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Case Report: Six Cases of Paratyphoid Fever due to *Salmonella* Paratyphi A in Travelers Returning from Myanmar between July 2014 and August 2015

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Abstract. We report six cases of *Salmonella enterica* serotype Paratyphi A infections in travelers returning from Myanmar. In 2015, 31 cases of paratyphoid fever were reported in Japan, and 54.8% of those traveled to Myanmar. Among them, six patients presented to our hospital. They had traveled to Myanmar from July 2014 to August 2015 for business purposes. All six isolates were phage type 1, and they were resistant to nalidixic acid.

INTRODUCTION

Typhoid fever is the predominant enteric fever; however, *Salmonella enterica* serotype Paratyphi A has been increasingly reported in Asian countries.[1] Although an outbreak of typhoid fever in Myanmar was reported in 2000,[2] little is known about paratyphoid fever in travelers who visit Myanmar. We report six patients with paratyphoid fever caused by *S*. Paratyphi A who traveled to Myanmar from July 2014 to September 2015.

CASE REPORTS

All six patients (1–6) had traveled to Myanmar from July 2014 to August 2015. Patients' median age was 40.5 years (range, 30–60 years), and five of six patients (83%) were men.

Patient 2 had a history of panhysterectomy due to adenomyosis uteri, and patient 5 had hyperlipidemia and hyperuricemia. In all cases, the purpose of travel was business. Four of six patients only traveled to Yangon, patient 2 traveled to Yangon and Naypyidaw, and patient 3 traveled to Khamti. Two of six patients were vaccinated against *Salmonella typhi* before they traveled. All patients presented with a high fever. Three (50%) also had a headache and one (16.6%) had myalgia, arthritis, and a rash. Four of six cases presented with relative bradycardia. Patient 6 was coinfected with *Giardia*. Patients' characteristics are summarized in Table 1.

LABORATORY FINDINGS

Blood samples were obtained, and all blood culture results were positive for *S*. Paratyphi A. The antimicrobial susceptibility test was performed by using the MicroScan WalkAway (Siemen's Diagnostics) in accordance with the Clinical and Laboratory Standards Institutes guidelines.[3] The minimum inhibitory concentrations (MICs) of levofloxacin and ciprofloxacin were also determined by using the E-test. All isolates were resistant to nalidixic acid, and they were categorized as intermediate or resistant to ciprofloxacin. The MICs of various antibiotics for *S.* Paratyphi A are shown in Table 2. All six isolates were phage type (PT) 1. Pulsed-field gel electrophoresis (PFGE) of chromosomal DNA was performed, and the isolates had almost identical profiles (Figure 1).

TREATMENT AND OUTCOME

In all cases, we started treatment with ceftriaxone (2 g/day). All patients, except cases 4 and 5, fully recovered after receiving ceftriaxone for 14 days. Patient 4's fever did not subside after treatment with ceftriaxone for 7 days. Subsequently, we changed the antimicrobial treatment to oral azithromycin (1 g daily for the first day and then 500 mg/day for 6 days). After 7 days of azithromycin treatment, he fully recovered. Patient 5 received ceftriaxone (2 g intravenously for 7 days), and then the treatment was changed to cefotaxime (6 g/day) because her aminotransferase level continued to increase. After 7 days of cefotaxime treatment, he fully recovered.

DISCUSSION

In Japan, approximately 20–30 cases of paratyphoid have been reported yearly from 2005 to 2012, and they were mainly from the Indian subcontinent.[4] In 2012, 2013, and 2014, 23, 50, and 16 cases of paratyphoid fever, respectively, were reported to the National Epidemiological Surveillance of Infectious Diseases in Japan.[4] Among them, zero of 23 cases (0%), six of 50 cases (12.0%), and three of 16 cases (18.7%) were travelers from Myanmar. The reason for the increase in cases of paratyphoid fever in 2013 was the increase in imported cases from Cambodia.[5] In 2015, 31 cases of paratyphoid fever were reported. Among them, 17 patients (54.8%) had traveled to Myanmar. The reason for this increase may be associated with increases in the number of Japanese travelers to Myanmar[6]; however, 36 cases of typhoid fever were reported during the same period, and only three were travelers returning from Myanmar. This difference may be attributed to vaccinations for typhoid fever. Another possibility is that an outbreak of paratyphoid fever might occur in Myanmar.

