Clinical considerations in the diagnosis and management of enteric fever and its complications

Rishab Martins[1], Shilpa Sule[1], Milly Tadigiri[1], and Bheemeswara Reddy Yeruva[2]

[1]Bharati Vidyapeeth (Deemed to be University)
[2]Zaporizhzhia State Medical University

September 01, 2024

Clinical considerations in the diagnosis and management of enteric fever and its complications

Dr. Rishab Julius Martins[1], Dr. Shilpa Sule[2], Dr. Milly Tadigiri[3], Dr. Bheemeswara Reddy Bheemeswara Yeruva Doctor[4]*

[2] professor of medicine, Bharati Vidyapeeth (deemed to be university), Pune, Mahahrashtra, India

[3] Bharati Vidyapeeth (deemed to be university), Pune, Mahahrashtra, India

[4] Zapporizhzhia state medical university, medicine, Zhaporozhye, Ukraine

Authorship contributions

Dr. Rishab Julius Martins- Conceptualization, Data curation, Formal analysis,Visualization, Writing – original draft**; Dr. Shilpa Sule-** Investigation, Methodology, Project administration, Supervision, Writing – review & editing; **Dr. Milly Tadigiri-** Data curation, Visualization, Writing – review & editing;**Dr. Bheemeswara Reddy Bheemeswara Yeruva Doctor -** Writing – review & editing.

Conflict of Interest

None

Consent and ethical statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. This case report was exempt from ethical approval at our institute as it reports a single case that emerged during routine practice.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

There was no funding for this case report

Acknowledgements

None

not-yet-known not-yet-known

not-yet-known

unknown

Key clinical message A 24 year old male in Maharashtra, India presented with a fever and rash. This case highlights the importance of careful differential diagnosis and treatment of enteric fever and its complications in tropical and sub-tropical regions.

Case history

A 24-year-old male, with no history of recent out of state travel, presented to the emergency department on with the chief complaints of fever with chills for 3 days, vomiting (3 episodes with nausea but not blood-stained), diarrhea, dull aching abdominal pain, body ache, and burning urination for 2 days. He reported no chest pain or breathlessness. There were no past complaints and family history was not significant. The patient denied any addictions and followed a vegetarian diet.

On examination, the patient's general condition was stable and maculopapular rash was noted on his torso. His pulse was 82 beats per minute, respiratory rate was 18/min, oxygen saturation was 98% on ambient air, and temperature was 102°F. a blanching rash was noted on the torso. On review of systems a dry cough was observed along with mild weakness (4/5) was noted on the right side. The remainder of the physical exam was normal.

The patient brought with him previous investigation reports from 2 days prior showing a hemoglobin of 15.6 g/dL, white blood cell count of 8300 /µL, and platelets of 300,000 /µL. He verbally reported outside testes for Dengue IgM and NS1, and Leptospira were negative, but could not provide any documentation. ELISA for COVID-19 was negative in the emergency room.

The differential diagnosis at this time included enteric fever, influenza-like illness (ILI), urinary tract infection (UTI), legionella, and malaria.

Investigations ordered included hemogram with differential count, urine routine examination, electrocardiogram, chest X-ray, blood sugar (fasting, postprandial, random), abdominal ultrasound, blood urea/creatinine, electrolytes, cardiac markers, skin biopsy, urine analysis along with blood urine and stool cultures.

The patient was advised hospital admission and treated with intravenous (IV) fluids for rehydration, injection pantoprazole 40 mg once daily, injection ondansetron 4 mg three times daily, injection paracetamol 500 mg three times daily, and, empirically, with intravenous injections of ceftriaxone.

Conclusion

The patient was counselled on the need of proper hand hygiene both for him and the members of this household. Unfortunately, a minority of patients among the low-income communities served are able to adhere to such guidance in the long term. Even though the risk of carrier status in non-typhoid salmonella is low at 0.15% in adults [30] the patient was counselled on the same.

