Case Report

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Pancytopenia unveils hidden coinfections of scrub typhus and leptospirosis in a malaria case.

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ABSTRACT

Background : Tropical infections are the leading cause of acute undifferentiated febrile illnesses (AUFI). While they are commonly suspected and tested through protocolized workup, sometimes the infections occur concurrently. Patients with concurrent infections present with atypical findings that delay diagnosis and treatment.

Case Report : This case report describes a rare case of triple coinfection with an atypical clinical presentation. This patient presented with a fever in May and tested positive for Malaria. The patient was started on anti-malarial therapy. However, further workup revealed pancytopenia along with an abnormal renal and liver profile. Repeat testing for AUFI revealed concurrent scrub typhus as well as Leptospirosis. The treatment was accordingly adjusted, which led to recovery.

Conclusion : Patients presenting with AUFI and having a residence or history of travel to endemic areas should be investigated for tropical infections. Moreover, a high index of suspicion should be borne in mind in cases of AUFI patients presenting with atypical signs and symptoms before ruling them out.

INTRODUCTION

Tropical infections are one of the leading causes of acute undifferentiated febrile illness.[1] In developing countries like India, tropical infections like Malaria, dengue, scrub typhus, Leptospirosis, and chikungunya are seen around the year, with outbreaks during the monsoon and post-monsoon period.[2] The reason for these outbreaks is proposed to be the vector-borne transmission of these diseases, which is increasing multifold during the rainy season.[3] Due to such a high prevalence of these diseases during epidemics, concurrent infections with more than one pathogen are possible and have been reported.[2,4-8] Coinfection with malaria scrub typhus and scrub typhus and Leptospirosis have been reported.[5,6,8] While coinfections with two pathogens are uncommonly reported, concurrent infections by three pathogens are exceedingly rare, with little literature.[9,10] In this case report, we concurrently describe a coinfection with Malaria, scrub typhus, and Leptospirosis.

AUFI patients usually present with nonspecific manifestations such as fever, thrombocytopenia, hepatic involvement, or leucopenia. Concurrent infections can cause atypical clinical findings, resulting in a substandard treatment response.[3] Due to overlapping clinical features and laboratory findings among tropical infections, diagnoses of concurrent infections pose a challenge, hence emphasizing a high suspicion in endemic regions, especially in a patient with unusual presentation.

CASE REPORT

A 24-year-old patient from the Indian state of Punjab presented with chief complaints of on-and-off fever. The fever was associated with chills, rigors, and headaches. There were no other complaints. On physical examination, the patient was conscious, oriented, and pale. Cardiovascular, abdominal, respiratory, and central nervous systems were normal on physical examination. Blood investigations were sent, and on complete blood count, pancytopenia was found with elevated reticulocyte count. With suspicion of hemolysis, Direct and Indirect Coombs tests were done and found to be positive.

Moreover, malaria parasites were seen on peripheral blood

Journal of Infectious Diseases (ISSN 2831-8064)

film (PBF). Liver function tests (LFT) and Renal function tests (RFT) were also deranged. Blood samples to rule out Leptospirosis, kala-azar, scrub typhus, and dengue were also sent as a part of protocolized tropical fever workup and were found to be negative. The patient was started on Antimalarial therapy. Although there was an improvement in blood count, there was no improvement in the patient's fever. Repeat testing for tropical infections was ordered based on high prevalence within the demographics. While tests for leishmania antibody and dengue IgM were initially negative, the patient tested positive for Leptospira through IgM ELISA (OD value =0.964; test cut-off value of 0.432). The patient also tested positive for Scrub typhus IgM ELISA (OD value =0.784; Test cut-off value of 0.427). The patient was hence diagnosed with concurrent tropical triple infection and was started on Doxycycline 100 mg twice daily and Cefixime 400 mg twice daily orally, which resulted in improvement in both clinical and laboratory values. Table 1 shows before and after treatment lab values.

