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ORIGINAL ARTICLE

# ***Salmonella Typhi* Associated Endogenous Endophthalmitis: A Case Report and a Review of Literature**

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## ABSTRACT

**Aim:** To report a rare case of *Salmonella typhi* associated endogenous endophthalmitis in an immunocompetent male and to review the available literature.

**Methods:** Retrospective chart review.

**Results:** A 28-year-old immunocompetent male presented with a 3-day-old history of pain, redness and diminished vision in his left eye. Conjunctival chemosis, corneal haze, and hypopyon were noted and yellowish exudates filled the vitreous cavity. A detailed elicitation of history revealed that patient had been treated for enteric fever that presented with diarrhea and fever, two weeks prior to current presentation. Blood and vitreous cultures grew Gram negative bacilli, identified as *S. typhi*. Despite intensive intravitreal and systemic antibiotic therapy, an evisceration had to be performed.

**Conclusions:** Endogenous endophthalmitis can be one of the rare sequelae of enteric fever and may present in the acute and relapsing phases and often times have a rapidly fulminant course with poor visual outcomes.

**Keywords:** Endogenous endophthalmitis, evisceration, infection, *Salmonella*, septicemia, typhoid fever, Widal

## INTRODUCTION

Endogenous endophthalmitis is caused by the hematogenous spread of infectious organisms from distant sites of the body into the eye. These sequestered organisms, having overcome the blood-ocular barriers, cause inflammation within the eye and can potentially cause severe visual loss.<sup>1</sup> As compared to exogenous endophthalmitis, where the offending organism is introduced into the eye via ocular surgery, open globe trauma or intravitreal injections, endogenous endophthalmitis is relatively rare, accounting for only 2–15% of all cases of endophthalmitis.<sup>2</sup>

Previously published case series have reported that the most common bacterial organism responsible for endogenous endophthalmitis is *Staphylococcus aureus* and the

most common fungal organism is *Candida* species.<sup>3</sup> *Salmonella* species is not one of the commonly encountered organisms responsible for causing endophthalmitis. In this communication, we report the case of a 28-year-old immunocompetent patient with a past history of enteric fever, which presented with endogenous endophthalmitis. We also review the contemporary literature available on the subject matter.

## CASE REPORT

A 28-year-old male presented with a three-day history of redness and sudden, painful diminution of vision in his left eye. The best-corrected visual acuity was 6/6 in

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the right eye and the perception of light with inaccurate projection was in the left eye. On examination, the right eye was unremarkable. However, in the left eye, lid edema, conjunctival chemosis, corneal edema, and 1 mm hypopyon were seen (Figure 1A). The pupil was dilated and nonreactive to light. Yellow-colored exudates were seen plastered to the posterior surface of the lens and filling the entire vitreous cavity obscuring any view of the retina. There was no proptosis and ocular motility was normal. The patient was afebrile.

There was no recent history of trauma, surgery, lasers, or intravitreal injections. He had a history of typhoid fever two weeks prior to presentation for which he had been hospitalized. His treatment charts and laboratory reports from the time of admission were retrieved and it showed that in addition to supportive intravenous fluids and antipyretics, he was treated with oral chloramphenicol 500 mg for 14 days. Investigations done at the time of fever (101.4° F) showed leucopenia and positive Widal test (titers for *S. typhi* "O" antigen—1:320, titers for *S. typhi* "H" antigen—1:160). The fever had resolved by the 6th day; however, the oral antibiotic therapy continued for two weeks. Three days after cessation of the oral chloramphenicol therapy, he developed redness and diminution of vision, which rapidly progressed over the next three days.

He was initiated on intravenous ceftriaxone (750 mg QID) and topical fortified cefazoline eyedrops (q1h). Laboratory investigations done now showed leukocytosis with normal erythrocyte sedimentation rate and normal C-reactive protein level. Investigations for co-existing diseases—namely, HIV, hepatitis B, syphilis, and tuberculosis (Tuberculin Skin Sensitivity and QuantiFERON TB Gold ®) were equivocally negative. Urine analysis, computed tomography (CT) of the chest, and ultrasonography of the abdomen showed no abnormal findings. Serum complement levels were

also normal. Blood cultures drawn prior to intravenous antibiotics, however, grew gram-negative bacilli, which were identified as *Salmonella typhi* based on Gram staining, the oxidase test, the catalase test, motility, triple-sugar iron (TSI) fermentation, and colony morphology. Antibiotic susceptibility using Kirby–Bauer Disk diffusion method showed the strain to be sensitive to chloramphenicol, vancomycin, gentamicin, ciprofloxacin, ceftazidime, ofloxacin, gatifloxacin, and moxifloxacin. It was resistant to ampicillin, amoxicillin, piperacilin, and azithromycin.