Discussion on the differential diagnosis and management

Differential diagnosis

Every year the monsoon brings with it an uptick in number febrile illnesses. Of these, the deferential diagnosis for an acute diarrheal illness with a rash in the subcontinental region is still extensive; However, we will endeavor to discuss the most likely culprits

Bacterial

The diagnosis of typhoid fever comes to mind off the bat given the region and the economically disadvantaged disposition of the patient. The dermatological manifestations seen are well explained by this diagnosis

classically described in the literature as "rose spots", though they are known to be difficult to see in people with darker skin tones [1]. However, the classic illness caused by Salmonella typhi does not usually cause diarrhea until 1 to 3 weeks after the febrile phase of the illness. Enteric fever casuesed by paratyphi species could be a possible explanation for the presentation. Rickettsial, caused by Rickettsia conorii, Orientia tsutsugamushi and Rickettsia typhi, diseases remain a not uncommon cause of febrile illnesses in the region, with some reports of their prevalence as high as 15% in the state of Maharashtra [2]. While rash, reported as maculopapular in 4.9% to 98% of febrile patients, was the second most common clinical feature, the classical finding of eschar was less frequently reported in Indian studies (4% to 21.1%), with diarrhea occurring in 22.2% of cases [3]. Given the atypical presentation and the lack of clinical history of a tick bite places rickettsial illness lower on the list of differentials. Leptospirosis commonly transmitted through indirect contact with contaminated water amongst rice farmers as they work their fields during the monsoon season, during which this patient presented to our emergency department, should also be given due consideration. Even as this diagnosis explains several clinical manifestations on first blush, as well as the transaminitis, splenomegaly, and thrombocytopenia which would later be found, on closer examination the lack of subconjuctival suffusion along presence of a rash suggest an alternative diagnosis; The unusual case of "Fort Bragg Fever" caused by L. interrogans had an erythematous rash limited to the pretibial areas [4].

Viral

Arboviral infections, which frequently cause fever in India, include viruses like dengue, chikungunya, Japanese Encephalitis (JEV) and the tick borne Kyasanur forest disease (KFD). It is essential to prioritize ruling out dengue fever, as was done at an outside clinic in this case, because of its potential severity, as early supportive care can greatly improve patient outcomes. Dengue fever typically arises within a few days after a mosquito bite, presenting with nonspecific symptoms such as fever, headache, and in severe cases petechial rash. The rash and lack of neurological findings make JEV less likely, while chikungunya remains on the cards and is therefore important to rule out given the protracted clinical course that is characterized by While chikungunya remains on the cards and is therefore important to rule out given the protracted clinical course that is characterized by, the post-acute stage of chikungunya, occurring from the fourth week to the end of the third month, includes persistent inflammatory symptoms such as inflammatory arthralgia, arthritis, tenosynovitis, and bursitis, and may exacerbate pre-existing degenerative or traumatic joint conditions, leading to local issues such as reactionary edema, entrapment syndromes, joint stiffness, or neuropathic pain, while the chronic stage, starting after the third month and lasting from a few months to several years, is defined by the persistence of these symptoms, including painful flare-ups in overused joints[5]. KFD named after a forest in the neighboring state of Karnataka is transmitted mainly by hard ticks belonging to the genus Haemaphysalis, which transmit the infection among wild non-human primates such as red-faced bonnet monkeys (Macaca radiata) and black-faced langurs (Semnopithecus entellus) [6]. Though the lack of hemorrhagic symptoms and the low annual incidence of around 400 cases a year [7] make it less likely. Cases of Zika, while they do present with a similar rash and fever, have not been reported in the state since 2021 [8].

Parasitic

A usual suspect in patients presenting with an acute febrile illness during the monsoon is malaria. With India contributing 77% of the total malaria burden in Southeast Asia [9]. However, our patient's cutaneous manifestation would not be explained by this diagnosis [10]. Though the protozoal disease most commonly caused by Leishmania Donovani locally known a Kala Azar since the 1800's [11], would explain some symptoms, its common cutaneous manifestations of nodules, ulcers and in severe cases leonine faces were not to be found [12]. Only 2 cases of human babesiosis has been reported in the country, the last one being from within the state in 2022 [13], that long with the lack of hemolysis or the classic "Maltese cross" cross appearance on blood smear male it highly unlikely. Adult trypanosomal infections have not been reported in India.

