

Fluoroquinolones may delay the diagnosis of tuberculosis

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ABSTRACT

Introduction: Fluoroquinolones (FQs), frequently used for many common infections such as community-acquired pneumonia and urinary tract infection, are also effective against *Mycobacterium tuberculosis*. This study describes a series of patients in whom the empirical use of FQs for what appeared to be common community-acquired infections led to a delay in the diagnosis of tuberculosis (TB).

Methods: We reviewed the records of five patients with TB in whom the early use of FQs led to partial symptom resolution and a prolonged relapsing and remitting course.

Results: Of the five patients described, four presented with community-acquired pneumonia and one with urinary tract infection. All were given FQs and improved, though not completely. Their illnesses took a relapsing and remitting course. TB was eventually diagnosed, in four of them by culture and in one by characteristic histopathology (this patient required surgical resection of a lung abscess).

Conclusion: FQs may lead to partial symptom resolution in TB. We highlight the problem of a delayed diagnosis, and voice our concern about inadvertent monotherapy of TB in such cases.

Keywords: fluoroquinolones, *Mycobacterium tuberculosis*, tuberculosis

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INTRODUCTION

Tuberculosis (TB) continues to be a major health concern. The World Health Organisation (WHO) declared TB a global emergency in 1993. In Singapore, TB continues to be endemic, with 40.8 new cases per 100,000 resident population in 2003⁽¹⁾. Fluoroquinolones (FQs) are broad-spectrum anti-

bacterial agents that block deoxyribonucleic acid replication and kill bacterial cells. They have found utility in a wide variety of infections. In the 1990s, new FQs (moxifloxacin and gatifloxacin) were developed for use against gram-positive pathogens. These demonstrated excellent activity against *Streptococcus pneumoniae*. These “respiratory” quinolones have been recommended as first-line therapy for community-acquired pneumonia (CAP) in adults⁽²⁾. FQs are also a first-line option for the management of urinary tract infection (UTI)⁽³⁾.

In addition, FQs have good in-vitro activity against *Mycobacterium tuberculosis* (MTBc). This has been comprehensively reviewed by Drlica et al⁽⁴⁾. Both animal and clinical studies have shown that FQs can play a role in treating TB, including drug-resistant TB⁽⁵⁻⁷⁾. Indeed, moxifloxacin has been shown in mice to be as effective as isoniazid in its mycobactericidal efficacy⁽⁸⁾. FQs are popular among clinicians who resort to them whenever patients on standard anti-TB medications develop intolerance or toxicity. Since TB has protean manifestations, it is inevitable that the widespread use of FQs would result in their being given to patients with TB. This may have consequences such as partial symptom resolution, and therefore a delayed diagnosis of TB, as well as inadvertent monotherapy. We present a series of cases in which the use of an FQ led to partial symptom resolution, with recrudescence of symptoms after cessation of the FQ.

METHODS

After the problem was first recognised by one of the authors, we started looking out for patients with similar case histories. We have included in this series, five patients identified from the personal referral logs of the two senior authors. For inclusion, patients had to be negative for human immunodeficiency virus (HIV) infection, and had to have a long-drawn illness with improvement in symptoms temporally related to the commencement of FQs and relapses following their cessation. Tuberculosis had to be proven by

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a positive culture for MTBc or by a characteristic histopathology.

RESULTS

Case 1

A 97-year-old Chinese woman, with a 13-year history of diabetes mellitus, was admitted to our hospital in February 1999 with fever and anorexia. On examination, her general condition was good, with stable vital signs. She had left basal crepitations and bilateral expiratory rhonchi. Chest radiograph on admission showed bilateral lower zone opacities. The haemoglobin (Hb) was 11.5 g/dL, white cell count (WCC) was $10.84 \times 10^9/L$ (77.5% polymorphs), and platelet count was $309 \times 10^9/L$. Serum for Legionella antibody was 1/128 (inconclusive). Laryngeal swabs were negative for acid-fast bacilli (AFB) on two occasions. Sputum cultures were negative.

