Gastroenteritis in Japanese Females Caused by *Shigella flexneri* without Definite Infection Route: A Case Report and Mini-Review of Literature

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**Abstract**

In Japan, the incidence of Shigellosis is low at approximately 150 cases per year, with the majority of these being imported, mainly from Asia. Sporadic domestic occurrences are also reported, with no epidemiological association. We report a case of gastroenteritis caused by *Shigella flexneri* in a 60-year-old Japanese female who recovered fully following treatment with levofloxacin. While we were unable to identify the route of infection, we suspected imported frozen marine products that may have been handled or processed in an unsafe manner. Shigellosis should be included in the differential diagnosis when presented with a patient exhibiting symptoms of gastrointestinal infection, even in the absence of a history of travel to an endemic area.

**Keywords:** *Shigella flexneri*, Japan, Infection route

**Introduction**

Shigellosis is a significant problem throughout the world with the highest prevalence in tropical and subtropical climates, particularly in areas where living standards may be low and access to sufficient safe drinking water and proper excreta disposal systems are limited [1]. Bacterial dysentery due to *Shigella* species is a major cause of morbidity and mortality with 165 million cases occurring annually worldwide and 1 million associated deaths. *Shigella* is the third leading cause of diarrhea mortality in children under five years of age [2].

In Japan, the number of reported cases had been decreasing annually, and the rate has remained generally flat since 2013 at approximately 150 cases per year [3]. Most of these are imported cases, especially from Asia, including India, Indonesia, the Philippines, and Cambodia, in decreasing order of occurrence [3]. However, domestic cases are also reported [3]. According to bacterial strain, reported cases of *Shigella sonnei* are the most frequent followed by *S. flexneri* [3,4]. Domestic outbreak due to *S. sonnei* occurred at a kindergarten in 2014, and an elementary school in 2015. Domestic outbreak due to *S. flexneri* has not been reported [3]. With the exception of outbreak, the majority of domestic cases have occurred sporadically with unknown epidemiological association [3]. As far as we know, there have been no reported cases of domestic sporadic gastroenteritis caused by *Shigella*, including *S. flexneri*, with identified infectious route in Japan. We report a case with a brief review of literature.

**Case Report**

In June, a 60-year-old Japanese female presented to our hospital complaining of sudden-onset physical fatigue, fever, epigastralgia, vomiting and watery diarrhea. She was well nourished and reported her occupation as housewife. She visited our hospital regularly for hypertension, diabetes mellitus, and hyperlipidemia, and was under treatment with aliskiren, azelnidipine, sitagliptin, and rosuvastatin. She was negative for immunodeficiency syndrome, and denied the use of tobacco or alcohol. She had no history of travel abroad for the past ten years, and denied unspecified sex partners. She had received a medical check-up four month prior to her visit and no abnormality had been detected. She had no history of eating raw or undercooked food for the past 7 days. She was married and lived with her husband of the same age, who was retired and had no relevant medical history. Her husband and neighbors were negative for similar symptoms.

Her vital signs revealed tachycardia and high-grade fever. Physical examination revealed tenderness to the epigastric fossa. Routine blood tests showed leukocytosis, elevation of C-reactive protein and decline of sodium and potassium, while the results of urinalysis were within normal limits. Plain chest-abdominal computed tomography showed thickening mucosa of the ascending colon and small intestine (Figure 1). A tentative diagnosis of gastroenteritis without definite suspected infection route was made and she was admitted under contact infection precautions.

Sulbactam/ampicillin 9 g/day was started as empiric therapy; however, fever and abdominal symptoms persisted. 2/2 sets of blood culture test taken at admission were negative. Cystic forms of *Entamoeba histolytica* were not observed on microscopic examination of stool, and serological fluorescent antibody technique were negative for amebic antibody. On day 3 of hospitalization, colonies grown on bromothymol

**Figure 1:** Chest-abdominal computed tomography in admission.

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blue lactate agar and Salmonella-Shigella agar using stool resulted in a diagnosis of gastroenteritis caused by S. flexneri (Figure 2). It was resistant to sulbactam/ampicillin by drug susceptibility testing, and we changed antibiotics to 500 mg/day intravenous administration of levofloxacin. On the same day, her fever resolved and her abdominal symptoms lessened. She was started on oral ingestion on day 4 hospitalization. Later, levofloxacin was terminated on day 7 of hospitalization. She complained of epigastric distress and fever on day 8 of hospitalization. On day 9 of hospitalization, esophagogastroduodenoscopy revealed normal findings. Stool cultures taken on day 11 and 12 of hospitalization were negative. The patient recovered fully and was discharged on day 15 of hospitalization without antibiotics or antipyretic drugs. In this case, the infection route remained unknown.