The PFGE profiles of isolates were almost identical; in addition, all isolates were classified as PT 1. These results suggest that all six isolates are genetically related. According to the National Institute of Infectious Diseases in Japan, among 21 isolates of *S*. Paratyphi A from travelers from Myanmar isolated from 2012 to 2015, 18 were PT 1, and three were PT 2 and PT 6.[7] After March 2013 when PT 2 isolates were isolated, all isolates were PT 1. However, the PTs of isolates from Japanese travelers from Cambodia in 2013

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TABLE 1

Summary of patients with paratyphoid fever due to *Salmonella* Paratyphi A among travelers returning from Myanmar, Japan, from July 2014 to August 2015

Patient no.	Age, sex	Medical history	Duration	Destination
1	30, M	None	July 1, 2014 to July 8, 2014	Yangon
2	54, F	Panhysterectomy for adenomyosis uteri	November 30, 2014 to December 12, 2014	Yangon, Naypyidaw
3	39, M	Asthma	December 17, 2014 to December 31, 2014	Khamti
4	34, M	None	December 29, 2014 to April 13, 2015	Yangon
5	60, M	None	April 20, 2015 to May 24, 2015	Yangon
6	42, M	Hyperlipidemia, hyperuricemia	August 16, 2015 to August 26 2015	Yangon

Travel purpose	Date of onset	Typhoid fever vaccination	Treatment	Outcome
Business	July 3, 2014	No	CTRX 2 g q.d. for 14 days	Cured
Business	December 26, 2014	No	CTRX 2 g q.d. for 14 days	Cured
Business	January 12, 2015	No	CTRX 2 g q.d. for 7 days; CTX 2 g t.i.d. for 7 days	Cured
Business	April 11, 2015	Yes	CTRX 2 g q.d. for 14 days	Cured
Business	May 1, 2015	No	CTRX 2 g q.d. for 7 days; AZM 1 g q.d. for 1 day and then 500 mg q.d. for 6 days	Cured
Business	September 11, 2015	Yes	CTRX 2 g q.d. for 14 days	Cured

AZM = azithromycin; CTRX = ceftriaxone; F = female; M = male; q.d. = once daily; t.i.d. = three times daily.

TABLE 2

Minimum inhibitory concentrations of various antibiotics for *Salmonella enterica* serotype Paratyphi A isolated from travelers returning from Myanmar, Japan, from July 2014 to August 2015

Antibiotic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Ampicillin	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S
Ampicillin/sulbactam	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S	≤ 4, S
Piperacillin/tazobactam	≤ 8, S	≤ 8, S	≤ 8, S	≤ 8, S	≤ 8, S	≤ 8, S
Ceftriaxone	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S
Ceftazidime	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S
Cefepime	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S
Aztreonam	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S	≤ 2, S
Meropenem	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S
Nalidixic acid	≥ 64	≥ 64	≥ 64	≥ 64	≥ 64	≥ 64
Levofloxacin	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S	≤ 1, S
Levofloxacin (E-test)	1.0, I	2.0, R	2.0, R	1.0, I	1.0, I	1.0, I
Ciprofloxacin (E-test)	0.5, I	1.0, R	1.0, R	1.0, R	0.5, I	0.5, I

I = intermediate; R = resistant; S = susceptible.

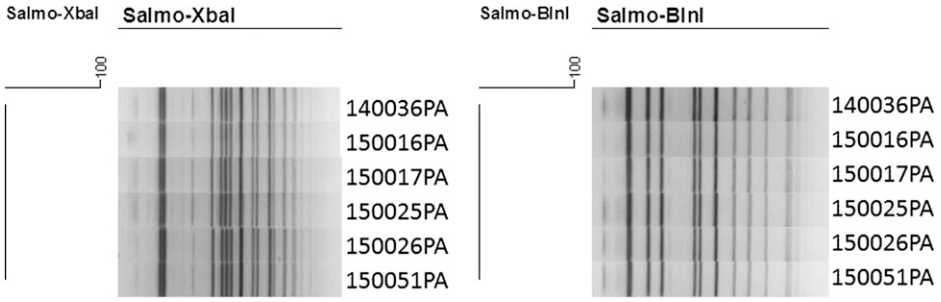

FIGURE 1. Pulsed-field gel electrophoresis of chromosomal DNA of S. Paratyphi A derived from travelers returning from Myanmar, Japan, from July 2014 to August 2015.

were mainly PT 2,[5] and they were the same PT of isolates identified from European travelers from Cambodia in 2013.[8]

Hassing and others reported the susceptibility of *S. typhi* and *S.* Paratyphi A isolates to ciprofloxacin among travelers to southeast Asia.[9] Isolates from travelers to Indonesia and Cambodia were sensitive to fluoroquinolones; yet, in this report, resistance or reduced susceptibility to fluoroquinolones was found in travelers to India and Pakistan. Meltzer and others reported an outbreak of *S.* Paratyphi A infection among Israeli travelers to Nepal.[10] In their report, all isolates had the same PFGE pattern and were resistant to nalidixic acid. Other studies have also reported that *S.* Paratyphi A strains resistant to quinolones were associated with travel to the Indian subcontinent.[11,12] In 2013, an increase in cases of paratyphoid fever in travelers returning from Cambodia was reported, and all isolates were sensitive to fluoroquinolones.[13] Shwe and others reported that *S. typhi* was most commonly isolated from blood cultures among children admitted to a hospital in Yangon,[14] and all isolates were sensitive to nalidixic acid. However, there was no case of *S.* Paratyphi in this report. In a report on an outbreak of typhoid fever in Myanmar, all three isolates were pansensitive.[2] In our cases, all isolates were resistant to nalidixic acid, and they were categorized as intermediate or resistant to fluoroquinolones. Although Myanmar is a country in southeast Asia, the antibiotic susceptibility pattern of *S.* Paratyphi A may resemble that in the Indian subcontinent.