CT scans of the orbits showed irregular iso-to-hyperdense shadows occupying the entire vitreous cavity (Figure 1B). An ultrasound of the eye was showed multiple medium-density echoes clumped together in the vitreous cavity suggestive of dense vitritis with a closed funnel retinal detachment (Figure 1C). Therefore, with a diagnosis of *S. typhi*-induced endogenous endophthalmitis, three doses of intravitreal injections of vancomycin (1 mg/0.1 ml), ceftazidime (2.25 mg/0.1 ml), and dexamethasone (0.4 mg/0.1 ml) were administered in the left eye on alternate days. At the end of one week, the response to treatment was found to be sub-optimal with no improvement in clinical signs; an intravitreal injection of imipenem (50 µg/0.1 ml) and colistin (0.1 mg/0.1 ml) was administered. This decision was taken as visualization of the posterior segment was poor due to corneal edema. Therefore, it was decided to delay the vitrectomy till we could have a better view. The intravitreal injections were administered through the pars plana route into the vitreous cavity, taking care to avoid injecting into the subretinal space. Following this, the patient was taken into the operating room for a vitrectomy; however, it had to be abandoned midway in view of severe intraoperative bleeding and poor visualization. However, a undiluted vitreous aspirate taken at the time of surgery was sent for

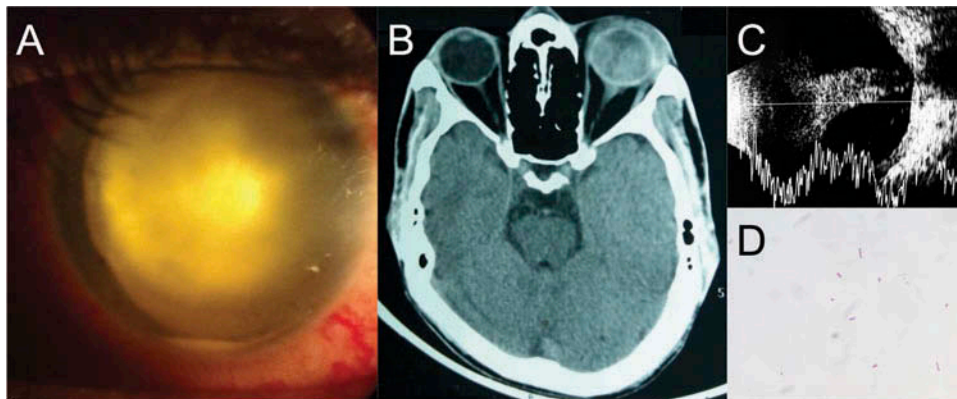


FIGURE 1. (A) Clinical photograph showing conjunctival congestion, corneal edema, iris neovascularization, and streak hypopyon along with leukocoria. (B) Axial computed tomography (CT) scan cut showing irregular iso-hyperdense shadows occupying the entire vitreous cavity and minimal preseptal swelling. (C) Ultrasound of the eye showing multiple medium density echoes clumped together in the vitreous cavity suggestive of dense vitritis with a closed funnel retinal detachment. (D) High magnification photomicrograph showing multiple rod shaped organisms, which were later identified as *Salmonella typhi*. (Grams' stain, 100x; oil immersion)

microbiological analysis and the smears showed small, rod-shaped bacilli that were Gram-negative on Gram's stain (Figure 1B). The cultures from this aspirate did not grow any organisms; therefore, an antibiogram was not available to guide further medical management. This organism was also subsequently identified as *S. typhi*, which was confirmed using an automated biochemical kit system.

Eventually, 12 days after initial presentation, the vision dropped to no perception despite systemic and intravitreal therapy and subsequently the patient's left eye was eviscerated. Postoperatively he received oral ciprofloxacin 500 mg PO for 2 weeks. At the 6-month follow-up, the socket was healthy and he had had no relapses of enteric fever, with stool and blood cultures being negative.