The patient was started on intravenous (IV) ceftriaxone and oral erythromycin. Her antibiotics were changed to IV ceftazidime, and then IV imipenem, in quick succession, but the fever persisted. Because of unresolving fever and persistent infiltrates on chest radiographs, a bronchoscopy and bronchoalveolar lavage (BAL) was performed on March 3, 1999. The tracheobronchial tree was normal. Bronchial washings had 1+ polymorphs but no organisms on gram stain. BAL cultures were negative for bacteria and Legionella. A smear of the BAL fluid was negative for AFB.

Computed tomography (CT) of the thorax showed changes in the right upper lobe compatible with granulomas, suggestive of previous TB infection. There was also extensive consolidation in both lower lobes. The patient completed a seven-day course of imipenem and erythromycin. Temperature was low grade, and she was discharged on March 13, 1999 with 14 days' dosage of oral ciprofloxacin. On review at the outpatient clinic on April 5, 1999, the patient reported an improved sense of well-being and weight gain. However, serial chest radiographs taken between April and July 1999 showed persistent patchy densities in both lung bases, as well as in the right upper and mid zones.

In January 2000 she was re-admitted to the hospital with a three-week history of fever, chills and rigors. Prior to this admission, she had been treated at the government outpatient clinic for Klebsiella UTI with oral ciprofloxacin. On examination, there were bilateral basal crepitations. The blood count was unremarkable. Urine microscopy showed pyuria, but results of urine culture were not available. Chest radiograph on admission showed patchy nodular

densities in the right mid-zone and both lower zones, consistent with bronchopneumonia. Two samples of sputum for AFB were negative on smears. Sputum for TB culture was not sent. A tuberculin skin test was read at 10 mm at 72 hours. Her temperature remained elevated after three doses of IV ceftriaxone. She was switched to oral ciprofloxacin, whereby her fever completely resolved. She was discharged with four days' dosage of oral ciprofloxacin.

On review at the respiratory clinic in February 2000, the patient reported that her appetite and well-being had improved after the recent course of antibiotics, but she had noticed intermittent episodes of fever once again. This was attributed to recurrent UTI because of persistent cloudy urine. She remained on follow-up at the respiratory clinic. Serial chest radiographs showed no progression. Between May 2001 and July 2001, the patient had three further admissions for fever and cough, and was treated for infective exacerbations of bronchiectasis. During these admissions, she received a variety of antibiotics including augmentin, cefepime, erythromycin, ciprofloxacin and piperacillin-tazobactam. She continued to have a low-grade fever.

In the third of these admissions (July 2001), she was discharged with home oxygen. In August 2001, a sputum sample sent from one of her earlier admissions was reported to grow MTBc, sensitive to streptomycin, rifampicin, isoniazid and ethambutol. Anti-TB therapy was started in August 2001 and completed in April 2002. The patient is currently well, with no requirement for oxygen and reports complete resolution of her fever.

Case 2

A 37-year-old Chinese woman was referred to our hospital for persistent cough. Prior to this, she had been seen by several family physicians over an eight-month period (between July 2001 and February 2002) for chronic cough. Her cough was productive of dark yellow sputum. She also gave a history of weight loss of 4 kg over the preceding eight months. There was no breathlessness, haemoptysis or chest pain. During the eight-month period, she had received a total of four courses of oral antibiotics. These included clarithromycin and ofloxacin, following which serial chest radiographs obtained between September 2001 and October 2001 had shown improvement of the right lower zone infiltrates.

On examination, she appeared well. She was afebrile with stable vital signs. There was no cervical adenopathy. The chest was clear to auscultation. Blood investigations showed Hb of 11.4 g/dL, WCC of $6.88 \times 10^9/L$, (63.2% polymorphs), and platelets of

$417 \times 10^9/L$. Erythrocyte sedimentation rate (ESR) was 50 mm/h. Chest radiograph showed right lower zone infiltrates. She was sent home with oral ciprofloxacin, and sputum AFB smears were ordered. The sputum was positive for AFB and cultures yielded MTBc sensitive to streptomycin, rifampicin, isoniazid and ethambutol. She was recalled and given anti-TB treatment, to which she responded very well.