The diagnosis of enteric fever is mainly clinical, among the Salmonella enterica serovars, human-restricted serovars Typhi and Paratyphi A, B, and C cause enteric fever, with more than half of the world cases

occurring in India in 2017 [21]. Therefore, the diagnosis sits at the forefront of most clinician's minds during the history and examination. Lab reports of hepatitis, bicytopenia along mild pulmonary findings serve to corroborate the diagnosis. The crucial decision to be made in the treatment of enteric fever is the choice of anti-microbial agent(s) as disease progression beyond the first week often implies a poor prognosis; The following paragraph serves as the basis for our choice.

Treatment

Several reports have indicated the global spread of Typhi and Paratyphi strains resistant to all first-line antibiotics—ampicillin, chloramphenicol, and co-trimoxazole—collectively known as multidrug-resistant (MDR) Salmonella [14]. All MDR Typhi and Paratyphi carry the IncHI1 plasmid [15], though more recently in has been found that their prevelance in India is declining and being replaced by the emergence and spread of QRDR Salmonella strains resistant [16] to fluoroquinolones that has been acquired through chromosomal mutations in the quinolone resistance gene qnrS and/or the quinolone resistance determining region (QRDR) harboring gyrB, parE, gyrA, and parC genes [17], with the later 2 being the most common mutations here. Resistance to third-generation cephalosporins is associated with the acquisition of several extended-spectrum β-lactamase (ESBL) genes. The XDR H58 S. Typhi strain, resistant to ampicillin, chloramphenicol, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins, was first identified in Pakistan in 2016 [18]. Azithromycin and carbapenems are last resort antibiotics for treating Salmonella infections, but there have been reports of S. Typhi strains developing resistance to azithromycin and invasive non-typhoidal Salmonella (NTS) becoming resistant to carbapenems [19] [20]. Given India's position as locus for the transmission of XDR H58 S [22] and the clinical picture the decision was made to empirically treat the patient with ceftriaxone.

HLH remains a very rare but potentially fatal complication of enteric fever with atleast 53 cases being reported in the literature [22]. Though our patient only had a 3-5% probability or 119 points on the Hscore [23] at the height of his illness, a high a high index of suspicious is required given the unexplained neurological symptoms [24], low local availability of drugs like etoposide and tests like sCD25 levels. The MRI findings only had the effect of heightening our suspicions. The hyperintensity in the splenium of the corpus callosum, known as the boomerang sign [25], is a documented cytotoxic lesions of the corpus callosum [26]. Whereas the T2 shine through (a hyperintesity on DWI and T2 with true restriction of diffusion as confirmed on ADC) is typically indicative of vasogenic edema [27]. Given the excessive release of pro-inflammatory cytokines [28] in HLH it may be a plausible radiologic manifestation. While further work-up for the disease and an empiric dose of dexamethasone was recommended by hematology, but given the rapid improvement thereafter it was withdrawn.

Other complications one must remain vigilant for include include gastrointestinal hemorrhage, acute kidney injury, myocarditis, pneumonia, anemia, disseminated intravascular coagulation, encephalopathy, cholecystitis, intestinal perforation, and hepatitis [29].

References

[1] Bhandari J, Thada PK, Hashmi MF, et al. Typhoid Fever. [Updated 2024 Apr 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:

[2] Danave, Deepali, and S. N. Kothadia. "Role of Weil Felix Test for Rickettsial Infections." *IOSR-JDMS* 14 (2015): 52-54.

[3] Krishnamoorthi S, Goel S, Kaur J, Bisht K, Biswal M. A Review of Rickettsial Diseases Other Than Scrub Typhus in India. Trop Med Infect Dis. 2023 May 16;8(5):280. doi: 10.3390/tropicalmed8050280. PMID: 37235328; PMCID: PMC10222352.

[4] GOCHENOUR WS Jr, SMADEL JE, JACKSON EB, EVANS LB, YAGER RH. Leptospiral etiology of Fort Bragg fever. Public Health Rep (1896). 1952 Aug;67(8):811-3. PMID: 12983521; PMCID: PMC2030907.

[5] Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: Epidemiology, Pathogenesis,

Clinical Features, Management, and Prevention. Infect Dis Clin North Am. 2019 Dec;33(4):1003-1025. doi: 10.1016/j.idc.2019.08.006. PMID: 31668189.

