

**Occupational Tuberculosis Despite Minimal Nosocomial Contact in a Healthcare Worker
Undergoing Treatment with a Tumor Necrosis Factor Inhibitor**

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A 37-year-old woman presented with abrupt onset of wheeze and fever. The patient, who is a health care worker, was undergoing treatment for ankylosing spondylitis with the anti-tumor necrosis factor inhibiting (anti-TNF) agent, Etanercept. Eight years previously, after returning from voluntary healthcare work in Africa, she had received 6-months standard treatment for drug-sensitive tuberculosis (TB). Blood testing for HIV was negative. A chest radiograph showed right upper lobe consolidation prompting antibiotic treatment for community-acquired pneumonia.

A sputum sample tested positive using the Xpert MTB/RIF (Cepheid, USA) molecular test for *Mycobacterium tuberculosis* and negative for genotypic rifampicin resistance. Antibiotics were stopped and anti-TB treatment with rifampicin, isoniazid, ethambutol and pyrazinamide was commenced. Drug sensitive *M. tuberculosis* was isolated after 14 days growth in liquid culture (Bactec MGIT™960, Becton Dickinson).

MIRU-VNTR (Mycobacterial Interspersed Repeat Unit-Variable Number Tandem Repeat) genotyping was performed which identified an isolate differing in 9 loci compared to her previous isolate, thereby excluding reactivation of previous TB (Figure 1a). However, it matched a unique isolate in the National Mycobacterial Reference Laboratory database identified 2-years previously in a person living with HIV (index patient) diagnosed with smear-positive drug-sensitive pulmonary TB. Whole genome sequencing (WGS), using the Illumina HiSeq platform, confirmed the findings of the typing with 1 single nucleotide polymorphism (SNP) difference between the isolate from the index patient and the isolate from our patient, refuting any link with the our patient's previous *M. tuberculosis* isolate which differed by 422 SNPs (Figure 1b).

At the time of diagnosis, the index patient had been admitted to an open bay on the general Infectious Diseases ward. On the day of admission, a sputum sample was positive by smear microscopy for acid fast bacilli (smear-grade 1+). Respiratory infection control practices were instituted immediately, including confinement of the patient in a negative pressure isolation room, which was monitored daily to ensure appropriate air-flow, and use of FFP3-masks for prolonged patient contact. Extensive investigation was undertaken to assess exposure to staff, patients and contacts and adherence to infection control procedures.

During the hospitalization of the index patient, our patient had worked in the hospital and on the Infectious Diseases ward in a largely managerial role. Our patient was not involved in routine day-to-day patient care. There was no reported face-to-face contact between our patient and the index patient prior to, or after, patient isolation. Reviewing shift patterns and work diaries, the temporal overlap between the two cases on the same ward was minimal and estimated to be less than 30 minutes. Furthermore, at the time of the presumed exposure, our patient was on a 6-month break from Etanercept and was not receiving any other immunosuppressing agents. Etanercept was re-commenced in the weeks following this exposure and continued until our patient's second TB presentation.

No other health care worker developed active TB and there were no Tuberculin Skin Testing (TST)/Interferon Gamma-Release Assay (IGRA) conversions to suggest transmission to other health care workers or social contacts at the hospital.

Discussion

Nosocomial transmission of TB has been well-documented in seminal experiments conducted by Riley and colleagues in 1950s, where guinea pigs in air ventilation ducts from a TB ward were frequently infected (1). Health care workers are often affected and are routinely identified by epidemiological surveys as being at higher risk for TB, even in low-incidence settings (2, 3). Infection control measures to reduce occupational TB transmission in the UK are only partially effective, and consequently, health care workers remain at increased risk (4).

There are scant data on the occupational risk of TB in health care workers receiving anti-TNF therapy. However these drugs are known increase the relative risk of TB up to 25-fold in the general population (5). They are often used as disease modifiers in rheumatological and other inflammatory disorders, and are frequently introduced early in the clinical pathway. Etanercept has been shown to be least likely of the most commonly used TNF inhibitors to cause TB (6, 7).

The Joint Tuberculosis Committee of the British Thoracic Society provides guidance to reduce the risk of TB in patients commencing anti-TNF therapies (8). They recommended that active TB should be excluded, or treated for at least 2 months, prior to commencing anti-TNF treatment. Patients with latent TB, including HCWs, should be offered chemoprophylaxis where the risk of TB exceeds that of drug-induced hepatitis. They propose that patients such as our health care worker, with a history of previous adequately treated TB, should be monitored clinically every 3 months during anti-TNF therapy; those with respiratory symptoms should have a chest radiograph and sputum examination for TB.