Case 3

A 62-year-old Chinese man was admitted to our hospital on July 10, 2000 with a three-day history of fever, chills, rigours, and cough productive of yellow sputum. On examination, his general condition was good. Crepitations were heard in the right mid-chest posteriorly. He had smoked heavily in the past and was known to have chronic obstructive lung disease with lung bullae. He had undergone coronary artery bypass three years before. There was also a history of psoriasis and of hypoplastic anaemia, for which he was on oxymethalone.

Blood investigations showed Hb of 12.2 g/dL, WCC of $4.1 \times 10^9/L$, (69.7% polymorphs), and platelets of $225 \times 10^9/L$. Chest radiograph showed right upper zone infiltrates. While breathing supplemental oxygen at 2 L/min, the pO_2 was 74.5 mmHg and pCO_2 was 31.8 mmHg. Blood cultures were negative, sputum was negative for AFB on smears. Sputum for gram stain showed polymorphs 2+, with no predominant organism. Sputum culture yielded *Streptococcus pneumoniae* (*S. pneumoniae*) with a minimal inhibitory concentration (MIC) to penicillin of 1.5 µg/ml and an MIC to ceftriaxone of 1.0 µg/ml. The strain was also resistant to chloramphenicol, erythromycin, tetracycline and trimethoprim-sulfamethoxazole. The patient was started on IV ceftazidime and IV erythromycin on admission, but was switched to IV vancomycin when the sputum culture result was received.

He remained febrile (up to 39°C) in spite of vancomycin and underwent a BAL on July 14, 2000. The tracheobronchial tree was normal. Gram stain of the BAL fluid had 1+ polymorphs, but no organisms were seen. The culture was negative. BAL fluid was also negative for Legionella antigen by immunofluorescence and for AFB by smear. A repeat sputum culture grew *S. pneumoniae* with a similar susceptibility pattern. On July 21, 2000, levofloxacin was substituted for vancomycin. The temperature trended downwards, and he was discharged.

He was re-admitted on August 7, 2000 with fever and chills that had recurred after completion of levofloxacin. He had not been feeling well after discharge, but had not come back until the fever

recurred (one day after completing levofloxacin). Clinical examination was not much changed, though this time bronchial breathing was heard in the right upper chest posteriorly. Blood counts were again unremarkable. Blood cultures were negative. He was started on IV ceftriaxone and then switched to IV clindamycin when he remained febrile. CT of the thorax revealed multiple air-fluid levels in the right upper lobe. This was attributed to infected bullae as he was known to have bullae. He was switched to oral gatifloxacin on August 16, 2000, and discharged on August 19, 2000 when the temperature appeared to be settling.

He was reviewed on August 22, and September 6, 2000. He had been monitoring his temperature at home, and the records showed that the temperature hovered between 37.0 and 37.7°C. He reported feeling slightly better. The chest radiographs still showed upper lobe consolidation with air-fluid levels. He was maintained on oral gatifloxacin for two weeks, then switched to moxifloxacin for another two weeks without improvement in his sense of well-being or in his chest radiographs. The case was discussed and a decision was made for lobectomy.

Intraoperatively, the right upper lobe was found to be consolidated and plastered to the chest wall. A right upper lobectomy was performed. Histopathological examination revealed necrotising granulomatous inflammation characterised by areas of necrosis rimmed by epithelioid histiocytes, with scattered multinucleated giant cells. AFB were identified on Ziehl-Neelsen stains. Unfortunately, specimens sent for mycobacterial culture went missing. The patient was started on anti-tuberculous drugs (isoniazid, rifampicin, ethambutol and pyrazinamide). He gained weight and had an improved sense of well-being. He completed nine months of therapy.