[6] Shanmugam, Lakshmi; Kumaresan, Mahalakshmi; Kundu, Ramit; Gunalan, Anitha; Dhodapkar, Rahul. Arboviruses in Human Disease: An Indian Perspective. International Journal of Advanced Medical and Health Research 9(2):p 69-77, Jul–Dec 2022. | DOI: 10.4103/ijamr.ijamr_237_22

[7] Holbrook MR. Kyasanur forest disease Antiviral Res. 2012;96:353–62

[8] https://www.who.int/emergencies/disease-outbreak-news/item/zika-virus-disease-india

[9] Kumar A, Valecha N, Jain T, Dash AP. Burden of malaria in India: retrospective and prospective view. Am J Trop Med Hyg. 2007 Dec;77(6 Suppl):69-78. PMID: 18165477.

[10] Farkouh CS, Abdi P, Amatul-Hadi F, Anthony MR, Ali Khan Q, Manja K, Manja C, Ali SM. Cutaneous Manifestations of Malaria and Their Prognostic Windows: A Narrative Review. Cureus. 2023 Jul 11;15(7):e41706. doi: 10.7759/cureus.41706. PMID: 37575836; PMCID: PMC10414550.

[11] Steverding D. The history of leishmaniasis. Parasit Vectors. 2017 Feb 15;10(1):82. doi: 10.1186/s13071-017-2028-5. PMID: 28202044; PMCID: PMC5312593.

[12] Maxfield L, Crane JS. Leishmaniasis. [Updated 2023 Jun 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531456/

[13] Godbole R, Gaur A, Nayar P, Kiruthiga K, D'Costa P, Manchanda R, Khilari A, Shanmugam D, Muglikar KD, Kundu K. Case Report: A Fatal Case of Babesiosis in a Splenectomized Male Patient from Western India. Am J Trop Med Hyg. 2022 Feb 21;106(5):1421–5. doi: 10.4269/ajtmh.20-1118. Epub ahead of print. PMID: 35189595; PMCID: PMC9128672.

[14] Akhtar S., Sarker M.R., Jabeen K., Sattar A., Qamar A., Fasih N. Antimicrobial resistance in *Salmonella enterica* serovar typhi and paratyphi in South Asia-current status, issues and prospects. *Crit. Rev. Microbiol.* 2015;41:536–545. doi: 10.3109/1040841X.2014.880662.

[15] Holt K.E., Phan M.D., Baker S., Duy P.T., Nga T.V., Nair S., Turner A.K., Walsh C., Fanning S., Farrell-Ward S., et al. Emergence of a globally dominant IncHI1 plasmid type associated with multiple drug resistant typhoid. *PLoS Negl. Trop. Dis.* 2011;5:e1245.

[16] Britto CD, John J, Verghese VP, Pollard AJ. A systematic review of antimicrobial resistance of typhoidal *Salmonella* in India. Indian J Med Res. 2019 Feb;149(2):151-163. doi: 10.4103/ijmr.IJMR_830_18. PMID: 31219079; PMCID: PMC6563740.

[17] Ingle D.J., Nair S., Hartman H., Ashton P.M., Dyson Z.A., Day M., Freedman J., Chattaway M.A., Holt K.E., Dallman T.J. Informal genomic surveillance of regional distribution of *Salmonella* Typhi genotypes and antimicrobial resistance via returning travellers. *PLoS Negl. Trop. Dis.* 2019;13:e0007620.

[18] Klemm E.J., Shakoor S., Page A.J., Qamar F.N., Judge K., Saeed D.K., Wong V.K., Dallman T.J., Nair S., Baker S., et al. Emergence of an Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. *mBio.* 2018;9:e00105-18. doi: 10.1128/mBio.00105-18.