Discussion

This case was neither imported nor the result of outbreak at a restaurant or institution, which are the most common cause of infection in Japan. While the infection route was not identified, there was a report of a mass gastroenteritis outbreak caused by Shigella spp in which imported frozen marine products including attached ice was suspected as the source of infection. In addition, unsafe food handling and processing can serve as a vehicle for transmission [4-6]. From this point of view, we suspected that contaminated imported frozen marine products might have been the route of infection. On the other hand, shigellosis has been reported in men with a history of homosexual activity in developed countries, including Japan; therefore, attention to sexual behavior as a potential route of transmission is recommended [7,8].

Shigella, a gram-negative bacterium, is responsible for Shigellosis/ bacillary dysentery; and four serotypes are seen in Asia: S. flexneri, S. sonnei, S. dysenteriae, and S. boydii. While these are a global concern, they predominate in developing countries [9]. S. flexneri is the most common species of Shigella causing diarrhea and dysentery in developing countries in Asia [10,11]. In Japan, S. flexneri is estimated to account for 18% of bacterial dysentery [12]. We have included a table of published articles related to S. flexneri in Asia from January 2014, searched in the PubMed database using the keywords S. flexneri, Asia, and human (Table 1). The search yielded 35 articles including a total 42,942 cases [9,10,13-38]. According to the table, the greatest number of articles came from China with 13 articles and 35,794 cases, followed by India with 6 articles and 972 cases.
Table 1: Published articles of Shigella flexneri in Asia from January 2014.

| Country          | From | To               | All ages | \# |
|-----------------|------|-----------------|----------|----|
| Pakistan        | 2001 | December 2014   |          | 242 | [9] |
| Pakistan        | Over 5 years (Not specified) | Children aged from birth–9 months | 84 | [28] |
| Pakistan        | December 2011 to November 2013 | All ages | 25 | [36] |
| Israel          | 1998 to 2012 | All ages | 3.428 | [37] |
| Israel          | 2005 to 2009 | All ages | 1.058 | [38] |
| Nepal           | January 2001 to December 2014 | All ages | 99 | [9] |
| Thailand        | January 2001 to December 2014 | All ages | 24 | [9] |
| **Total**       |      |                 |          | 42.942 |

Shigella organisms can survive transit through the stomach due to their lower susceptibility to acid than another bacteria exhibit. For this reason, as few as 10 to 100 organisms can cause disease [39]. There are several virulence factors contributing to the colonization and invasion of epithelial cells and the eventual death of host cells [34]. Shigella also has the ability to carry multiple plasmids in relation to virulence [40]. The ial gene was the most frequent virulence gene among isolated bacterial strains followed by ipaH, set1B, and set1A; and S. flexneri possessed all (ial 66%, ipaH 59%, set1A 12%, and set1B 22%) [35].

Patients with Shigella gastroenteritis typically present with high fever, abdominal cramps, and bloody, mucoid diarrhea: fever (30% to 40%), abdominal pain (70% to 93%), mucoid diarrhea (30% to 85%), bloody diarrhea (35% to 55%), watery diarrhea (30% to 40%), and vomiting (35%) [41]. Both severe intestinal disease and extra-intestinal manifestations of shigellosis occur with infection by any of the four species of Shigella; however, they are most common with S. dysenteriae type 1 [41]. Among several severe extra intestinal manifestations, encephalopathy is one of the most common complications; and it has been associated with a higher rate of death [31]. The common manifestations of Shigella encephalopathy are seizure, altered consciousness and coma [31]. Encephalopathy is usually reversible; however, it can sometimes fulminate and be fatal [31].

