Reviewer's report

Title: Multidrug Resistant M. tuberculosis from Multiple Cutaneous Abscesses in a Patient with Polymyositis: Response to treatment

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Reviewer: Hendrik Simon S Schaaf

Reviewer's report:

General
This case report claims to describe the development of miliary tuberculosis and multiple tuberculosis skin abscesses with the further complication of the development of multidrug resistance in a non-HIV-infected but immune compromised patient receiving corticosteroids and methotrexate for polymyositis. (Note that the title page states polymyositis, but the first sentence in the abstract mentions pyomiositis, which are quite different conditions). The authors claim that the organism responsible for the tuberculosis disease starts off as a fully susceptible Mycobacterium tuberculosis isolate that developed resistance, over a period of 6 months despite compliant therapy with a four-drug antituberculosis regimen, not only to the best available first-line drugs that the patient received, but also to an extended spectrum of drugs that the patient did not receive – streptomycin, amikacin, PAS, cycloserine and ciprofloxacin.

Despite receiving appropriate treatment at the initial diagnosis, the patient re-presented with extensive disease and now MDR tuberculosis. However, the patient responded when given a regimen which only included drugs to which the organism was resistant.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Was treatment of the first episode, i.e. before drug resistance was identified, supervised? Although it is stated that there was no history of irregular drug taking, history of compliance is notoriously unreliable.
2. It is most unlikely that resistance would develop against drugs which the patient did not receive, such as the aminoglycosides, PAS, cycloserine and ciprofloxacin. The explanation that HIV-infected patients are more likely to develop resistance to antituberculosis drugs, and possibly therefore also other immune compromised patients, is incorrect. In general, HIV-infected patients are not more likely to develop MDR tuberculosis, and the reports that state this refers to institutionalized patients who are newly infected with MDR M. tuberculosis strains. The only drug to which HIV-infected patients may more often tend to develop resistance to, is rifampicin, and several reports have shown an increase in rifampicin-mono-resistance in HIV-infected patients.
3. The patient was then retreated with a regimen including 6 antituberculosis drugs, all of which the patient’s organism was likely to be resistant. In the case of isoniazid it is possible that the organism might have had low-level resistance and thus shown some response. However, in the manuscript the authors mention two INH-concentrations at which susceptibility tests were performed, but both are stated as 1 microg/ml. If the second test was at 10 microg/ml, the INH resistance is also complete and certainly INH at 5 mg/kg will have no effect. All of the remaining 8 drugs for which susceptibility was tested also had high-level resistance. Although kanamycin and sparfloxacin were used in the treatment regimen, it is well known that amikacin and kanamycin is very closely related and cross resistance will usually be present. (Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210 1996: 39) This is also the case with all of the quinolones so that if the patient was highly resistant to ciprofloxacin, resistance to sparfloxacin is
also most likely. (Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210 1996: 41-42, and Berning SE. The role of fluoroquinolones in tuberculosis today. Drugs 2001; 61 (1): 9-18) It is thus quite likely that the patient received no drugs to which the isolate was susceptible during the second phase (episode?) of disease and that the response that occurred was due to reconstitution of the immune system. The authors, however, fail to disclose whether the immune suppressive therapy (steroids and methotrexate) was continued during the initial treatment and during the second phase of treatment with the new regimen. The withdrawal of such therapy could be the explanation of eventual cure of this patient rather than the antituberculosis drugs received.

4. It is mentioned in the abstract and the discussion (but sputum not mentioned in the case report) that both sputum and aspirates from an abscess(es) were cultured and susceptibility tests done. It would help to know on how many different cultures from different sites the susceptibility tests were actually done, both on initial diagnosis and on follow-up, as laboratory contamination could occur. Although the authors do refer to M. tuberculosis in the follow-up specimens, they do not state that this was again confirmed with the methods previously described in the manuscript. Furthermore, restriction fragment length polymorphism (RFLP) analysis of the isolates at the two different occasions would have assisted the authors’ case, but there are too many other uncertainties in this case that can not be explained with the information currently available. Reinfection is also known to occur in high TB incidence areas even with MDR TB strains, and this possibility has not been considered/explored by the authors. (Van Rie A, et al. Classification of drug-resistant tuberculosis in an epidemic area. Lancet 2000;356:21-24)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. As it is a case report, the abstract should just be a short summary of the case and maybe a final conclusion but not divided into sub-headings as is currently done.
2. As English is also my second language, I do understand the authors’ problem, but the manuscript certainly needs some language corrections.
3. The terminology for drug resistant TB has recently been changed. Primary drug resistance as referred to by the authors (defined as resistance in a patient not previously treated for tuberculosis) is now called “New drug resistance” and acquired drug resistance is now referred to as drug resistance in previously treated patients. The reason for this is that many cases of MDR TB are transmitted rather than acquired through previous treatment even in patients who had previous treatment. (see also article Van Rie et al. referred to above)
4. Abbreviations such as AFB, USG should first be written in full before used as abbreviations.
5. The biopsy result from the axillary lymph node is a typical presentation in immune compromised patients. This should be discussed.
6. Do all the tests referred to, to identify M. tuberculosis actually distinguish M tuberculosis from the other species in the M. tuberculosis complex?
7. At what stage did the miliary pattern appear on the chest radiograph of this patient – this is not quite clear from the manuscript, although it seems to be after the cultures became positive.
8. What is meant by miliary TB of the “non-reactive type”?

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No

Declaration of competing interests:

None