

# Thrombocytopenia to Reactive Thrombocytosis in Scrub Typhus- The Play of Platelets

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Dear Editor,

Platelets play a major role in primary hemostasis and apart from that, they are acute phase reactants. Platelet counts increase in response to systemic infections, inflammation, bleeding. This response is called reactive or secondary thrombocytosis. Reactive thrombocytosis is different from primary/essential thrombocytosis which occurs due to a clonal proliferation of platelet progenitors in the bone marrow. We present the case of a young male infected with Scrub typhus, who had initial thrombocytopenia and later developed reactive thrombocytosis.

A 35-year-old male presented with complaints of intermittent fever, myalgia and headache since four days. There was no history of photophobia, disorientation, vomiting, diarrhoea, haematochezia, malena, haematemesis, chest pain, cough and dyspnea. On examination, he was febrile (101°F), pulse 110/min, regular, peripheral pulses were palpable. Blood pressure was 124/76 mmHg, respiratory rate was 18 breaths/min. Pallor icterus, lymphadenopathy were absent. There were no petechial rashes on the body. Cardiovascular and respiratory system examination was within normal limits. Per abdomen examination as well as Central nervous system examination was normal. There were no signs of meningeal irritation.

**Investigations revealed:** Total Leucocyte Count (TLC)-4900/mm<sup>3</sup> with 78% polymorphs, Hb-11.2 gm%, Absolute Platelet Count (APC)-74×10<sup>9</sup>/L. Aspartate aminotransferase (AST) was 90 IU/L, Alanine aminotransferase (ALT) 106 IU/L, total bilirubin 1.8 mg/dL, indirect 0.9 mg/dL, direct-0.9 mg/dL, Prothrombin Time (PT) 12.2 seconds, activated partial thromboplastin time (a-PTT)-40.4 seconds. Peripheral smear for malarial parasite, malarial antigen test, IgM/IgG dengue, IgM leptospira were negative. IgM ELISA was positive for Scrub typhus. Serum ANA, dsDNA and RA factor was negative. Chest radiograph was normal. 2D echo was normal.

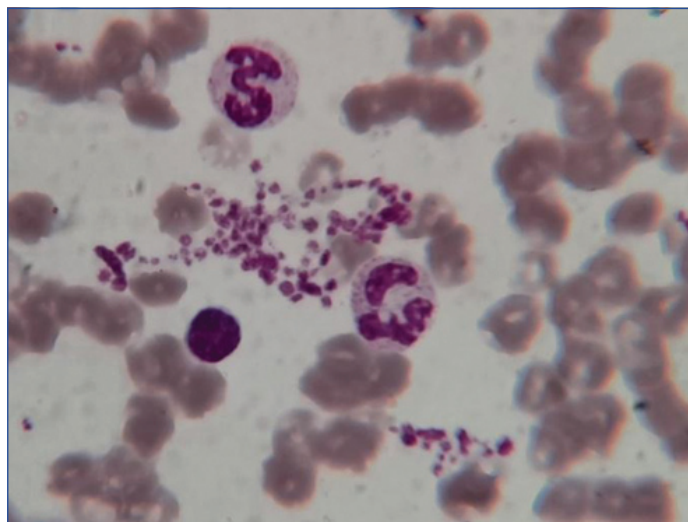
A diagnosis of Scrub typhus was made and the patient was started on tablet doxycycline 100 mg per oral twice a day. On the 4<sup>th</sup> day of treatment, his platelet count increased to 3.5 lacs/mm<sup>3</sup>.

Fever was still persistent. Doxycycline was continued. On the 6<sup>th</sup> day, his complete blood count was repeated which revealed APC of 857×10<sup>9</sup>/L. There were no new symptoms. Patient became afebrile on the 7<sup>th</sup> day but the platelet counts raised to 1074×10<sup>9</sup>/L. Peripheral smear showed increased platelets appearing in clumps [Table/Fig-1]. ESR was 112 in first hour. C-reactive protein 9.8 mg/dL.

Reactive thrombocytosis was contemplated and tablet aspirin 75 mg, with adequate hydration was initiated to avoid thrombosis. On 10<sup>th</sup> day of therapy, the platelet count was 845×10<sup>9</sup>/L. The patient was prescribed doxycycline for 14 days and Aspirin 75 mg was suggested to be continued.

On 2<sup>nd</sup> week follow-up, the platelet count was 728×10<sup>9</sup>/L. The patient was asymptomatic. On follow-up after 1 month, the repeat parameters were; APC-388×10<sup>9</sup>/L, ESR-35 mm in 1<sup>st</sup> hour, C-Reactive Protein (CRP) 3.5 mg/dL. Aspirin was then stopped.

