Skin infection with *Mycobacterium szulgai*: complex, complicated but successful treatment

JE Horsley Downie[1], H Davidson[2], F.Charlton[3], A Robb[4], S Kanagasundaram[5], E Hunter[1]

1. Dept. of Infection and Tropical Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) – ewan.hunter@nuth.nhs.uk
2. Clinical Pharmacy Directorate, NUTH
3. Cellular Pathology, NUTH
4. Microbiology, NUTH
5. Renal Service Directorate, NUTH

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Presentation

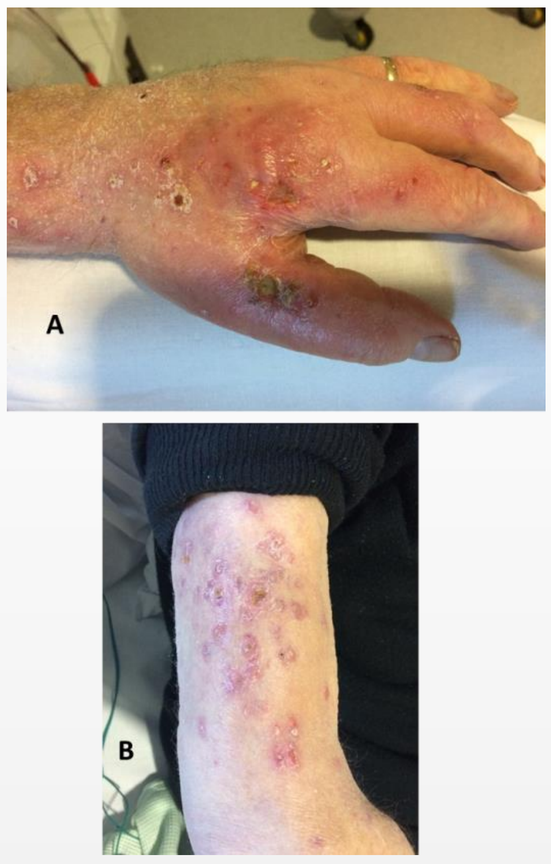
A 56 year old man was referred to dermatology with pruritic skin lesions affecting the dorsum of both hands and upper arms. He had first noticed similar lesions during a prolonged ITU admission with urinary sepsis 5 months previously.

Other medical history:

- haemodialysis-dependent secondary to reflux nephropathy
- two previous renal transplants in 1993 and 2002
- long term iatrogenic immunosuppression with prednisolone, tacrolimus and azathioprine
- metallic aortic and mitral valve replacements necessitating warfarin therapy
- peripheral vascular disease
- HIV negative

At the time of initial referral he was taking tacrolimus and prednisolone 10mg daily. A pustular, nodular eruption over the dorsum of both hands and upper arms was noted (**Figure 1**), with ongoing development of subdermal nodules which subsequently ulcerated. An infective dermatitis was suspected, tacrolimus therapy was stopped and a skin biopsy from the left arm was sent for histopathology and microbiology investigations.

Figure 1: Pre-treatment lesions on dorsum of right hand (A) and left upper arm (B)



Investigation and diagnosis

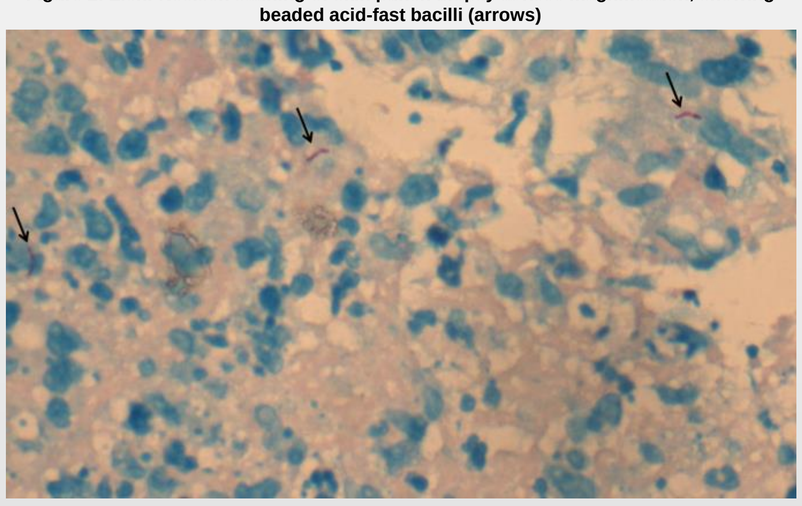
Biopsy showed granulomatous inflammation with occasional elongated, slightly beaded acid fast bacilli, morphologically suggestive of an atypical mycobacterial infection (**Figure 2**).

The biopsy specimen subsequently yielded scanty growth of a mycobacterium. PCR was negative for *M. tuberculosis* and equivocal for *M. chelonae-abscessus*. The National Mycobacterial Reference Service in Birmingham identified *M. szulgai* using whole genome sequencing.

Due to the slow-growing nature of *M. szulgai* full antimicrobial sensitivities were not available until 4 months after the biopsy was taken. In this period the lesions became drier and very few new lesions developed. The patient remained systemically well with no fevers, stable inflammatory markers, and no other evidence of deep-seated or visceral infection.

Isolate sensitivities: amikacin, ethambutol, clarithromycin, linezolid, moxifloxacin, rifampicin.

Figure 2: Ziehl-Neelsen staining of skin punch biopsy at x600 magnification, showing beaded acid-fast bacilli (arrows)



Initial management

Due to dependence on warfarin, corticosteroids and haemodialysis it was felt that rifampicin should be avoided due to potential enzymatic interactions and pharmokinetic unpredictability that might impair efficacy, and an ethambutol –based regimen was selected.