[19] Hooda Y., Sajib M.S.I., Rahman H., Luby S.P., Bondy-Denomy J., Santosham M., Andrews J.R., Saha S.K., Saha S. Molecular mechanism of azithromycin resistance among typhoidal *Salmonella* strains in Bangladesh identified through passive pediatric surveillance. *PLoS Negl. Trop. Dis.* 2019;13:e0007868. doi: 10.1371/journal.pntd.0007868

[20] Fernández J., Guerra B., Rodicio M.R. Resistance to Carbapenems in Non-Typhoidal *Salmonella enterica* Serovars from Humans, Animals and Food. *Vet. Sci.* 2018;5:40. doi: 10.3390/vetsci5020040

[21] John J, Bavdekar A, Rongsen-Chandola T, Dutta S, Gupta M, Kanungo S, Sinha B, Srinivasan M, Shrivastava A, Bansal A, Singh A, Koshy RM, Jinka DR, Thomas MS, Alexander AP, Thankaraj S, Ebenezer SE, Karthikeyan AS, Kumar D, Njarekkattuvalappil SK, Raju R, Sahai N, Veeraraghavan B, Murhekar MV, Mohan VR, Natarajan SK, Ramanujam K, Samuel P, Lo NC, Andrews J, Grassly NC, Kang G; NSSEFI Study Team. Burden of Typhoid and Paratyphoid Fever in India. N Engl J Med. 2023 Apr 20;388(16):1491-1500. doi: 10.1056/NEJMoa2209449. PMID: 37075141; PMCID: PMC10116367.

[22] Meena DS, Kumar A, Kumar D, Bohra GK, Purohit A. Enteric Fever-Associated Hemophagocytic Lymphohistiocytosis: A Systematic Review of Clinical Characteristics and Outcomes. Am J Trop Med Hyg. 2024 Apr 2;110(6):1217-1222. doi: 10.4269/ajtmh.23-0787. PMID: 38579699; PMCID: PMC11154042.

[23] Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690. PMID: 24782338.

[24] Song Y, Pei RJ, Wang YN, Zhang J, Wang Z. Central Nervous System Involvement in Hemophagocytic Lymphohistiocytosis in Adults: A Retrospective Analysis of 96 Patients in a Single Center. Chin Med J (Engl). 2018 Apr 5;131(7):776-783. doi: 10.4103/0366-6999.228234. PMID: 29578120; PMCID: PMC5887735.

[25] Conti M, Salis A, Urigo C, Canalis L, Frau S, Canalis GC. Transient focal lesion in the splenium of the corpus callosum: MR imaging with an attempt to clinical-physiopathological explanation and review of the literature. Radiol Med. 2007 Sep;112(6):921-35. English, Italian. doi: 10.1007/s11547-007-0197-9. Epub 2007 Sep 20. PMID: 17885738.

[26] Starkey J, Kobayashi N, Numaguchi Y, Moritani T. Cytotoxic Lesions of the Corpus Callosum That Show Restricted Diffusion: Mechanisms, Causes, and Manifestations. Radiographics. 2017 Mar-Apr;37(2):562-576. doi: 10.1148/rg.2017160085. Epub 2017 Feb 6. PMID: 28165876.

[27] Casey S. "T2 washout": an explanation for normal diffusion-weighted images despite abnormal apparent diffusion coefficient maps. AJNR Am J Neuroradiol. 2001 Sep;22(8):1450-1. PMID: 11559488; PMCID: PMC7974568.

[28] Planas R, Felber M, Vavassori S, Pachlopnik Schmid J. The hyperinflammatory spectrum: from defects in cytotoxicity to cytokine control. Front Immunol. 2023 Apr 28;14:1163316. doi: 10.3389/fimmu.2023.1163316. PMID: 37187762; PMCID: PMC10175623.

[29] Marchello CS, Birkhold M, Crump JA. Complications and mortality of typhoid fever: A global systematic review and meta-analysis. J Infect. 2020 Dec;81(6):902-910. doi: 10.1016/j.jinf.2020.10.030. Epub 2020 Nov 2. PMID: 33144193; PMCID: PMC7754788.

[30] Walker, J., Chaguza, C., Grubaugh, N.D. *et al.* Assessing the global risk of typhoid outbreaks caused by extensively drug resistant Salmonella Typhi. *Nat Commun* **14** , 6502 (2023). https://doi.org/10.1038/s41467-023-42353-9

Hosted file

`Clinical considerations in the diagnosis and management of enteric fever and its complications aso imag`
available at https://authorea.com/users/825602/articles/1221198-clinical-considerations-in-the-diagnosis-and-management-of-enteric-fever-and-its-complications