Failure of oral antibiotic therapy, including azithromycin, in the treatment of a recurrent breast abscess caused by *Salmonella enterica* serotype Paratyphi A

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We report a case of recurrent, multifocal *Salmonella enterica* serotype Paratyphi A breast abscesses, resistant to ciprofloxacin, which relapsed despite surgery, aspiration and multiple courses of antibiotics, including co-trimoxazole and azithromycin. The patient was cured after a prolonged course of intravenous ceftriaxone.

Keywords: *Salmonella enterica* serotype Paratyphi A, Breast abscess, Azithromycin, Failure

Introduction

Breast abscess is an uncommon but well recognized complication of enteric fever.^{1,2} The isolation of *Salmonella enterica* serotype Typhi from a breast abscess was described as early as 1907 when Thayer and Hazen reported a breast abscess in a young housemaid presenting to the John Hopkins Hospital, Baltimore.³ Since this time, case reports have described breast and other extra-intestinal abscesses as a complication of infection by both *S. enterica* serotype Typhi and Paratyphi.^{2,4-9} These reports illustrate uncomplicated and effective clearance of abscesses with single courses of oral antibiotic agents such as ciprofloxacin or co-trimoxazole, together with surgery in some cases: none have reported the need for prolonged or multiple courses of antibiotic therapy.⁴⁻⁹ Recent literature has demonstrated a trend towards increasing resistance to oral agents.^{10,11} Reviews have recommended azithromycin as an effective choice in uncomplicated enteric fever especially in the presence of fluoroquinolone resistance.^{12,13} This case reviews the unusual presentation of recurring breast abscess in a returning traveller.

Case Report

A 33-year-old Bangladeshi woman who had been residing in Australia for several years presented in December, 2009 after noting a painful, erythematous lump in her right breast. She visited Bangladesh in

October 2009 and whilst overseas experienced a single episode of fevers and rigors and was prescribed oral cefixime for one week, with improvement in symptoms. She had otherwise been well during her stay and had no subsequent systemic symptoms. The patient was a non-smoker and was not currently breast-feeding. In January 2010 she underwent surgical review with two lesions detected on ultrasound. Core needle biopsy revealed the presence of granulomatous mastitis and fibroadenoma; Ziehl-Neelsen and PAS stains were negative. Investigations showed a peripheral white cell count of $7.9 \times 10^9/l$.

Over the subsequent four months she experienced at least two further episodes of painful breast inflammation and was prescribed sequential empiric courses of oral cephalexin without effect. In May, 2010, she underwent repeat surgical review and pus was aspirated from a right breast collection. *S. enterica* serotype Paratyphi A resistant to nalidixic acid but susceptible to ampicillin, ceftriaxone and trimethoprim-sulphamethoxazole was cultured. As measured by Vitek 2 (bioMérieux Diagnostics, Marcy l'Etoile, France) breakpoint testing, the ceftriaxone MIC was <1 mg/l and ampicillin MIC <2 mg/l. Chloramphenicol was not tested.

Whilst remaining clinically well, the patient continued to experience additional breast collections, and surgical incision and drainage was performed in June 2010, 6 months after her initial presentation. Again, cultures grew *S. enterica* serotype Paratyphi A with the identical susceptibility profile. A ciprofloxacin E-test (AB Biodisk, Solna, Sweden) revealed an MIC of

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0.5 mg/l indicating reduced susceptibility; azithromycin was in the suggested susceptible range with an E-test MIC of 12 mg/l.¹⁰ Stool cultures excluded gastrointestinal carriage of *S. enterica* serotype Paratyphi A and an abdominal ultrasound excluded the presence of gall-stones. She was commenced on a 10-day course of oral trimethoprim-sulphamethoxazole 160/800 mg, twice daily.