Scrub typhus is an acute febrile illness caused by *Rickettsia Orientia tsutsugamushi*. It is under-diagnosed in India due to its non-specific clinical presentations, limited awareness and low index of suspicion among clinicians. Hence high index of suspicion and



**[Table/Fig-1]:** Peripheral smear stained with Leishman stain (oil immersion 100X) showing normocytic normochromic RBCs and increased Platelets seen in aggregates features of thrombocytosis.

early treatment is the key to successful outcome. Incubation period is of about 6-12 days. Common haematologic manifestations include anaemia, leucopenia and thrombocytopenia [1,2]. However, reactive thrombocytosis has been rarely reported with scrub typhus. Platelets being acute phase reactants can increase due to stimuli like systemic infections, inflammatory conditions, and tumours [3-5]. This phenomenon is known as reactive or secondary thrombocytosis. It is different from primary or essential thrombocythemia which is a myeloproliferative disorder due to a clonal expansion of bone marrow progenitor cells.

Pluripotent haematopoietic stem cells present in the bone marrow serves as the progenitor cell for all haematopoietic cellular elements. These stem cell elements then undergo subsequent cell divisions. Thrombopoietin (TPO) is a trophic hormone which orchestrates the differentiation of megakaryocytes to mature platelets by becoming the ligand for the platelet growth factor c-mpl. Serum levels of thrombopoietin vary inversely with the circulating platelet count. Thrombocytopenia leads to elevated serum levels of thrombopoietin and this elevation in thrombopoietin serves as a stimulator of megakaryocytopoiesis leading to secondary or reactive thrombocytosis. Conversely, thrombocytosis results in depressed serum levels of thrombopoietin [6]. Reactive thrombocytosis also occurs due to overproduction of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-11, CRP, ESR that occurs in chronic inflammatory, infective, and malignant states [7,8]. In a study, 81% of patients with thrombocytosis had elevated serum levels of either IL-6 or C-reactive protein suggesting the contribution of acute phase reactants in reactive thrombocytosis [8].

The pathogenic sign of scrub typhus is disseminated vasculitis. The systemic complications like vascular leaks, pulmonary oedema, disseminated intravascular coagulation, hepatic failure including multiple organ dysfunction syndrome of scrub typhus are usually secondary to this phenomenon [9]. Approximately, about one

third of patients diagnosed with typhus may develop multi-organ dysfunction [10,11]. The systemic inflammatory/immune vasculitis leads to release of various chemical mediators that give rise to systemic manifestations. Reactive thrombocytosis is one such manifestation [12].

Most patients are asymptomatic and are identified on routine blood counts. The secondary thrombocytosis (reactive thrombocytosis) requires the underlying cause of the thrombocytosis to be treated. For patients with platelet counts in excess of 1,000,000/ $\mu$ L, aspirin daily may be considered to minimise the rare development of stroke or thrombosis [13].

## REFERENCES

- [1] Hornick RB. Rickettsial Diseases. (Chapter 371). In: Bennett JC, Plum F, editors. Goldman: Cecil Textbook of Medicine. 21<sup>st</sup> ed. Philadelphia, USA: WB Saunders Company; 2000. p. 1911-12.
- [2] Dumler JS, Siberry GK. Scrub Typhus (Orientia Tsutsugamushi). (Part XVI. Section 11. Chapter 226). In: Kliegman RM, Behrman Re, Jenson HB, Stanton BF, editors. Nelson Textbook of Pediatrics. 18<sup>th</sup> ed. Philadelphia: Saunders, Elsevier; 2007. p. 1295-96.
- [3] Vora AJ, Lilleyman JS. Secondary thrombocytosis. Arch Dis Child. 1993;68(1):88-90.
- [4] Chiarello P, Magnolia M, Rubino M, Liguori SA, Miniero R. Thrombocytosis in children. Minerva Pediatr. 2011;63(6):507-13.
- [5] Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2017;92(1):94-108.
- [6] Matondang AV, Widodo D, Zulkarnain I, Rengganis I, Trihandini I, Inada K, Endo S. The correlation between thrombopoietin and platelet count in adult dengue viral infection patients. Acta Medica Indonesiana. 2004;36(2):62-69.
- [7] Tefferi A, Ho TC, Ahmann GJ, Katzmann JA, Greipp PR. Plasma interleukin-6 and C-reactive protein levels in reactive versus clonal thrombocytosis. Am J Med. 1994;97(4):374-78.
- [8] Kutti J, Wadenvik H. Diagnostic and differential criteria of essential thrombocythemia and reactive thrombocytosis. Leuk Lymphoma. 1996;suppl(1):41-45.
- [9] Dogra S. Recent advances in understanding pathophysiology of scrub typhus. JK Sci. 2010;12:70-71.
- [10] Peter JV, Sudarsan TI, Prakash JA, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. World J Crit Care Med. 2015;4(3):244-50.
- [11] Ittyachen AM, Abraham SP, Krishnamoorthy S, Vijayan A, Kokkat J. Immune thrombocytopenia with multi-organ dysfunction syndrome as a rare presentation of scrub typhus: A case report. BMC Res Notes. 2017;10(1):496. <https://doi.org/10.1186/s13104-017-2826-z>.
- [12] Suresh E. Diagnostic approach to patients with suspected vasculitis. Postgrad Med J. 2006;82(970):483-88. doi:10.1136/pgmj.2005.042648.
- [13] Harrison CN, Bareford D, Butt N, Campbell P, Conneally E, Drummond M, et al. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010;149:352-75.

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