of the manuscript entitled 'Tuberculosis after a borderline QuantiFERON result during screening before infliximab', one in which all changes are in red and one without.

With kind regards,

Jonathan W. Uzorka

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4. Tuberculosis Reference Laboratory, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

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Summary: Development of tuberculosis after a borderline QuantiFERON result during screening before TNF-α antagonist therapy

To the Editor:

Patients who are eligible for treatment with immunosuppressive drugs such as antagonists of tumour necrosis factor-α (TNF-α) must be screened for latent tuberculosis infection (LTBI), as stated in the recent European Standards for TB Care [1]. Although there are controversies regarding optimal screening [2], interferon gamma release assays (IGRA) such as QuantiFERON-TB Gold (QFT) are nowadays frequently used. The formal cut-off for a positive QFT is ≥ 0.35 IU/mL interferon-γ. However, a recent study published in *European Respiratory Journal* found that a significant proportion of results just below this cut-off, so called 'borderline results', represented true infection with *Mycobacterium tuberculosis* (*Mtb)* [3]. We present a patient who clearly illustrates the clinical significance of borderline QFT results in patients screened before immunosuppression.

December 2017, a 33-year-old woman who was 33 weeks pregnant presented to Leiden University Medical Center with headache, spiking fever and night sweats since three weeks. She was born in Morocco and had moved to The Netherlands in 2003. She had ulcerative colitis for which she was treated with low dose prednisone, mesalazine and infliximab once per six weeks, the latter since June 2017. The temperature was 39.0 °C, but physical examination revealed no other abnormalities, in particular no neurological signs. Laboratory data showed a C-reactive protein of 56 mg/L (normal value: <10 mg/L) and a normal white-cell count. A chest radiograph (CXR) showed hilar lymphadenopathy and a diffuse nodular pattern, suspect of miliary TB. Computed Tomography imaging of the brain showed no signs of cerebral TB and cerebrospinal fluid was without abnormalities. Standard quadruple TB therapy was immediately started. The QFT result was positive (TB1: 5.37 IU/mL, TB2: 5.55 IU/mL). The clinical course is shown in Figure 1. Auramine staining and polymerase chain reaction for *Mtb* on gastric lavage fluid and sputum were positive. MGIT cultures of gastric

lavage fluid and sputum cultures became positive for *Mtb* after 15 days. Susceptibility testing later showed full susceptibility.

The pre anti-TNF screening was reviewed. Five months prior to admission she had been screened for LTBI in a local hospital, when she was not yet using any immunosuppressive therapy. The patient was BCG-vaccinated and had reported contact with a relative with active TB 20 years earlier. She had visited Morocco several times since 2003. Her tuberculin skin test result was 10 mm induration, which appeared to be overlooked by the attending physician, and QFT test result was negative (TB1: 0.11 IU/mL, TB2: 0.22 IU/mL). Because of the pregnancy, no CXR had been performed at that time. Thus no preventive therapy was started. The original colon biopsies were reviewed, but no granulomas were found.

During TB treatment, mesalazine and prednisone were continued, but infliximab therapy was withheld. The patient had a favourable clinical response and 20 days later gave birth to a healthy daughter without signs of congenital TB and negative histology of the placenta. The new-born was given isoniazide preventive therapy which was discontinued after the tuberculin skin test was negative three months later. Variable-Number Tandem Repeat (VNTR) typing of the patient's *Mtb* isolate was performed by the National Institute for Public Health and the Environment (RIVM), showing a unique VNTR number (9007047) which strongly argues in favour of exposure abroad.

This patient who developed miliary TB during pregnancy and after starting infliximab, preceded by a negative QFT result in the borderline range, illustrates the clinical relevance of a borderline QFT in this setting. Infliximab is a monoclonal antibody directed against TNF-α. TNF-α plays a major role in recruitment and organisation of mononuclear cells into well-structured granulomas. Anti-TNF therapy can result in disintegration of granulomas and reactivation TB [4]. However, this cannot be extrapolated directly to biologicals with a different mechanism of action and some, such as rituximab, are even considered safe in this

