

'Pseudo' treatment failure of pulmonary tuberculosis in association with a tuberculoma

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Failure of tuberculosis patients to respond to treatment is usually explained by one or more of five mechanisms: improper drug prescription; patient nonadherence to prescribed therapy; primary or acquired drug resistance; drug malabsorption; and rarely, exogenous reinfection with a drug-resistant isolate. Response to treatment is best measured bacteriologically; two different smear and one culture criteria for failure are widely used. Patients meeting either smear, but not culture, criteria for treatment failure may be said to have 'pseudo' treatment failure. Whether a patient can meet both smear criteria for failure, and not have a mechanism for treatment failure nor meet culture criteria, is unknown. A case of 'pseudo' treatment failure is reported in which both smear criteria for failure were met, but no mechanism for failure was proven to be operative.

Key Words: *Treatment failure; Tuberculosis; Tuberculoma*

Pseudo-échec du traitement de la tuberculose pulmonaire associée à un tuberculome

RÉSUMÉ : L'échec du traitement de la tuberculose est en général causé par l'un des cinq phénomènes suivants : mauvais choix de médicament, non-observance au traitement de la part du patient, résistance primaire ou acquise au médicament, mauvaise absorption du médicament et, plus rarement, réinfection exogène par une souche résistante au médicament. La réponse au traitement se mesure le mieux par les analyses bactériologiques. On utilise le plus souvent deux frottis différents et une culture. Les patients qui répondent aux critères des frottis et non de la culture pour la définition de l'échec thérapeutique subiraient ce qu'on appelle un pseudo-échec du traitement. On ignore si un patient peut répondre aux critères associés au frottis pour l'échec thérapeutique et ne présenter aucun des phénomènes explicatifs ni répondre au critère associé à la culture. Un cas de pseudo-échec du traitement est décrit ici; il se caractérise par la présence des deux critères associés aux frottis, sans mécanisme explicatif.

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Figure 1) Posterior-anterior chest radiograph taken June 20, 1998, showing a 3.4 cm spherical lesion in the left upper lung zone and no disease elsewhere

Assuming that a curative regimen is available and can be tolerated, instances of tuberculosis (TB) treatment failure are almost always explained by one or more of five mechanisms: improper drug prescription; patient nonadherence to prescribed therapy; primary or acquired drug resistance; drug malabsorption; and rarely, exogenous reinfection with a drug-resistant isolate (1-3). Depending upon their availability, sputum smear (World Health Organization [WHO]) or culture (American Thoracic Society [ATS]) criteria may be used to determine the presence of treatment failure. For the WHO, treatment failure is said to exist when a patient remains or again becomes smear-positive five months or more after starting treatment. It also is a patient who was initially smear-negative before starting treatment and becomes smear-positive after the second month of treatment (4). For the ATS, failure exists when the sputum culture fails to convert after five to six months of treatment (5). Culture criteria are the gold standard, but they have limited application globally because most regions lack culture capability and rely totally upon direct microscopy to determine bacteriological response to treatment. When both smears and cultures are regularly available, and patients meet one or the other smear, but not culture, criteria for failure, they may be said to have 'pseudo' treatment failure. Whether a patient can meet both smear criteria for failure and not have a mechanism for treatment failure nor meet culture criteria is unknown. The following case demonstrates that, within the setting of a tuberculoma, such a response is indeed possible.

CASE PRESENTATION

A 45-year-old male immigrant to Canada from China presented on July 17, 1998 with a history of fever and cough of several weeks duration. He had no past history of TB nor any underlying condition known to compromise the immune system. Human immunodeficiency virus serology was negative.

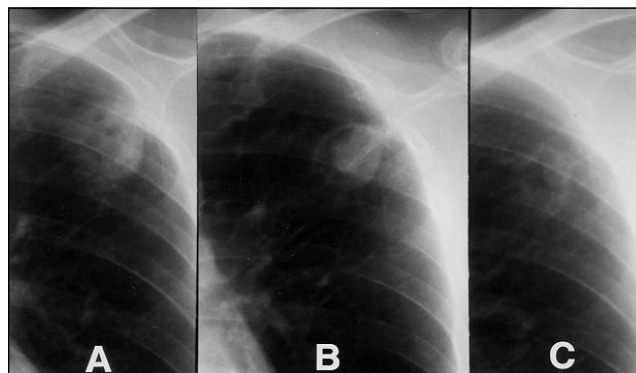


Figure 2) A Posterior-anterior view of the left upper hemithorax taken June 20, 1998, showing a 3.4 cm spherical lesion in the left upper lung zone. An irregular area of translucency suggestive of cavitation is visible within the lesion. B Same view of the left hemithorax taken November 24, 1998, showing a reduction in the widest diameter of the lesion, now 3.0 cm, with a well-defined, eccentric focus of cavitation. C Same view of the left hemithorax taken May 5, 1999, demonstrating further reduction in the diameter of the lesion, now 2.2 cm, and further excavation