## DISCUSSION

The bacterial pathogen *S. enterica* is a highly ubiquitous species consisting of more than 2600 different serovars that can be divided into typhoidal and non-typhoidal *Salmonella* (NTS) serovars.<sup>4</sup> NTS serovars such as *Typhimurium* and *Enteritidis* are generalist pathogens with broad host-specificity. In contrast, a few *S. enterica* serovars including *Typhi*, *Sendai*, and *Paratyphi* A, B, or C are highly adapted to the human host that is used as their exclusive reservoir. These specialist pathogens, collectively referred to as typhoidal *Salmonella* serovars, are the causative agents of enteric fever. Enteric fever is also known as typhoid or paratyphoid fever if caused by serovar typhi or paratyphi, respectively.<sup>4</sup> Enteric fever is a major public health problem causing an estimated 11.9–26.9 million cases and 129 000–217 000 deaths worldwide each year.<sup>5</sup> In contrast to enteric fever, which is common in the developing world, NTS salmonellosis occur worldwide. Despite global morbidity, mortality due to NTS infection is rare.<sup>4</sup> One of the most important differences between typhoidal serovars and NTS serovars is the clinical manifestation of the disease they cause: in immunocompetent individuals, NTS serovars cause self-limiting gastroenteritis; in immunocompromised patients, the disease may be associated with invasive extraintestinal infections. In contrast, typhoidal serovars routinely cause invasive, systemic disease even in immunocompetent individuals as was seen in our case.<sup>4</sup>

An exhaustive review of the literature shows that there are only 13 previously reported cases of microbiologically proven *Salmonella*-Associated Endogenous Endophthalmitis (SAEE) with ours being the 14th such reported case.<sup>6–18</sup> The salient clinical findings of these cases are summarized in Table 1.

Risk factors for salmonellosis include gastric hypochlorhydria, recent use of antibiotics, extremes of age, and a variety of immunosuppressive conditions.<sup>19</sup> Ten of the

thirteen previously published cases had at least one of these risk factors present. Furthermore, recent hospitalization, which was present in the current case, and immunosuppressed states are also independent risk factors associated with endogenous endophthalmitis.<sup>20</sup>

In nearly half the cases of SAEE, the patients were one-year old or younger. The other immunocompromised conditions in which SAEE has been reported include chronic immunosuppression due to oral steroids and chemotherapy, HIV infection, premature birth, co-existing malaria, and anemia and also infancy,<sup>6–15</sup> when the immune system is still developing.<sup>21</sup> Out of all the reported cases of SAEE, it was noted that in four cases—the patients were immunocompetent. Furthermore, in three out of these four immunocompetent patients, the offending organism was *S. typhi*.

An associated focus of infection is often identifiable in patients with endogenous endophthalmitis.<sup>16</sup> As was the case in our patient who had a previous history of diarrhea and fever caused by the focus of *S. typhi* infection in the gastro-intestinal tract. However, our patient developed SAEE despite a two-week long course of chloramphenicol. Recently, it has been reported that most isolates of *Salmonella* are reverting to susceptibility to older drugs like chloramphenicol.<sup>21</sup> However, at the same time it must be borne in mind that relapse rates in patients treated with chloramphenicol can be as high as 10%. While reinfection can be distinguished from relapse by molecular typing of isolates, in our case molecular typing was not done. This underscores the importance of performing a blood culture early in the course of infection.

With regard to lab investigations, in most of the reported cases, either positive aqueous or vitreous cultures were taken as confirmatory sign of *Salmonella* endophthalmitis. Blood cultures, bone marrow, and stool cultures have also been examined in previous cases. A positive Widal test has been reported only in three cases including the present case.<sup>16,17</sup>

Different serotypes belonging to the *Salmonella* species have been associated with SAEE. The reported organisms include *S. typhimurium*, *S. arizonae*, *S. London*, *S. choleraesuis*, and *S. typhi*. Among the previously reported cases of SAEE due to *S. typhi*, in the case reported by Arora et al., an immunocompetent male developed bilateral SAEE during the acute phase of the infection.<sup>16</sup> However, the patient did not have any gastrointestinal symptoms or focus; instead, a pulmonary focus in the form of bronchopneumonia was identified. In the other case reported by Sinha et al., the ocular symptoms started nearly 2 months after initial febrile illness.<sup>17</sup> Relapse usually occurs about three weeks after the last febrile day or about two weeks after cessation of antibiotics.<sup>17</sup> Therefore, in our case, it is plausible that inadequate treatment led to bacteremia which led to the development of endophthalmitis. However, it must be noted that the

TABLE 1. Summary of the findings of previously published cases of *Salmonella* endogenous endophthalmitis.