regard [5]. Yet, even in the screening era the risk has remained increased, probably reflecting suboptimal performance of diagnostic tests for LTBI in this setting [6]. In our patient the positive TST screening result was unfortunately overlooked. Of note, the effect of BCG vaccination, if given before one year of age, on the TST is negligible beyond ten years after vaccination [7]. Thus, the TST should have been qualified as true positive anyway, which was strengthened by the self-reported TB contact. According to the manufacturer's cut-off, her QFT screening result of 0.22 IU/mL was indeed negative. This low value can be explained by the decreased sensitivity of QFT for detection of a remote *Mtb* infection [8]. However, recent studies showed that a result just below the cut-off includes patients with true *Mtb* infection [3, 9] and additional data support and extend this notion (manuscript in press). One retrospective study showed that individuals with a borderline QFT result (defined as 0.20 to 0.34 IU/mL) developed active TB significantly more often compared to those with a negative result [10]. However, further research is needed to corroborate our observation, e.g. by retrospective analysis of quantitative QFT results in all patients who developed active TB despite screening. In our opinion, until more data are available, lowering the QFT cut-off should be limited to patients who will receive significant immunosuppression and should not be applied in normal or low risk settings.

This case emphasizes the value of TST irrespective of BCG-vaccination and shows that a borderline QFT result in a patient screened before immunosuppression should be considered as a risk factor for reactivation TB. In this setting, a borderline QFT result with or without any other risk factor, be it origin, known exposure, past or present positive TST result and/or suggestive abnormalities on CXR, in our opinion justifies preventive therapy.

References

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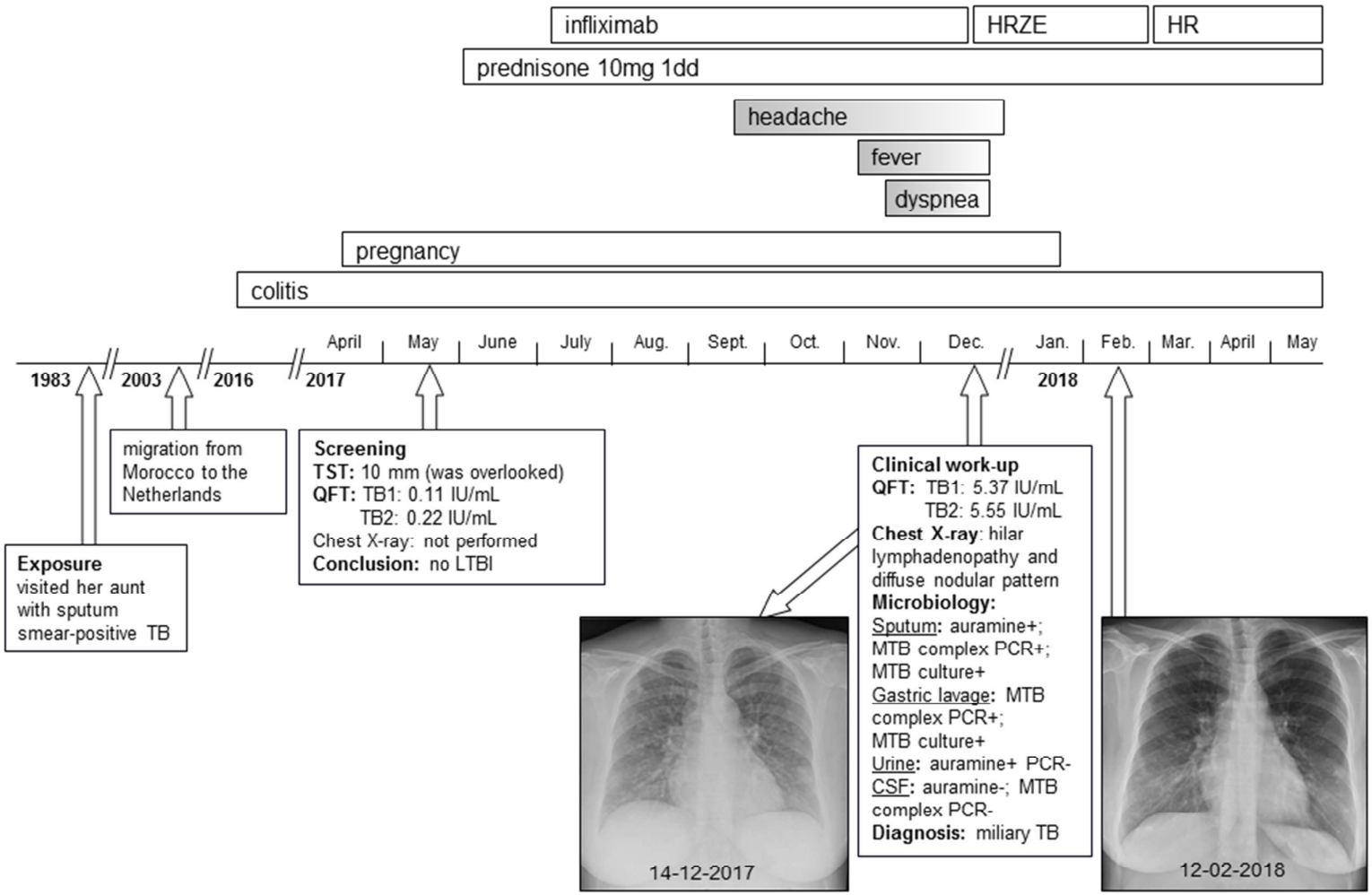
Legends