His cough was productive of white phlegm. He denied hemoptysis. A plain chest radiograph revealed a well-circumscribed, noncalcified spherical lesion measuring 3.4 cm in diameter in the apical-posterior segment of the left upper lobe (Figures 1, 2A). An irregular area of translucency suggestive of cavitation was visible within this lesion. A sputum specimen that had been submitted by his referring physician on July 1, 1998 was acid-fast bacilli (AFB) smear negative (auramine-rhodamine), but culture positive (BACTEC 460, Becton-Dickinson Microbiology Systems, Sparks, Maryland) for *Mycobacterium tuberculosis*, and was susceptible to all first-line antituberculous drugs (Provincial Laboratory of Public Health, Edmonton). Directly observed daily therapy was started on July 17 (isoniazid [INH] 300 mg, rifampin [RIF] 600 mg, pyrazinamide [PZA] 1500 mg and ethambutol [EMB] 1000 mg) and continued until mid-September when it was reduced to twice weekly directly observed INH and RIF, 900 mg and 600 mg, respectively. Complete adherence to the treatment regimen was observed, and no drug intolerance was reported or measured. Between the start of therapy and October 9, 1998, five additional sputum specimens were submitted; all were smear negative and three were culture positive (Figure 3). The patient's fever resolved, his weight increased from 58.3 kg on July 17 to 61.6 kg on October 13, and a small (3 mm) reduction in the diameter of the presumed tuberculoma was reported on his chest radiograph. On October 13, a routine follow-up sputum specimen was AFB smear-positive in small numbers (less than 10 per slide).

This result, together with positive smears on subsequent sputum specimens, came as a complete surprise because the patient had been fully adherent to his directly observed therapy, had a fully drug susceptible isolate and had no gastrointestinal symptoms that would lead one to suspect drug malabsorption. A decision was made to admit the patient to

SPUTUM SMEAR #Positive # Submitted	0/3	0/1	0/1	6/12	7/18	4/10	2/7	0/6	2/4	0/6
SPUTUM CULTURE # Positive # Submitted	3/3	0/1	1/1	3/12	0/18	0/10	0/7	0/6	0/4	0/6
	7/98	8/98	9/98	10/98	11/98	12/98	1/99	2/99	3/99	4/99
	Month /Year									

Figure 3) Sputum smear and culture results during the course of treatment of a 45-year-old patient. Results are expressed as the number positive over the number submitted each month

hospital for respiratory isolation, observation and further investigation. During this hospitalization, chest radiographs demonstrated reduction in size and increased excavation of the left upper lobe tuberculoma (Figure 2B). A computed tomographic scan of the thorax confirmed the presence of an eccentric focus of cavitation within the tuberculoma, as well as an eccentric quantity of calcification not visible on the plain film. Small volume hemoptysis was reported for the first time. On October 22, twice weekly intermittent therapy was discontinued and replaced with daily INH, RIF, PZA and EMB at the original dosages. Specimens of sputum from October 13, 20 and 24 were ultimately culture positive, and drug susceptibility testing was repeated on the isolate grown from the October 13 specimen; it was again fully drug susceptible. The original isolate from July 1 and the isolate from October 13 were also submitted to molecular diagnostics for molecular typing. The fingerprint profiles were generated by *PVU*II restriction digestion of chromosomal DNA followed by Southern blot hybridization with *IS6110* as the probe (6). Both profiles were identical to each other. Finally, although no evidence of gastrointestinal disturbance was witnessed in or out of hospital, a noncompartmental pharmacokinetic analysis (10 plasma samples over 24 h) of drug concentrations of INH (300 mg), RIF (600 mg) and PZA (1500 mg), measured

after oral ingestion at 08:00 on November 25, was performed at steady state. The bioavailability of RIF and PZA was not different than reference norms (7). The bioavailability of INH was lower than the reference norm but as to what caused this no distinction could be made among altered absorption, altered distribution or altered first pass metabolism. This notwithstanding, during the entire sampling interval, plasma concentrations of INH were always well above the minimum inhibitory concentrations for *M tuberculosis* (0.1 mg/L or less) (8). Four-drug oral therapy was continued until December 8 when twice weekly INH and RIF was resumed.