Given the increased risk of TB during anti-TNF therapy, occupational restrictions on health care workers are sensible, though there is little evidence on which to base what may be career-limiting decisions. Prior to the advent of molecular typing, occupational transmission events were frequently misclassified using routine epidemiological investigations. One study of presumed occupationally acquired TB in Denmark, a low TB burden country, indicated that one third of reported cases were in fact 'unlikely' on the basis of Restriction Fragment Length Polymorphism (RFLP) and/or MIRU typing (9). WGS offers unrivalled resolution to confirm or refute transmission events with greater discrimination than MIRU-VNTR, and can identify missing links in chains of transmission even where people in the chain remain unknown (10). WGS may also be able to demonstrate "directionality" of transmission given the biological rarity of backward mutations. However, WGS is currently limited by the lack of national and international databases of TB isolates.

The minimal contact between the index patient and our patient that led to transmission in this case, despite standards of infection control expected in a specialist Infectious Diseases unit in a high-income country, highlights the difficulty in protecting immunocompromised health care workers. In resource-limited settings, the occupational risk to health care workers of TB is greater and TB infection control measures are more challenging (11).

The risk is compounded in areas of high rates of HIV co-infection. A case-control study of health care workers in South Africa, where HIV prevalence is 17%, identified HIV as conferring a greater than 6-fold risk of occupational TB compared to non-HIV infected health care workers (12). The poor outcomes for health care workers occupationally-infected with drug-resistant TB raise further ethical issues surrounding the socio-political aspects of infection control and

highlight the responsibility of the state to protect and support those health care workers who place themselves at risk in the line-of-duty. The extension of TB care to community and home-based settings is likely to further complicate infection control procedures.

This case highlights the risk of occupational TB transmission in a health care worker receiving anti-TNF therapy after minimal exposure, despite adherence to reasonable infection control precautions in a resource rich setting. Further data are required to quantify the occupational risk of TB in health care workers receiving anti-TNF therapies and so provide the evidence for sensible and safe infection control policies.

References

1. Riley RL, Mills CC, Nyka W, Weinstock N, Storey PB, Sultan LU, et al. Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. 1959. *Am J Epidemiol.* 1995;142(1):3-14.
2. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. *Emerging infectious diseases.* 2011;17(3):488-94.
3. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2007;11(6):593-605.
4. Meredith S, Watson JM, Citron KM, Cockcroft A, Darbyshire JH. Are healthcare workers in England and Wales at increased risk of tuberculosis? *Bmj.* 1996;313(7056):522-5.
5. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *The European respiratory journal.* 2010;36(5):1185-206.
6. Ai JW, Zhang S, Ruan QL, Yu YQ, Zhang BY, Liu QH, et al. The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-alpha Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies. *J Rheumatol.* 2015;42(12):2229-37.
7. Cantini F, Niccoli L, Goletti D. Adalimumab, etanercept, infliximab, and the risk of tuberculosis: data from clinical trials, national registries, and postmarketing surveillance. *J Rheumatol Suppl.* 2014;91:47-55.
8. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax.* 2005;60(10):800-5.
9. Pedersen MK, Andersen AB, Andersen PH, Svensson E, Jensen SG, Lillebaek T. Occupational Tuberculosis in Denmark through 21 Years Analysed by Nationwide Genotyping. *PloS one.* 2016;11(4):e0153668.
10. Walker TM, Kohl TA, Omar SV, Hedge J, Del Ojo Elias C, Bradley P, et al. Whole-genome sequencing for prediction of Mycobacterium tuberculosis drug susceptibility and resistance: a retrospective cohort study. *The Lancet infectious diseases.* 2015;15(10):1193-202.
11. Verkuil S, Middelkoop K. Protecting Our Front-liners: Occupational Tuberculosis Prevention Through Infection Control Strategies. *Clin Infect Dis.* 2016;62 Suppl 3:S231-7.
12. Tudor C, Van der Walt ML, Margot B, Dorman SE, Pan WK, Yenokyan G, et al. Occupational Risk Factors for Tuberculosis Among Healthcare Workers in KwaZulu-Natal, South Africa. *Clin Infect Dis.* 2016;62 Suppl 3:S255-61.

Figure Legends

Figure 1: (a) MIRU-VNTR typing healthcare worker (HCW) and patient living with HIV (PLWH) *Mycobacterium tuberculosis* isolates compared to HCW previous historical isolate; differences highlighted in grey. **(b)** Representation of *Mycobacterium tuberculosis* isolates identified by whole genome sequencing generated using PopART (Population Analysis with Reticulate Trees), New Zealand; purple circles represent patient and HCW TB isolates, numbers in brackets show single nucleotides variations (SNPs) between isolates, supporting transmission between PLWH and HCW with isolates (1 SNP) and distinct from HCW workers previous episode (422 SNPs)

1a

Isolate	MIRU-VNTR typing																							
PLWH	2	1	4	3	3	2	4	2	2	6	1	6	3	2	1	4	3	4	4	1	5	2	-	2
HCW	2	1	4	3	3	2	4	2	2	6	1	6	3	2	1	4	3	4	4	1	5	2	7	2
HCW (2006)	2	2	2	3	5	2	4	2	2	6	-	4	3	2	3	4	3	4	4	2	1	1	3	2

1b