Table 1: Before and after treatment investigations.

INVESTIGATIONS	Before treatment	After treatment
Hemoglobin	6.9 gm/dl	10.gm/dl
Red blood cell count	2.31 X 1012/L	3.48 X 1012/L
MCV	90.5fL	91.7fL
Reticulocyte count	3.47%	
Total Leucocyte count	1.30 X 109/L	5.17 X 109/L
Platelet count	15 X 109/L	133 X 109/L
SGOT/SGPT/Total serum bilirubin(mg/dl)	122/59/7.4	
Total protein	5.7gm%	
Blood urea/serum creatinine (mg/dl)	52/1.0	
PTi/INR/aPTT	82.7%/1.21/33.6s	100%/1/38.9s
CRP	209mg/L	129mg/L
LDH	1121IU/L	

DISCUSSION

Malaria is a great healthcare burden on both humanity and the socio-economic aspects of any country. According to WHO reports from 85 endemic countries, there were about 241 million cases of Malaria diagnosed in 2020, with the WHO southeast region accounting for about 2% of the total disease burden. India alone accounts for 83% of the cases in the WHO Southeast Asia region.[10] A study approximates Plasmodium Falciparum cases to be more than twice the reported number based on epidemiological estimates of clinical episodes.[11]

Another common cause of AUFI in the country is scrub typhus found all over India. It is caused by a bite from chigger mites of the Trombiculidae family [12]. An important differential diagnosis of scrub typhus and Malaria is Leptospirosis, a spirochetal infection transmitted indirectly or directly by exposure to infected host reservoir animals such as Rodents. It is one of the most widespread zoonotic diseases worldwide and is responsible for causing epidemics, especially during monsoon season.[13] Leptospirosis has been known to cause high rates of morbidity and mortality, with 58900 global deaths each year. These trends are notably intense in Southeast Asian countries such as India, where tropical infections are considerably under-reported [14]. Although in the WHO Southeast Asia region, the incidence of Malaria has reduced by 83% due to measures taken by the government[10], coinfections are still a major problem associated with malaria[15]. It has been associated with concomitant Acute Febrile Illnesses (AFIs) such as scrub typhus[16], Leptospirosis [17], Chikungunya[18], visceral leishmaniasis[19], and dengue[20,21]. There have been many reasons postulated for coinfections. Although dual infections are rare, there have been a few reported in the past, while triple infections are exceedingly uncommon in literature[22,23,24]. Our case of triple coinfection with Malaria, Scrub Typhus, and Chikungunya is extremely rare and has not been documented in the literature, according to our review.

There could be many possibilities for the cause of coinfection in our case. Malaria parasites have been thought to cause defective immune responses, causing a state of immunodeficiency [25] and increasing the chances of coinfections. Large

Journal of Infectious Diseases (ISSN 2831-8064)

geographic overlap of all three vector-borne diseases with overlapping epidemics is also important in increasing the risk of coinfection.[26] While there is an increasing argument stating the overlap in clinical definitions of tropical infections, cross-reactivity, and increased incidence of subclinical infections as the cause of raised titer[1], studies have demonstrated the risk of coinfection.[1,2]

Concurrent infections offer multiple challenges for clinicians. [27] These range from the difference in clinical symptoms, outcomes, prognosis, and treatment compared to Mono-infections. In general, these tropical fevers present with nonspecific features like fever, headache, GI symptoms, and thrombocytopenia [3], but in cases with mixed infections, clinical findings, not usually seen in these infections, are encountered, which results in difficulty and delay in diagnosis. [27] One study showed that a patient with mixed infection of Leptospirosis and scrub typhus developed Gullian-Barre Syndrome(GBS).[8] Another patient with a coinfection with malaria and scrub typhus developed severe septic shock. [6] These rare presentations can complicate the diagnostic process of the clinical team in the absence of a pre-set testing protocol and possibly endanger the patient due to delayed initiation of treatment for the underlying cause. However, these presentations should also arouse suspicion of possible concomitant infection. In our case report, the patient presented with findings of pancytopenia with deranged LFTs and RFTs while undergoing antimalarial monotherapy.