Paratyphoid fever is increasingly reported in Asia,[12] and considering our findings, it should be considered as a differential diagnosis in febrile patients returning from Myanmar. As there are no licensed vaccines against *S.* Paratyphi A infection,[15] travelers to countries where paratyphoid fever is endemic should be educated about dietary precautions against foodborne infections, and available vaccines against paratyphoid fever are expected. In addition, physicians need to consider fluoroquinolone resistance when treating patients with paratyphoid fever from Myanmar.

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REFERENCES

1. Arndt MB, Mosites EM, Tian M, Forouzanfar MH, Mokhdad AH, Meller M, Ochiai RL, Walson JL, 2014. Estimating the burden of paratyphoid a in Asia and Africa. *PLoS Negl Trop Dis 8:* e2925.
2. Aye TT, Siriarayapon P, 2004. Typhoid fever outbreak in Madaya Township, Mandalay Division, Myanmar, September 2000. *J Med Assoc Thai 87:* 395–399.
3. Clinical and Laboratory Standards Institute (CLSI), 2016. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement*. M100-S26. Wayne, PA: CLSI.
4. National Institute of Infectious Diseases, 2015. *Infectious Diseases Weekly Report Japan*. Available at: http://www.nih.go.jp/niid/ja/idwr.html. Accessed April 12, 2016.
5. Saitoh T, Morita M, Shimada T, Izumiya H, Kanayama A, Oishi K, Ohnishi M, Sunagawa T, 2016. Increase in paratyphoid fever cases in Japanese travellers returning from Cambodia in 2013. *Epidemiol Infect 144:* 602–606.
6. Ministry of Hotels and Tourism, 2015. *Myanmar Tourism Statistics*. Available at: http://www.myanmartourism.org/index.php/publication/tourism-statistics. Accessed April 12, 2016.
7. National Institute of Infectious Diseases, 2015. *Infectious Agents Surveillance Report*. Available at: http://www.nih.go.jp/niid/ja/iasr.html. Accessed April 12, 2016.
8. ECDC, 2013. *Rapid Risk Assessment. Unusual Increase in Reported Cases of Paratyphoid: A Fever among Travelers Returning from Cambodia*. Available at: http://www.ecdc.europa.eu/en/publications/Publications/paratyphoid-fever-cambodia-rarap-risk-assessment.pdf. Accessed April 12, 2016.
9. Hassing RJ, Menezes GA, van Pelt W, Petit PL, van Genderen PJ, Goessens WH, 2011. Analysis of mechanisms involved in reduced susceptibility to ciprofloxacin in *Salmonella enterica* serotypes Typhi and Paratyphi A isolates from travellers to southeast Asia. *Int J Antimicrob Agents 37:* 240–243.
10. Meltzer E, Stienlauf S, Leshem E, Sidi Y, Schwartz E, 2014. A large outbreak of *Salmonella* Paratyphi A infection among Israeli travelers to Nepal. *Clin Infect Dis 58:* 359–364.
11. Hassing RJ, Goessens WH, Mevius DJ, van Pelt W, Mouton JW, Verbon A, van Genderen PJ, 2013. Decreased ciprofloxacin susceptibility in *Salmonella typhi* and Paratyphi infections in ill-returned travellers: the impact on clinical outcome and future treatment options. *Eur J Clin Microbiol Infect Dis 32:* 1295–1301.
12. Crump JA, Mintz ED, 2010. Global trends in typhoid and paratyphoid Fever. *Clin Infect Dis 50:* 241–246.
13. Tourdjman M, Le Hello S, Gossner C, Delmas G, Tubiana S, Fabre L, Kerléguer A, Tarantola A, Fruth A, Friesema I, Thorstensen Brandal L, Lawrence J, Fisher I, Dufour M, Weill FX, de Valk H, 2013. Unusual increase in reported cases of paratyphoid A fever among travellers returning from Cambodia, January to September 2013. *Euro Surveill 18:* 20594.
14. Shwe TN, Nyein MM, Yi W, Mon A, 2002. Blood culture isolates from children admitted to Medical Unit III, Yangon Children's Hospital, 1998. *Southeast Asian J Trop Med Public Health 33:* 764–771.
15. Sahastrabuddhe S, Carbis R, Wierzba TF, Ochiai RL, 2013. Increasing rates of *Salmonella* Paratyphi A and the current status of its vaccine development. *Expert Rev Vaccines 12:* 1021–1031.