Figure 1. Time line of the clinical course

Abbreviations used: CSF: cerebrospinal fluid; HRZE: H= isoniazide, R=rifampicin, Z=pyrazinamide, E=ethambutol; LTBI: latent tuberculosis infection; MTB: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; QFT: QuantiFERON-TB Gold Plus; TB: tuberculosis; TST: tuberculin skin test;

Figure 1


infliximab
HRZE
HR
prednisone 10mg 1dd
headache
fever
dyspnea
pregnancy
colitis
April
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Aug.
Sept.
Oct.
Nov.
Dec.
Jan.
Feb.
Mar.
April
May
1983
2003
2016
2017
2018
Exposure
visited her aunt with sputum smear-positive TB
migration from Morocco to the Netherlands
Screening
TST: 10 mm (was overlooked)
QFT: TB1: 0.11 IU/mL
TB2: 0.22 IU/mL
Chest X-ray: not performed
Conclusion: no LTBI
Clinical work-up
QFT: TB1: 5.37 IU/mL
TB2: 5.55 IU/mL
Chest X-ray: hilar lymphadenopathy and diffuse nodular pattern
Microbiology:
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Gastric lavage: MTB complex PCR+; MTB culture+
Urine: auramine+ PCR-
CSF: auramine-; MTB complex PCR-
Diagnosis: miliary TB
14-12-2017
12-02-2018

