

**Scrub typhus, myocarditis and a possible drug interaction****Saurabh Kohli<sup>1</sup>, Saurabh Agarwal<sup>2\*</sup>, Nidhi Kaeley<sup>2</sup>, Dilip Chander Dhasmana<sup>1</sup>, Anita Sharma<sup>2</sup>**

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**ABSTRACT**

Scrub typhus, caused by *O. Tsutsugamushi* is a re-emerging disease which is being increasingly reported from different parts of India. This disease has a wide spectrum of presentation which can range from uncomplicated febrile illness to life-threatening sepsis with multi-organ dysfunction. Myocarditis has been described as one of the rare manifestations of this infection and very few cases have been reported. Myocarditis in scrub typhus is usually subclinical and therefore many times ignored. Here, we report of a case of scrub typhus presenting without the typical rash and eschar with features of myocarditis requiring treatment. We highlight a possible drug interaction between ivabradine and doxycycline which were used in this patient. We also highlight the possibility of other drug interactions between the various drugs used in the treatment of scrub typhus and its complications and stress the need to be vigilant when prescribing multiple drugs, especially in a disease with such a varied presentation and multiple complications that require the use of a number of drugs.

**Keywords:** Cytochrome P450, Doxycycline, Myocarditis, Ivabradine, Scrub typhus

**INTRODUCTION**

Scrub typhus is a re-emerging disease that is widespread in many parts of the world and in India.<sup>1</sup> This disease is caused by the *Rickettsia Orientia tsutsugamushi* and usually manifests clinically as a non-specific febrile illness often accompanied by headache, myalgia, nausea, vomiting, diarrhea, cough or breathlessness. Presentation may vary from a subclinical illness to severe illness with multiple organ system involvements.<sup>2,3</sup> Mortality has been reported to be from 7-30%.<sup>4</sup> Though it usually presents with a typical rash and eschar, this may not always be so. Thus, it is grossly under diagnosed in India due to its non-specific clinical presentations, limited awareness and low index of suspicion among clinicians.<sup>5</sup> Complications usually develop after first week of illness and are directly related to the blood load of *O.*

*tsutsugamushi*. Serious complications include pneumonia, myocarditis, meningo-encephalitis, acute renal failure and gastrointestinal bleeding. Cardiac involvement is very rare but includes minor electrocardiogram (ECG) changes such as nonspecific ST segment, T-wave changes, and premature ventricular contractions. Myocarditis has been described as one of the rare manifestations of this infection and very few cases have been reported. Myocarditis in scrub typhus is usually subclinical and therefore many times ignored. Cardiomegaly and CHF may be present which could be secondary to myocardial or pericardial involvement.<sup>6-8</sup>

**CASE REPORT**

A 29 year old female presented to the emergency department in the night with complaints of high grade

continuous fever for the past 8 days which was associated with chills and rigor, and sudden progressive chest pain for the for the past 2 days. Past history was not significant. On examination, patient was conscious, oriented and afebrile on presentation. Her blood pressure was 80/40 mmHg, Pulse rate 126/min and SpO<sub>2</sub> 96% on room air. Rash and eschar were absent. On palpation, tenderness was present in the epigastric region. Malaria and typhoid were ruled out by appropriate tests. Further laboratory investigations revealed that the patient was suffering from scrub typhus as demonstrated by scrub typhus-rapid test positive and scrub typhus IgM as reactive. Other investigations revealed a platelet count of 60,000/cu. mm for which platelet infusion was given. Her ALT was 55IU/L and AST 91 U/L. Urine examination showed proteinuria. Chest X-ray PA showed bronchitis with left pleural effusion; USG abdomen showed mild splenomegaly with mild bilateral pleural effusion. 2D echo was advised and showed global hypokinesia of left ventricle with Grade 1 diastolic dysfunction and minimal pericardial effusion. Her left ventricular ejection fraction was 35%.CPK-MB was 55U/l and Troponin I was negative. Patient was started on Tablet azithromycin 500 mg once daily on admission. After confirmation of scrub typhus, tablet doxycycline 100mg twice daily was also started. She was treated for suspected myocarditis by judicious use of intravenous fluids appropriate antibiotics, steroids and inotropic support. Her blood pressure stabilized, but her heart rate was not controlled. She was started on Tablet ivabradine in a dose of 5mg twice daily in view of her increased heart rate and low ejection fraction. After 2 days, and 8 hours after the 4<sup>th</sup> dose, patient developed emergent bradycardia with a heart rate of 46 beats/minute. Inj. Atropine 0.6 mg IV stat was given and Ivabradine was immediately stopped. No further incidence of bradycardia was noted. Patient was discharged a few days later in a stable condition.

## DISCUSSION

Scrub typhus is a re-emerging disease caused by the Rickettsia Orientia tsutsugamushi. It is grossly under diagnosed due to its non-specific clinical presentations, limited awareness and low index of suspicion among clinicians.<sup>5</sup> In addition; complications involving various organ systems and the use of multiple drugs for these complications require increased awareness among clinicians.

Our case has a few interesting features. First, the absence of the typical rash and eschar, which can complicate the diagnosis of this disease. Secondly, the presence of myocarditis in this patient which was suspected based on the clinical manifestations like chest pain and hypotension requiring inotropic support and the abnormal cardiac parameters (echocardiogram and cardiac markers). Thirdly, the use of the newly approved drug ivabradine in this case along with doxycycline may have led to a possible, but oft unrecognized drug interaction. Though azithromycin was also used and is approved for

the treatment of scrub typhus, it is not considered as an inhibitor of CYP450 enzymes.<sup>9,10</sup> Doxycycline has been shown to be a moderate inhibitor of these enzymes and the use of these drugs together may lead to increased levels of ivabradine which is a substrate for these enzymes.<sup>11,12</sup> Bradycardia is a known side effect of ivabradine and though we could not confirm that the bradycardia in this patient was a side effect of ivabradine alone or was due to increased blood levels of ivabradine caused by CYP inhibition by doxycycline, we would like to highlight the importance of this possible drug interaction in this disease.<sup>13</sup> Of the many drugs shown to be effective in the treatment of this disease, the recommended drug doxycycline is a moderate inhibitor of CYP. Other macrolides have also been shown to be effective in this disease and have been successfully used and these drugs are also inhibitors of CYP450. Rifampicin, which has been shown to be superior to doxycycline is an inducer of this enzyme.<sup>10,14</sup> Thus, scrub typhus is not only complicated by the fact that it's diagnosis is not suspected in the first place but also by the fact that its treatment as well as that of its many and varied complications requires the use of multiple drugs; many of which have the propensity to cause serious drug interactions.

## CONCLUSION

In conclusion, scrub typhus is a re-emerging disease in India which is slowly spreading too many parts of our country with cases being reported from as far and wide as Goa and AP. The lack of a typical eschar and rash in many patients requires that a high index of suspicion be maintained and that it be increasingly considered in the differential diagnosis of acute febrile illness. Once diagnosed, its varying spectrum of complications and the possibility of various pharmacokinetic drug interactions need to be kept in mind while planning the treatment of this disease.

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