Case report

Typho-malaria: A case of extensively drug-resistant typhoid and complicated malaria co-infection

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Abstract

Typhoid fever and malaria are prevalent infectious diseases in low-income countries, including Pakistan. Both these endemic diseases have been associated with high mortality and a significant burden on health care systems. The occurrence of extensively drug-resistant typhoid and climate change in Pakistan has further complicated the rise of these endemics. Since both these diseases are transmitted via distinct routes, it is rare for patients to have co-infection. We report a case of a male patient diagnosed with extensively drug-resistant typhoid and complicated malaria co-infection.

***Keywords**: Typho-malaria; Extremely drug-resistant typhoid; Plasmodium vivax*

Introduction

Malaria and typhoid fever are major public health issues in tropical and subtropical countries. Both malaria and typhoid fever are caused by quite dissimilar organisms: protozoan parasites and Gram-negative bacilli, respectively, and are spread by distinct transmission routes.[1] Pakistan is a hub for infectious disease endemics, with malaria and typhoid fever among the most prevalent.[2] Since 2016, Pakistan has been battling unprecedented outbreaks of an extensively drug-resistant (XDR) typhoid strain, predominantly the H58 (genotype 4.3.1) lineage, with more than 15000 cases reported and transmission dynamics continuing to rise.[3] Simultaneously, anthropogenic climate anomalies, notably the 2022 catastrophic flood in Pakistan, have driven a massive resurgence in malaria transmission.[4] In 2022, more than 3.4 million suspected malaria cases were reported in Pakistan, with over 170,000 cases definitively confirmed by laboratory diagnostics.[5]

The literature has historically characterised the co-infection of both malaria and typhoid fever as "typho-malaria".[6] Although its true incidence is rare, this dual presentation can cause major

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systemic complications including severe anaemia, septic shock, multi-organ dysfunction and death. We present the first documented clinical case of a patient with typho-malaria demonstrating a simultaneous co-infection of complicated *Plasmodium vivax* malaria and an XDR *Salmonella* Typhi strain.

Case report

A 25-year-old male, with no known co-morbidities, fisherman by profession, presented to our emergency department in September 2024 with complaints of high-grade documented fever of 102 °F (38.9 °C) and loose stools for 7 days. On triage, he was hypotensive (blood pressure: 90/60 mmHg), tachycardiac (heart rate: 110 beats/min), and febrile (temperature: 102 °F), with a normal respiratory rate (22-24 breaths/min). On initial examination, he was dehydrated with a delayed capillary refill time (>2 seconds) but had no pallor or icterus. The rest of the physical examination was unremarkable. He was immediately resuscitated with intravenous isotonic fluids, given intravenous acetaminophen and all blood workup was sent (Table 1). Acute fever workup, including malaria parasite smear, dengue NS1 antigen test and blood cultures, was also sent. His chest X-ray was unremarkable.

Table 1: Comprehensive laboratory investigations and longitudinal tracking of the patient

Investigations	Reference Ranges	Hospital Day 1	Hospital Day 3	Hospital day 6
White Blood Cell count (WBC)	4.0 - 11.0 x 10^3 / µL	3.1 x 10^3 / µL	2.9 x 10^3 / µL	5.4 x 10^3 / µL
Haemoglobin (Hb)	13.5 - 17.5 g/dL	13.8 g/dL	12.9 g/ dL	13.1 g/dL
Platelet count	150 - 450 x 10^3 / µL	68 x 10^3 / µL	52 x 10^3 / µL	165 x 10^3 / µL
Serum creatinine	0.6 - 1.2 mg/dL	0.9 mg/dL	0.8 mg/dL	0.8 mg/dL
Total bilirubin	0.2 - 1.2 mg/dL	1.1 mg/dL	0.9 mg/dL	0.6 mg/dL
Alanine aminotransferase (ALT)	7 - 56 U/L	64 U/L	58 U/L	38 U/L
C-reactive protein (CRP)	< 5.0 mg/L	142.0 mg/L	118.0 mg/L	12.4 mg/L
Peripheral blood smear	No parasites seen	Positive *P. vivax*	-	Negative
Malarial ICT	Negative	Positive (non-falciparum)	-	-
Dengue NS1 Antigen	Negative	Negative	-	-
Blood Culture	No growth	on incubation	Gram-negative rods	Sterile (No growth)
Microbiology: DST Profile (CLSI M100 2025)	Sensitive strain	on incubation	on incubation	XDR Profile (carbapenem/azithromycin sensitive)

Initial workup revealed malaria parasite peripheral thin blood film examination to be positive for *P. vivax*. The malarial parasite immunochromatographic test (ICT) was also performed which corroborated a non-falciparum infection. According to the World Health Organization (WHO) guidelines, *P. vivax* malaria is classified as 'complicated' or 'severe' when it presents with clinical or laboratory features typically associated with severe *Plasmodium falciparum* in the absence of another obvious cause.[7] Our patient presented with severe haemodynamic instability, marked by persistent systemic hypotension (90/60 mmHg) and signs of impaired tissue perfusion (delayed capillary refill time >2 seconds) requiring aggressive intravenous fluid resuscitation, thus satisfying the definitive criteria for complicated malaria.[7] He was managed with intravenous Artesunate 2.4mg/kg stat and his hypotension improved with intravenous hydration.