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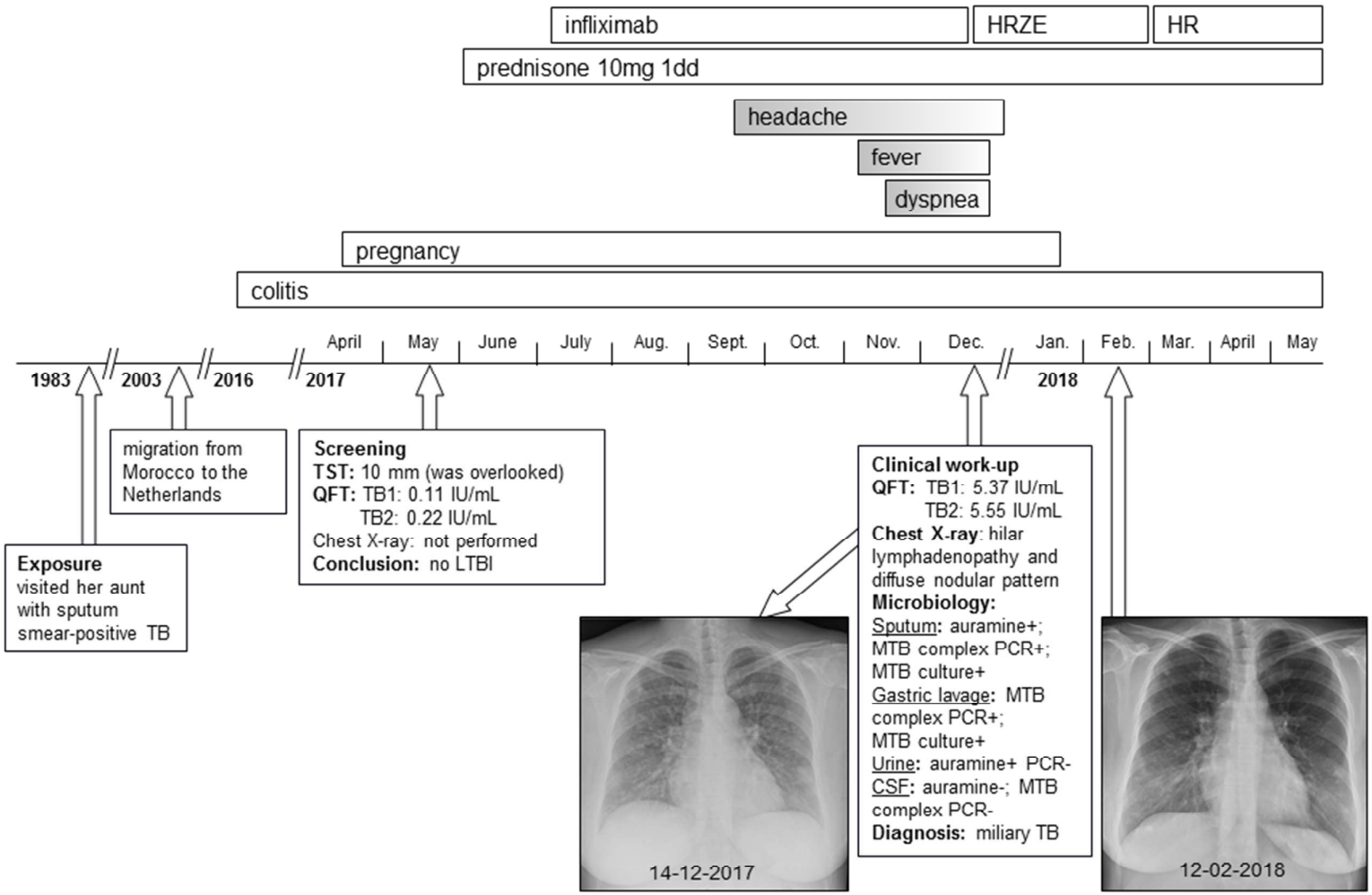
infliximab
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prednisone 10mg 1dd
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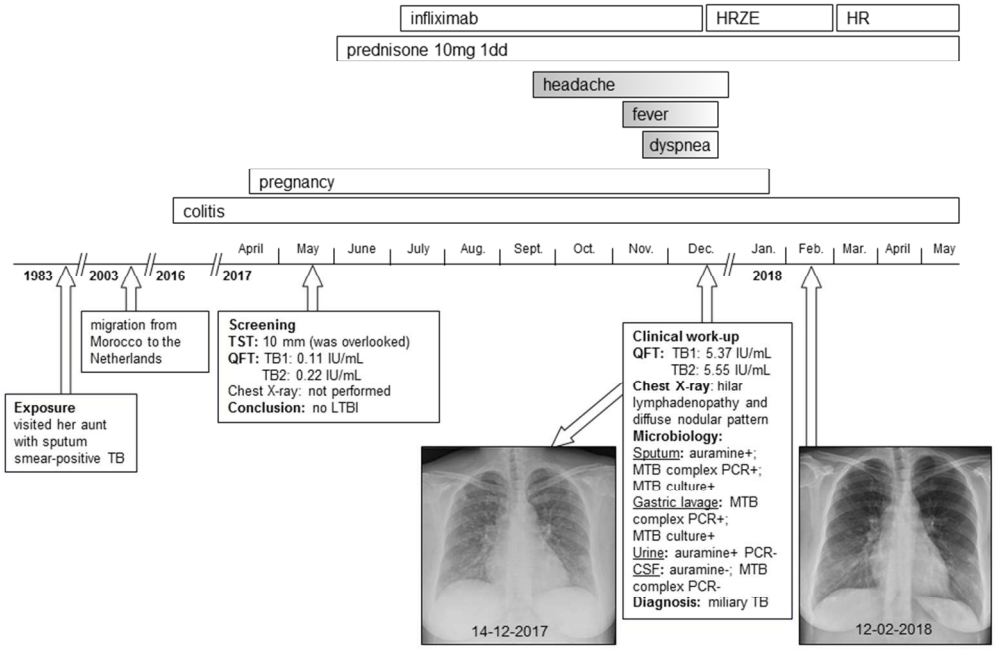

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