Pancytopenia is a rare presentation of non-falciparum Plasmodium[28], and various reasons have been postulated for this unusual manifestation. One possibility is Hyperactive Malarial Syndrome, also known as tropical splenomegaly syndrome, which leads to excess stimulation of B lymphocytes, leading to exaggerated production of IgM and cryoglobulins, which get deposited on reticuloendothelial cells, leading to overactivation and hepatosplenomegaly.[29] However, our patient did not have hepatosplenomegaly. One more possible cause is malaria infection, leading to the destruction of Bone marrow, causing aplastic anemia. However, the reticulocyte count in our patient was high, favoring a hemolytic cause.[30] Hemophagocytic Lymphocytosis, a syndrome of exaggerated immune activation, is another possible cause of pancytopenia reported in malaria and scrub typhus. However, this condition is seen to be very dangerous and life-threatening, contrary to our patient's clinical course, along with the absence of splenomegaly. [31,32] We propose that mixed infection causes abnormal functioning of B lymphocytes, causing autoantibody formation against blood cell lines and red blood cell hemolysis due to malarial parasites, leading to pancytopenia.

While the effect of coinfections on the severity or prognosis of the patient is not clearly understood and has not been extensively studied, there is a counterargument on the opposite side of the spectrum regarding the clinical ramifications of coinfections. A study has shown a decreased risk of severe organ dysfunction and hepatosplenomegaly in patients with scrub typhus and malaria coinfection.[2] It has also been proposed that the vasculitic pathogenesis of scrub typhus has a protective role against other coinfections. [2] The lack of clear evidence and proper understanding of coinfection effects necessitates more extensive research on the same.

While gold standard tests are available for definitive diagnosis of the pathogen causing AFI, the high number of patients and resource constraints, particularly in developing countries, limit feasibility. However, the wide availability of rapid diagnostic tests coupled with a low sensitivity of physician's clinical diagnosis necessitates regular usage of these rapid and accurate point of care(POC) tests in patients with acute AFI, especially during epidemics.[33] That being said, in regions with a high prevalence of tropical infections and an increased risk of coinfections, a regional or an institutional protocolized workup, including a tropical infection diagnostic kit, could be tested for every patient presenting with an AFI. The tropical infection diagnostic kit could contain the POC tests for endemic/current epidemic infections. These kits could reduce the chances of mixed diagnoses as well as the time to diagnosis and treatment. However, the widespread positive serologies in these endemic regions could increase false positives and might potentially cause misguided management and elevated anxiety levels by the patient. [34] Hence, more extensive research is required to gather evidence regarding the usage of such kits.

The treatment of such infections can pose significant challenges. There has been an increasing trend of rigorous prescription of antimalarial drugs to patients with AFIs in countries with high incidence of Malaria, such as Africa. [35,36] This often leads to missed or delayed diagnoses of co-existent AFIs and the increasing trend toward drug resistance.[37] Furthermore, these coinfections can change the treatment response to standard treatments, and some antimalarial treatments might not be effective in such cases. It would be more rational to prescribe antibiotics that have activity against multiple pathogens, for instance, doxycycline, which is active against Malaria, Murine typhus, Leptospirosis, and Scrub typhus.[27] We gave the patient Doxycycline and Cefixime, which showed an appropriate clinical response and a good recovery.

CONCLUSION

We describe a case of triple coinfection by Malaria, scrub typhus, and Leptospirosis to emphasize the importance of suspecting a mixed infection, especially in patients with atypical presentations in endemic regions. We also discussed

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the effect and reverberations of mixed infection on severity and management.

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2. Inayat Grewal: manuscript preparation
3. Prashant Ahlawat: concept, design, definition of intellectual content, literature search, data acquisition, manuscript editing and manuscript review.
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