Case 4

A 34-year-old Indonesian man, resident in Singapore for five years, first became symptomatic in March 2003 when he developed pain during micturition, as well as had episodes of gross haematuria. He was then on a job attachment in Germany and saw several doctors, who prescribed antibiotics for UTI. However, his symptoms persisted until he was given oral ciprofloxacin. After being symptom-free for a month, he again developed pain during micturition. He had no fever, headache, diarrhoea, cough or weight loss.

By this time, he had returned to Singapore and was referred to a urologist in our hospital. Another course of ciprofloxacin was given, resulting in improvement in his symptoms. An intravenous urogram was normal. In October 2003, his symptoms recurred and

a cystoscopy was performed, revealing a mass that, on biopsy, showed chronic inflammation. Urine was sent for TB cultures and these returned positive for MTBc. He was started on anti-TB drugs. There is no more gross haematuria and no more pain during micturition, but he continues to have frequency and is currently being evaluated for the complications of genitourinary TB, such as a contracted bladder.

Case 5

A 42-year-old Chinese man with hepatitis C had end-stage renal disease from chronic glomerulonephritis. He had received a renal transplant in 1993 but this was complicated by graft rejection. A transplant nephrectomy was performed in 1997, and he returned to haemodialysis. He presented on November 12, 2002 with fever, chills, rigours, and haemoptysis. On examination, he was febrile at 38.8°C and tachypnoeic (SpO₂ 89% on room air). There were coarse crepitations in the chest and bronchial breath sounds in the left lower chest. Chest radiograph showed bilateral air space shadowing with right mid-zone opacity. The Hb was 9.7 g/dL, WCC was 10.45 × 10⁹/L, (91.5% polymorphs), and platelets were 199 × 10⁹/L. Sputum for AFB smear was negative on three occasions.

He received IV vancomycin, ceftazidime and erythromycin. The temperature began a downward trend from Day 3 of admission, and settled completely after he was converted to oral moxifloxacin on Day 6. He was discharged with one week's dosage of moxifloxacin. On review, he reported a marked improvement in his cough. Subsequently, a sputum sample sent during his admission returned positive for MTBc, sensitive to the usual first-line agents. He was commenced on anti-TB medications, and is currently well on follow-up.

DISCUSSION

In the case histories above, we highlight HIV-negative patients (Cases 1-4) in whom the early administration of FQs may have contributed to partial treatment of TB, partial resolution of symptoms, initial negative cultures, and hence a prolonged clinical course. In Case 5, also HIV-negative, the symptoms resolved with FQs, but the diagnosis was not delayed as sputum TB cultures were ordered from the very outset. We use these case histories to make the following points: that the use of FQs in the empiric therapy of common community-acquired infections may lead to a delayed diagnosis of TB, and that partial symptom resolution may lead to a relapsing and remitting course (hence an emerging syndrome).

We are aware that existing guidelines for the management of community-acquired pneumonia and UTI recommend FQs as one of several options for first-line therapy^(2,3). Although these represented a small fraction of the large number of cases seen at our hospital, we do not know how many more patients had similar experiences, as this was not a systematic, institution-wide study of the problem. It is possible that there were many cases rather like that of Case 5, as TB cultures tend to be ordered very early in our hospital. These caveats notwithstanding, we feel that the sharing of these case histories with the general medical community is helpful, as the popularity of FQs is rising. We recommend that in Singapore, caution be exercised in applying guidelines that advocate FQs as first-line therapy in the empirical treatment of community-acquired infections. We also worry that such empirical use of FQs constitutes inadvertent monotherapy of TB, with its attendant risk of resistance development. As we do not test our MTBc isolates routinely for susceptibility to the FQs, we do not know if the MTBc isolates in our patients were FQ-resistant, but the literature suggests that there is an association between a short course of FQs and FQ-resistance in MTBc isolates^(9,10).