No.	Author/Year	Age/Sex	Presenting Feature	Laboratory Diagnosis*	Treatment	Risk Factors	<i>Salmonella</i> Species	Outcome
1	Corman et al./1979 <sup>[6]</sup>	7 w/M	Proptosis, Periorbital swelling, Leucocoria	Aqueous culture	Ampicillin (IV)	Infancy	<i>Salmonella enteritidis</i>	Enucleation
2	Weinstein et al./1982 <sup>[7]</sup>	48 y/M	Chemosis, corneal edema, pupillary membrane, anterior chamber reaction	Aqueous, blood and stool cultures	Methicillin, Gentamicin, Chloramphenicol, Cotrimoxazole (IV); Gentamicin (T); Cotrimoxazole (IVT)	Chronic lymphocytic leukemia	<i>Salmonella typhimurium</i>	Enucleation
3	Shohet et al./1983 <sup>[8]</sup>	1 y/M	Inflammation, Leucocoria	Blood, bone marrow, vitreous, stool cultures	Gentamycin, Cephalothin (IV)	Infancy	<i>Salmonella typhimurium</i>	No PL
4	Appel et al./1986 <sup>[9]</sup>	1 y/F	Lid edema, Inflammation, Corneal edema,	Blood, bone marrow, aqueous, stool cultures	Garamycin, Cephalothin (IV)	Infancy	<i>Salmonella typhimurium</i>	Not reported
5	Kestelyn et al./1986 <sup>[10]</sup>	11 m/M	Proptosis, chemosis, corneal edema, anterior chamber exudates	Blood culture	Cefotaxime (IV)	Infancy, Malaria, Anaemia	<i>Salmonella typhimurium</i>	Enucleation
6	Carvalho et al./1990 <sup>[11]</sup>	55 y/F	Conjunctival congestion, hypopyon	Blood and vitreous cultures	Garamycin, Cephalothin (IV); Gentamicin, Dexamethasone (SC); Tobramycin (T); Cotrimoxazole (PO)	Rheumatoid Arthritis, Immunosuppression on prednisone and azathioprine	<i>Salmonella arizonae</i>	Enucleation
7	Senft et al./1993 <sup>[12]</sup>	4 m/M	Periorbital swelling, proptosis, corneal melting, total hypopyon	Vitreous cultures	Cephazolin, Gentamicin (T); Cephazolin, Gentamicin (IV); Cephalixin (PO)	Prematurity, Infancy	<i>Salmonella</i> serotype B	Enucleation
8	Suvarnamani et al./1995 <sup>[13]</sup>	2 m/F	Conjunctival congestion, corneal haze, iris neovascularization, leucocoria	Vitreous, stool cultures	Ampicillin, Cloxacillin (IV)	Infancy	<i>Salmonella typhimurium</i>	Enucleation
9	Yu et al./2002 <sup>[14]</sup>	3 m	Redness, leukocoria, mild fever, diarrhea	Vitreous culture	Nafcillin, Cefotaxime, Metronidazole (IV); Vitrectomy, lensectomy	Infancy	<i>Salmonella London</i>	Not Reported
10	Yodprom et al./2007 <sup>[15]</sup>	54 y /M	HypHEMA, hypopyon, iris nodules, posterior synechiae	Aqueous, blood cultures	Amikacin (IVT); Ceftriaxone (IV); Ciprofloxacin (PO)	HIV infection	<i>Salmonella choleraesuis</i>	Phthisis

11	Arora et al./ 2008 <sup>[16]</sup>	32 y/M	Bilateral Proptosis, conjunctival congestion, corneal edema, anterior chamber exudates	Widal, blood culture	Vancomycin (T + IVT), Cefazidime (T + IVT), Ciprofloxacin (T + PO); Ceftriaxone, Gentamicin (IV); Vitrectomy	None	<i>Salmonella typhi</i>	No PL
12	Sinha et al./ 2012 <sup>[17]</sup>	4 y/M	Inflammation, Exudates in Anterior chamber	Widal, Vitreous culture	Gentamicin (IV); Vitrectomy	None	<i>Salmonella typhi</i>	No PL
13	Rachitskaya et al. /2012 <sup>[18]</sup>	12 y/M	Conjunctival congestion, anterior chamber exudates	Blood, stool cultures	Vancomycin, Cefazidime, Dexamethasone,	None	<i>Salmonella</i> Serotype B	No PL
14	Present case	28 y/M	Conjunctival congestion, hypopyon, leucocoria,	Widal; blood, vitreous cultures	Antibiotics (IV + IV)	None	<i>Salmonella typhi</i>	Evisceration

\* Only cultures that grew the identifiable organisms are mentioned here.

IV – intravenous; T – topical, IVT – intravitreal; PO – per Os/oral administration; PL – perception of light; HIV – human immunodeficiency virus



antibiotic sensitivity testing showed the organism to chloramphenicol which the patient had received for 14 days before ocular symptoms were seen.

The reported outcomes of SAE in the literature have been poor, despite intensive topical intravitreal and systemic antibiotic therapy. All cases have either progressed to total loss of vision resulting in phthisis bulbi or have required enucleation or evisceration highlighting the fulminant and refractory course that SAE has in both immunosuppressed and immunocompetent patients. *Salmonella* infections can affect the eye in the acute or relapsing phase and are often fulminant and devastating ocular infections and poor visual outcomes. Endogenous endophthalmitis is a rare complication of *Salmonella* infections.

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