Sputum specimens were taken on a regular basis (Figure 3), and surprisingly, smears continued to be positive into the eighth month of therapy; the last positive sputum smear was taken on March 15. Of a total of 55 specimens collected between October 13, 1998 and March 15, 1999, 20 (approximately 36%) were smear positive by fluorescence microscopy, six specimens in moderate numbers (one to 10 per field at 200x magnification). Of 20 sputum specimens collected after January 17, 1999 (after six months of directly observed therapy), four (20%) were smear-positive. Treatment was continued for a total of nine months; six months after the last positive culture (October 24, 1998). A plain chest radio-

graph at the completion of treatment demonstrated considerable reduction in the size of the tuberculoma. Further excavation had occurred (Figure 2C).

DISCUSSION

We have described a patient who met both WHO criteria for tuberculosis treatment failure (4) (sputum smears remained positive beyond five months of treatment and initially smear-negative disease became smear-positive after the second month of treatment). However, by ATS (culture) criteria, the gold standard, he did not actually fail (5), nor did he have operative any mechanism known to cause treatment failure (1-3). The patient was prescribed an appropriate regimen of antituberculous drugs and was fully adherent to prescribed therapy; his isolate was and remained fully drug susceptible, and proof of drug malabsorption could not be established. In addition, molecular typing did not support the unlikely possibility that he was populated with more than one strain of *M tuberculosis*, nor was he immunocompromised, although impairment of host immunological responses, such as occurs with human immunodeficiency virus infection, has little impact on bacteriological response to treatment (9).

It may be argued that our patient did not meet the second WHO criteria. Rather, his early negative smear results were simply a sampling artefact, because many more sputum specimens were submitted after sputum-smear positivity was detected than before positivity (Figure 3). However, the odds that none of six sputum specimens, submitted between July 1, 1998, the date the first specimen was submitted, and October 9, 1998, would be smear-positive are very low when six of 11 (55%) sputum specimens submitted between October 13 and 31, 1998 were smear-positive. This is particularly true given that smear-positivity is more, not less likely, the closer a patient is to being untreated. The likelihood of a patient meeting the second WHO criteria and having 'pseudo' treatment failure is not known but is judged to be very small.

The development during treatment of smear-positive, culture-negative status is well recognized, and may cause an estimated 5% of sputum smear-positive pulmonary TB patients to meet the first WHO criteria for treatment failure (smear positive at five months) without actually failing (cultures negative) (10-12). The tendency during treatment for sputum cultures to become negative before sputum smears has been associated with advanced disease and with treatment regimens that contained rifampin (10). Fluorochrome staining may contribute to a persistently smear-positive state because the auramine-rhodamine stain is more sensitive than the Ziehl-Neelsen stain (13); organisms apparently dead or rendered noncultivable by chemotherapy may still be fluorescence positive. Consideration of the treatment response in our patient focused on the nature of his lung lesion.

Tuberculomas are isolated nodular masses caused by the tubercle bacillus; they range in size from 0.5 to 4 cm in diameter, and are smooth and sharply defined (14-18). Macleod and Smith (15) described the necrotic tissue that forms the core of most of these lesions as having three appearances: "the ghost of tuberculous granulation tissue" – an interlacing

fibrous network enclosing poorly defined giant cells; "the ghost of bronchopneumonia" – where the alveolar structure of the lung is conserved; and completely amorphous areas without evidence of fibre structure or lining alveoli. Areas having this last appearance were reported as being sharply demarcated from areas of necrosis with a conserved structure. Amorphous necrotic tissue was generally seen well away from the edge of the lesion; where the tissue had been eccentrically placed and in relation to a bronchus, liquefaction and evacuation into the bronchus sometimes occurred. AFB were prominent in the amorphous areas. Conceivably, the unusual bacteriological response in our patient was because of the relative inability of antituberculous drugs to penetrate or destroy these isolated foci of tubercle bacilli, resulting in delayed liquefaction and erosion of the foci into the bronchus (19).

Reports of the finding of tubercle bacilli in the sputum of patients with tuberculomas have varied in different series; for example, Pugh and associates (17) reported the sputum positive for tubercle bacilli in only three of 28 cases, while Sochocky (18) reported sputum positive for tubercle bacilli on microscopy or on culture in 17 of 30 cases. Because closed tuberculosis lesions usually contain less than 10^4 organisms (20), patients with isolated closed lesions would not be expected to be sputum smear-positive because the latter requires 10^4 or more bacteria/mL of sputum to be present (21). The response to treatment of tuberculomas associated with bacillary positive sputum has not, to our knowledge, been reported previously. Given the importance of neoplasm in the differential diagnosis, tuberculomas are often resected (22), precluding any observation of their response to medical therapy alone.

In a recent report from Canada (12), 70% of patients meeting the first WHO criteria for treatment failure did not actually have failure. As our patient demonstrates, it is possible not only to meet the first, but both WHO criteria for treatment failure without actually failing or having operative a mechanism for treatment failure. This might influence the management of tuberculomas in developing countries.

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