He was admitted to a medical ward with a working diagnosis of acute febrile illness secondary to complicated *P. vivax* malaria. On the first day of admission, he received maintenance intravenous isotonic fluids and scheduled intravenous artesunate. His oral intake improved, and he remained vitally stable except for persistent fever spikes with a maximum temperature of 102 °F (38.9 °C). By the second day of admission, he had received three doses of intravenous artesunate, and his intravenous fluids were discontinued. However, his fever spikes continued with maximum temperature of 102 °F (38.9 °C). The infectious disease team was consulted, and they advised continuing targeted intravenous artesunate till fever completely subsided.

On the third day of admission, Gram stain performed on a positive blood broth showed Gram-negative rods. Subcultures on MacConkey agar yielded smooth, translucent, non-lactose-fermenting (NLF) colonies. Slide agglutination serotyping using specific somatic antisera demonstrated agglutination for factors O:9 and O:4, confirming *Salmonella enterica* serovar Typhi. Antimicrobial susceptibility testing (DST) was interpreted in strict accordance with the Clinical and Laboratory Standards Institute (CLSI) M100 standard (34th Edition, 2024).[8] According to the WHO and international consensus definitions, *Salmonella* Typhi is classified as XDR when it exhibits resistance to first-line regimens (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), fluoroquinolones (ciprofloxacin), and third-generation cephalosporins (ceftriaxone), while retaining susceptibility to carbapenems and azithromycin.[3, 8] The patient's phenotypic drug profile demonstrated resistance to ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole, chloramphenicol, and ciprofloxacin, while demonstrating susceptibility only to azithromycin and carbapenems (meropenem, imipenem, and ertapenem), confirming an XDR strain.

He was started on intravenous meropenem (1gram 8hrly) on the fourth day of admission following the DST confirmation. Simultaneously, his intravenous anti-malarial treatment was transitioned to oral artemether and lumefantrine combination. With a dual infection in a young male, further workup for immunosuppression was also done in our patient. His sugars and thyroid stimulating test were normal. His chest X-ray was not suggestive of tuberculosis, and his HIV blood test was negative. He was not malnourished with his serum albumin above 3. Within 48hrs of initiating intravenous meropenem, he became afebrile by the sixth day after admission. He was discharged on oral azithromycin (500mg once daily) for 7 days and oral artemether-lumefantrine for 2 more days.

The timeline of the patient’s illness is shown in Figure 2.