After discussion with his nephrologist and renal pharmacist a schedule of clarithromycin 500mg BD, moxifloxacin 400mg OD and ethambutol 1.2g 4 to 6 hours pre-dialysis three times weekly was started. Weekly ECGs were performed initially due to the risk of QTc prolongation with prolonged macrolide treatment.

The patient was advised that treatment for 1 year or more was likely to be necessary.

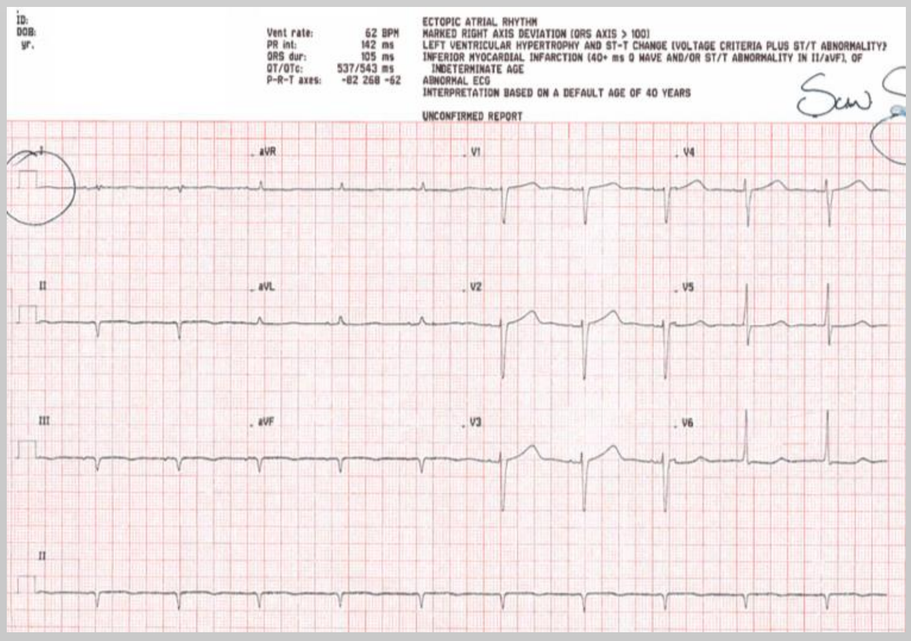
Progress

Three months after starting treatment the existing skin lesions were almost gone with no new lesions appearing. The initial QTc of 410 ms increased to c.470 ms over the first two months and then plateaued. It was considered safe to reduce ECG monitoring to monthly.

At 5 months the patient was admitted to hospital with a ventricular arrhythmia and a QTc of 543 ms (**Figure 3**). His potassium was 6.4 mEq/L. Antibiotics were stopped. ECGs 1-2 months later showed a normal QTc of <430 ms.

Given the good response to treatment and the clinical ambiguity as to the main cause of his arrhythmia, antimicrobials were not restarted and clinical vigilance was maintained for any new signs of skin or disseminated infection. Eight months after stopping therapy he remained well with no new lesions appearing.

Figure 3: Post-arrhythmia ECG showing prolonged QTc of 543 ms.



Discussion

Extrapulmonary infection with *M. szulgai* is rare, usually occurring in the context of immunosuppression. In the Netherlands only 5 cases in 7 years were recorded, of which 3 were successfully treated with non-rifampicin based therapy.[1] The British Thoracic Society has published guidelines on the diagnosis and treatment of pulmonary non-tuberculous mycobacterial infections,[2] but there is currently no consensus for the diagnosis or treatment of extrapulmonary *M. szulgai* infection. The majority of published case reports describe treatment with rifampicin-based therapies with durations of treatment ranging from 4 to 48 months.

In this case avoidance of rifampicin was desirable due to the factors cited. Given the precedent for successful treatment of *M. szulgai* skin infection,[1] a clarithromycin-based regimen was chosen, albeit with an anticipated treatment duration of 1 year or more. As evidenced by the absence of recurrence of lesions 8 months after stopping treatment, a 5 month course, shortened for pragmatic reasons, appears to have been successful. It is difficult to be certain however how much natural control of infection following recovery from sepsis along with a concomitant reduction in iatrogenic immunosuppression may have contributed to his recovery, highlighting the difficulty in judging when systemic treatment of *M. szulgai* and other slow growing, indolent non-tuberculous mycobacterial infections is truly indicated.

This case also highlights the importance of regular ECG monitoring in patients taking long term clarithromycin and moxifloxacin throughout treatment duration.

Finally, given the shortened treatment course, the question of potential prophylaxis in the context of a further renal transplant and associated immunosuppression was raised. Sadly, the patient subsequently died of an unrelated vascular complication before this could be given further consideration.

Conclusions

- *M. szulgai* skin infection in an immunocompromised patient may be successfully treated with 6 months or less of clarithromycin, moxifloxacin and ethambutol
- It is important to continue ECG monitoring for QT-prolongation throughout long term treatment with macrolide antibiotics
- It can be difficult to judge when to treat *M. szulgai* localised infection in an immunosuppressed patient whose immune system is recovering from sepsis and whose immunosuppressant drugs can be suspended/reduced

References

1. Van Ingen J, Boeree MJ, De Lange WCM, De Haas PEW, Dekhuijzen PNR, Van Soolingen D. Clinical Relevance of Mycobacterium szulgai in The Netherlands. *Clinical Infectious Diseases*. 2008;46:1200-1205.

2. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson AF, Leitch A, Loebinger MR, Milburn HJ, Nightingale M, Ormerod P, Shingadia D, Smith D, Whitehead N, Wilson R, Floto RA. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax.* 2017;72:ii1-ii64