The magnitude of shigellosis in developing countries is largely unknown because an affordable detection method is not available [42]. Current laboratory diagnosis of Shigella spp is laborious, time-consuming and has low sensitivity [42]. Hence, a molecular-based diagnostic assay which simultaneously amplifies four specific genes to identify Shigella genus was developed in a single reaction to detect and differentiate Shigella spp [42]. Validation with 120 Shigella strains and 37 non-Shigella strains yielded 100% specificity [42]. In addition, the sensitivity of pentaplex polymerase chain reaction (PCR) assay was further improved following preincubation of stool samples in gram-negative broth [42]. The developed pentaplex PCR assay is robust and is capable of providing information about target genes essential for the identification of the Shigella genus and the three Shigella species responsible for the majority of shigellosis cases [42]. Pulsed-field gel electrophoresis (PFGE) is convenient for evaluation of the clonal relatedness of the strains; however, in such geographical areas where the same clone is in circulation, use of antibiotic resistance typing and/or plasmid profile analysis together with PFGE would be useful for precise discrimination of Shigella strains [43,44].

Antibiotic treatment of shigellosis is required to prevent mortality [45]. Patients are often treated with antimicrobial agents to reduce the duration of illness, and the treatment is known to reduce the period of Shigella excretion [46]. Antibiotic susceptibility testing should be performed at the time of stool and/or blood culture, and at the start of outbreak; and antibiotic use should be restricted to cases of Shigella classified as severe based on resistance pattern variations observed in different regions [24]. Although antimicrobial susceptibility was considerably high to most commonly used drugs, genetic determinants were variable between countries over time; therefore, the data stress the need for a more careful selection of antibiotics in the treatment of shigellosis [47]. The majority of S. flexneri is sensitive to 3rd generation cephalosporins, and quinolones, especially ciprofloxacin, are commonly employed in the treatment of shigellosis [36,46]. However, in recent years, some Shigella strains have rapidly developed resistance to antimicrobial agents [9,23,46,48]. For example, more than 80% of isolates of S. flexneri have proven resistant to ampicillin, nalidixic acid, and tetracycline; and in China from 2004 to 2014, Shigella isolates were highly resistant to nalidixic acid (89%), ampicillin (89%), tetracycline (88%), and sulfamethoxazole (83%). During the study period, isolates resistant to ciprofloxacin and cefotaxime increased, respectively, from 9 and 8% in 2005 to 4 and 30% in 2014 [14,17,18]. Multi-drug-resistant Shigella, including extended spectrum β-lactamases producing Shigella, is also emerging; and has the potential to become a serious threat to public health [11]. Here, several mechanisms are responsible for the development of antimicrobial resistance in Shigella strains [46]. One prominent mechanism is the mutation of the genes related to antimicrobial resistance [46]. For example, about quinolone resistance, the target regions where mutations occur in the organism have been identified as topoisomerase IV (parC and parE) and DNA gyrase (gyrA and gyrB) [18,46]. Another mechanism depends on plasmid-mediated antimicrobial resistance [40,46]. For example, S. flexneri is divided into at least 19 serotypes, the majority of which being modifications of the same basic O-antigen by glycosylation and/or O-acetylation of its sugar residues by phage encoded serotype-converting genes [49]. Plasmid-encoded gene modification is an important serotype conversion mechanism in S. flexneri, in addition to glycosylation and O-acetylation [49]. Furthermore, quinolone resistance (PMQR) determinants are qnr, aac(6')-Ib-cr, and qepA [40,46]. Considering the above, monitoring of the drug resistance of Shigella strains should be strengthened, and rational use of antibiotics is required [17,50]. In addition, guidelines for therapy should be monitored and modified based on regional reports of resistance to antimicrobial agents [11].

Overall fatality rate was 10% and did not differ significantly by species; and the case-fatality-rate was significantly higher among the children with Shigella encephalopathy accompanied by symptoms including of documented seizure and unconsciousness, malnutrition, hyponatremia, and lower stool frequency [31,41]. Therefore, early identification and aggressive management may help to reduce morbidity and death, especially in resource-limited settings [31].

Conclusion

In summary, we experienced a case of gastroenteritis caused by S. flexneri whose infection route we were unable to identify; however, we suspected imported frozen marine products. The incidence is low in Japan although sporadic cases or outbreaks are sometimes confirmed. Therefore, we concluded that it should be included in the differential diagnosis when encountering patients with symptoms of gastrointestinal infection, even in the absence of a history of travel to an endemic area. In addition, constant epidemiological surveillance, improvement of personal hygiene and environmental sanitation are recommended for control of pathogen infection, especially for food handlers.

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