Recurrence of breast discomfort occurred three months later in September 2010 and ultrasound revealed a superficial collection (2 × 1 cm) lateral to original site, 0.5 ml of thick pus was aspirated and the same strain was isolated. Oral trimethoprim-sulphamethoxazole 160/800 mg, twice daily was again prescribed for 10 days. However, on review in early October 2010, further nodular subcutaneous collections had developed in new locations. C-reactive protein was noted at 1.2 mg/l and the peripheral white cell count was $7.7 \times 10^9/l$. A two week course of oral azithromycin (500 mg daily) was prescribed, following completion of trimethoprim-sulphamethoxazole therapy. When pus was again aspirated upon surgical follow-up two weeks later, the course of azithromycin was extended for a further four weeks.

In mid-November 2010, a repeat ultrasound again revealed multiple small abscesses in at least four different sites and up to 10 mm in size. Again, 0.5–1 ml of pus was aspirated and *S. enterica* serotype Paratyphi A was isolated despite continuing azithromycin therapy. The azithromycin E-test MIC was unchanged at 12 mg/l. When follow-up ultrasound in December 2010 demonstrated three further collections and pus was aspirated, she was commenced on a 6-week intravenous course of ceftriaxone, 2 g daily. On review 3 months post-cessation of ceftriaxone, she was clinically well with ultrasound showing improvement of the hypoechoic areas with less breast thickening than at anytime in previous year. There has been no clinical relapse 1 year after antibiotic treatment was ceased.

Discussion

The development of *Salmonella* breast abscess remains a rare and late complication of enteric

fever.^{1,4,9} It may occur with only a distant history of fever, and without the usual sequelae of concurrent systemic illness.⁴ Whilst there has been a recent upsurge in the frequency of case reports related to *Salmonella* breast abscess, perhaps due to increasingly resistant *Salmonella* strains, literature from the 1930s demonstrated that the incidence of mastitis in typhoid patients ranged from 0.3 to 0.5%.¹ There are less than 15 reported cases of *S. enterica* serotype Typhi breast abscess and no reported cases of Paratyphi breast abscess (Table 1). In a study of 6250 Salmonellosis cases, there were 100 cases of pyogenic infection and only one was related to breast abscess.²

The management of the extra-intestinal manifestations of multi-drug resistant *Salmonella* strains remains unclear. Increasing numbers of *S. enterica* serovars Typhi and Paratyphi are exhibiting resistance or decreased susceptibility to ciprofloxacin leading to treatment failure.^{11,12,14,15} *S. enterica* serotype Typhi and Paratyphi isolates with decreased ciprofloxacin susceptibility, ciprofloxacin MICs of 0.12–1 mg/l, have been shown to be associated with longer fever clearance times, and greater likelihood of treatment failure with fluoroquinolones.¹⁶ The majority of *Salmonella* strains isolated from the Indian subcontinent now have MICs >0.12 mg/l for ciprofloxacin.¹⁷

Suggested alternatives for fluoroquinolone resistant strains have included ampicillin, chloramphenicol, trimethoprim-sulphamethoxazole, third generation cephalosporins and azithromycin.^{11,13} Several studies have confirmed the usefulness of azithromycin in the treatment of multi-drug resistant, nalidixic acid resistant enteric fever.^{12,18,19} Parry *et al.*¹⁸ showed the increased efficacy of azithromycin alone, when compared to ofloxacin and to a combination of ofloxacin-azithromycin. Azithromycin use resulted in superior clinical cure rates, decreased mean fever clearance time and lower faecal carriage.¹⁸

Two studies directly comparing the use of ceftriaxone and azithromycin showed no difference in the odds of clinical or microbiological failure.^{19,20} While ceftriaxone was found to have lower fever clearance

Table 1 Choice and duration of antibiotic therapy for *Salmonella* breast abscess