The link between the use of FQs for common conditions and a delayed diagnosis of TB has been made before. Dooley et al, working at a hospital in which FQs were recommended as first-line treatment for CAP, noted that 48% of patients who received FQs for empirical treatment for presumed bacterial pneumonia had a delay in the initiation of appropriate anti-TB treatment⁽¹¹⁾. Our case series is not a duplicate of theirs as the majority of the patients in the report of Dooley et al were HIV-positive. Despite criticisms of its methods, the study, like our case series, highlights one problem we may encounter in using FQs freely and empirically⁽¹²⁾.

Our study does not permit us to comment on the possibility that short courses of monotherapy with FQs in a patient thought to have a bacterial infection but actually having TB, might be associated with the development of FQ resistance. However, the literature provides evidence for this. Ginsburg et al described an HIV-infected patient who presented with prostatic abscesses and who was given a seven-day course of levofloxacin followed by a six-day course of ciprofloxacin⁽⁹⁾. Urine cultures before and after abscess cultures after FQ therapy grew MTBc that could not be differentiated on molecular fingerprinting. The isolate prior to levofloxacin consumption was susceptible to FQs, but that after FQ consumption was resistant to all the FQs tested⁽⁹⁾. Ginsburg et al tested all MTBc isolates from 55 adult patients with

TB at their institution for susceptibility to FQs⁽¹⁰⁾. The two isolates that had reduced susceptibility to FQs came from HIV-infected patients who had received FQ monotherapy prior to anti-TB therapy. No FQ-resistant strain was isolated from persons who had not received previous FQ therapy. Of note (and concern), the median duration of FQ use in persons with FQ-resistant strains was four days.

It is possible to criticise the clinicians managing the cases in our series for not having considered TB earlier, or even from the outset. With the benefit of hindsight, which is always 20/20, these case histories, in their entirety, do bring TB to the mind of an experienced clinician. In defence of the clinicians who managed these patients, we wish to point out certain features that made the diagnosis of TB less than clear-cut. Case 1 is best viewed as a problem of TB in an older individual, which frequently results in a clinical and radiographical picture of a nonspecific, unresolving pneumonitis in the lower and middle lobes⁽¹³⁾. Further, she had "lower lung field" TB that is typically associated with delayed diagnosis, and symptoms lasting several months are not uncommon⁽¹⁴⁾. AFB is also more difficult to demonstrate in sputum smears and culture in this condition. In Case 3, while an upper lobe "abscess" may be considered suggestive of TB, a physician who had followed him from Day 1 would have known that he had presented acutely and that he was known to have lung bullae. Lung abscess as a complication of pneumococcal disease, though rare, has been well described⁽¹⁵⁾.

There is incontrovertible evidence that FQs possess anti-tuberculous activity⁽⁴⁾. The clinical data, though less impressive, nevertheless indicate that FQs may play a useful role in the management of TB. In a randomised controlled trial comparing isoniazid, rifampicin and ciprofloxacin with isoniazid, rifampicin, ethambutol and pyrazinamide, Kennedy et al found that in non-HIV-infected individuals, there were no statistically significant differences in outcomes⁽⁶⁾. Yew et al reported a series of 63 patients with drug-resistant TB in whom treatment with multi-drug regimens containing ofloxacin or levofloxacin were effective⁽⁷⁾.

FQs are recommended as first-line therapy for both CAP and UTI^(2,3). Our series highlights the possibility that, in patients in whom the underlying cause of the CAP or UTI is TB, the use of FQs may cause partial symptom resolution, and therefore contribute to

delayed diagnosis of TB. We suggest that guidelines developed in the West may not be applicable in their entirety to other parts of the world. We hesitate to say that FQs should not be used as empiric therapy for CAP or UTI in countries with moderate to high rates of TB, but emphasise that each patient must be individually assessed and monitored.

In summary, we have presented these cases in some detail not only to describe a new syndrome, brought about by the combination of new drugs and an old disease, but also to voice our concerns about the widespread empirical use of FQs in countries with moderate to high burdens of TB.

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