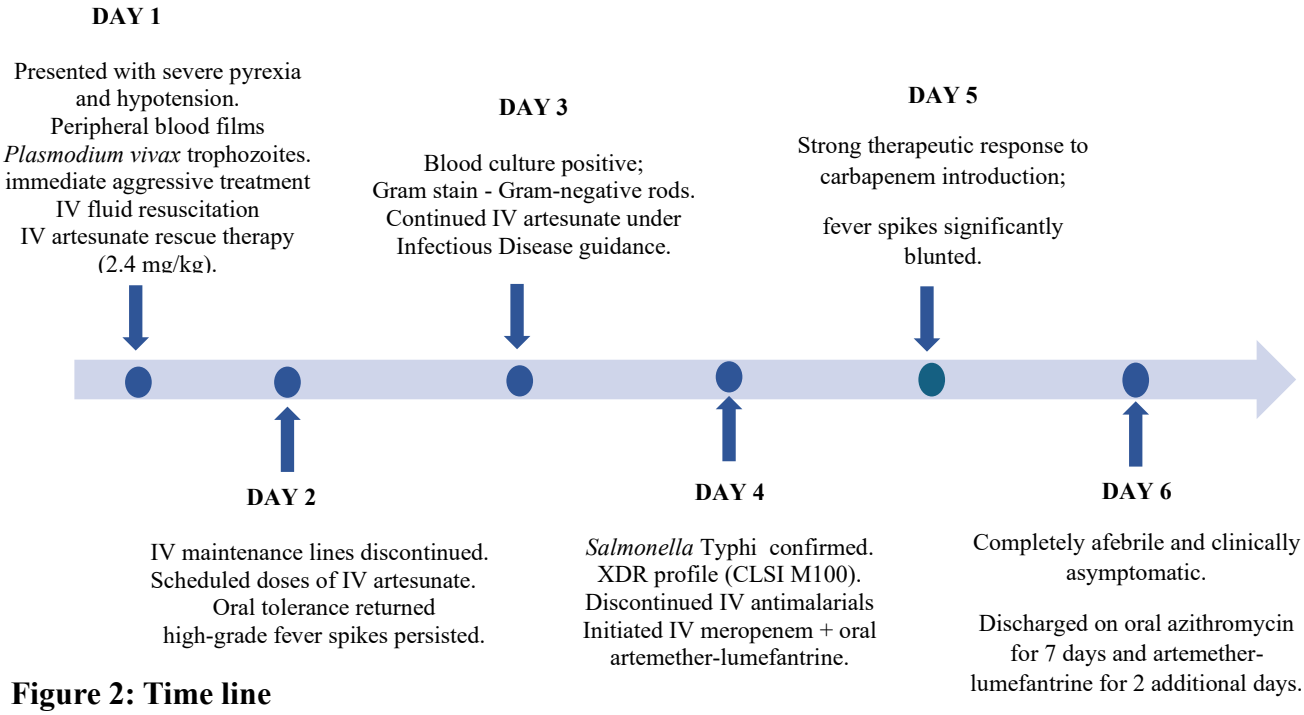

Figure 2: Time line

Discussion

Malaria and typhoid fever share the same clinical symptoms, predominantly fever, headache, and fatigue. The overlap in these symptoms can lead to diagnostic confusion and delayed proper management. Individuals with co-infection may experience a mixture of symptoms, complicating the differentiation between these two diseases. This is like our case where our patient initially presented with fever and loose stools. Although prior co-infections with malaria and typhoid fever have been reported, the co-occurrence of malaria and XDR typhoid in our patient introduces a unique and noteworthy clinical presentation.

The exact pathophysiological mechanisms governing this specific dual infection remain a subject of active research. One validated hypothesis posits that acute Plasmodium infections cause a transient downregulation of cell-mediated immunity and macrophage function, thereby facilitating systemic invasion by facultative intracellular pathogens such as *Salmonella*.[9] Alternatively, active intravascular haemolysis driven by malarial parasitaemia has been shown to cause macrophage iron overload, compromising the host's ability to clear Gram-negative bacillary infections—a pattern mirrored in sickle cell crisis and bartonellosis.[10] In our patient, the absence of overt clinical haemolysis paired with a persistent leukopaenia (3.1 x 10^3 / µL) highlights cell-mediated immunological suppression as the primary gateway for the bacterial super-infection.

The demographic profiling of our patient—a 25-year-old male fisherman—aligns with regional epidemiological surveys showing that young adult males aged 20–40 years bear the highest burden of typho-malaria.[11] This is primarily mediated by heightened outdoor environmental and

occupational exposures. A fisherman's daily activities dramatically elevate the probability of sustaining bites from nocturnal Anopheles vectors while concurrently interacting with water systems contaminated with faecal-oral pathogens like *S.* Typhi.

Ideally, the gold standard test for the diagnosis of typhoid fever is blood culture. However, in many low-income countries, the Widal serology test is still used for diagnosing typhoid fever. Ammah et al (1999) reported a 17% prevalence of co-infection of malaria and typhoid fever based on culture-proven diagnosis compared with 47.9% prevalence based on the Widal test.[11] Birhanie et al (2014) reported only a 0.5% prevalence of co-infection after diagnosis of typhoid fever with blood cultures.[12] In our case, the diagnosis of XDR typhoid was confirmed by blood culture.

Historically, cases of typho-malaria co-infection could be resolved efficiently with standard oral antimalarials coupled with affordable, first-line antibiotics such as ciprofloxacin or ceftriaxone.[9] However, the emergence of XDR *S.* Typhi strains in Pakistan renders these standard options entirely obsolete, creating an urgent clinical imperative to utilise restricted, resource-intensive carbapenems and azithromycin.[3] Managing a patient who is simultaneously managing a complicated parasitic infection requiring immediate intravenous artesunate, alongside an aggressive, multi-drug resistant bacterial bacteraemia, represents a major clinical challenge that requires rapid, dual-track diagnostic screening at the initial point of care.

Conclusion

In patients presenting with acute fever in tropical and sub-tropical countries, blood culture and malaria parasite through microscopic examination of peripheral smear should be sent on patients to document any co-infection. Similarly, in a malarial patient with persistent fever despite adequate therapy, one should consider concomitant infection with Typhoid fever.

Declaration

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Authors' contributions:
RH: Writing this manuscript
HA, WS: Data curation and Literature review
ANK: Conceptualization and writing this manuscript
FFH, LIA: Editing and Reviewing manuscript

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