Case report		Salmonella isolate	Antibiotic therapy			
Year	Breast pathology	Species	Antibiotic	Duration	Recurrence	Author
2009	Nil	<i>S. enterica</i> Typhi	Cefotaxime→Amoxycillin + Clavulanic acid	Unknown	Nil	Singh <i>et al.</i> ⁶
2008	Previous lumpectomy	<i>S. enterica</i> Typhi	3rd generation Cephalosporin	Unknown	Unknown	Salahuddin <i>et al.</i> ⁷
2007	Nil	<i>S. enterica</i> Typhi	Ciprofloxacin	2 weeks	Nil	Mahajan <i>et al.</i> ⁴
2003	Unknown	<i>S. enterica</i> Typhi	Ciprofloxacin	Unknown	Nil	Jayakumar <i>et al.</i> ⁵
2003	Nil	<i>S. enterica</i> Typhi	Amoxicillin + Clavulanic Acid→Ciprofloxacin	2 weeks	Nil	Viswanathan <i>et al.</i> ⁸
1998	Unknown	<i>S. enterica</i> Typhi	Chloramphenicol + Cloxacillin	2 weeks	Nil	Kumar ⁹
1970	Nil	<i>S. enterica</i> Typhi	Unknown	Unknown	Nil	Barrett and McDermot ¹

times, this result was not statistically significant.¹⁹ The likelihood of relapse was decreased with azithromycin and this was thought to be related to the long half-life of azithromycin in the intracellular compartment and tissues.¹⁹

Why the prolonged use of azithromycin failed to achieve cure in our patient remains unclear. The suggested azithromycin breakpoint for wild-type *Salmonella* isolates from India is 16 mg/l^{10,17} with MIC ranges for *S. enterica* serotype Typhi and Paratyphi being 4–8 and 6–12 mg/l respectively.¹⁵ Azithromycin resistance is considered to occur at MIC $\geq$ 32 mg/l.²¹ Despite the recommendations noted, there is insufficient current data relating azithromycin MICs, selection of susceptibility breakpoints and clinical outcomes. Treatment failure of azithromycin for *S. enterica* serotype Paratyphi A has been reported by Molloy *et al.*, however, in this instance both pre- and post-treatment isolates had raised MICs to azithromycin, with MICs of 64 and 256 mg/l respectively.²² Despite recurrence after azithromycin treatment, the *Salmonella* serotype Paratyphi A isolate in our patient remained susceptible to azithromycin with an MIC of 12 mg/l.¹⁰ With the emergence of literature showing the increasing prevalence of multi-drug resistant *Salmonella* species, and the evolving patterns of resistance, the need for continued surveillance of susceptibilities has become imperative.^{20–23}

Persistent typhoid infection may be related to the harbouring of *Salmonella* strains in iron replete haemophagocytic macrophages and survival in the reticuloendothelial system.²⁴ The presence of underlying breast pathology, as evident in our patient, increased age, a history of smoking and the need for surgical intervention have all been identified as predictors of abscess recurrence.^{5,25}

Azithromycin achieves high intracellular drug concentrations.²⁶ While the reported peak serum drug level of azithromycin is 0.4 g/l, levels of azithromycin in macrophages and neutrophils may be up to 100-fold greater than serum concentrations.²⁶ Hence, it is surprising that relapse occurred despite a prolonged azithromycin course. Other considerations, such as poor penetration into fibrotic breast tissue, and reduced azalide activity in the acidic environment of the abscess itself, may have contributed to treatment failure.

In view of growing therapy resistance, azithromycin is recommended as empirical antibiotic therapy for cases of enteric fever acquired in the Indian sub-continent or South-East Asia.^{10,12,17,23,27} Third generation cephalosporins are generally reserved for cases of prolonged fever or established drug resistance.¹¹ However, none of the studies in which azithromycin was used successfully for the

treatment of Salmonellosis were for extra-intestinal complications of enteric fever. This case emphasizes the need for caution with respect to the use of azithromycin and co-trimoxazole in extra-intestinal typhoid cases associated with abscess formation.

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