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# Severe Thrombocytosis in a Patient with Pulmonary Tuberculosis: A Case Report

***Abstract –*** Platelets are key players in the immunopathology of pulmonary tuberculosis (TB), and thrombocytosis is a rare complication of the disease. Thrombocytosis is defined as platelet counts exceeding 450 x 109/L. In TB, thrombocytosis is associated with other hematological changes and an increased risk of venous thromboembolism (VTE). An 80-year-old Chinese gentleman presented with a chronic cough for 2 weeks, without fever, weight loss, night sweats, family history of blood dyscrasia, or prior thrombotic events. Full blood count (FBC) showed leukocytosis with high white blood cells (WBC) (22.63 x 103/uL), neutrophils (19.49 x 103/uL), and platelets (1808 x 109/L). Peripheral blood film (PBF) showed leukocytosis with neutrophilia, monocytosis, and basophilia. Red blood cells (RBC) showed microcytic hypochromic anemia, and platelets were grossly increased with circulating megakaryocyte fragments. Essential thrombocytosis was suspected based on persistent thrombocytosis (normal range 150–450 x 109/L) for 1 week during admission; however, JAK2 mutation analysis was negative. Suspicion of pulmonary TB due to cough was confirmed via Gene-Xpert MTB/RIF sputum test (PCR). Subsequently, anti-tuberculosis therapy was initiated, and the patient responded well. The patient's platelet count was monitored, but the patient was not on any VTE prophylaxis. Platelets may directly sense Mycobacterium tuberculosis (M. tuberculosis). As a rapid innate immune response, platelets become activated and granulated, releasing pro-inflammatory cytokines. Platelets then undergo structural changes and upregulate platelet-activated gene transcripts. Tissue damage in TB results from platelet interactions with other leukocytes, which produce matrix metalloproteinases (MMPs) and cytokines such as Interleukin-10 (IL-10) that inhibit the host immune response. Conclusion: There should be a high index of suspicion for TB infection in patients presenting with respiratory symptoms and severe thrombocytosis, especially in older patients. Antiplatelet therapy may be considered alongside the standard antitubercular drug regimen as a potential host-directed therapy to improve outcomes and prevent VTE complications in patients with pulmonary TB and severe thrombocytosis.

***Keywords****: Thrombocytosis, Tuberculosis, Pulmonary, Platelet, Immunology*

## 1 INTRODUCTION

Tuberculosis (TB) is the second leading infectious disease after COVID-19, surpassing Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) worldwide. The World Health Organization (WHO) estimates that 1.3 million people died from TB in 2025 and that 10.7 million were infected with TB (5.8 million men, 3.7 million women, and 1.2 million children), even though TB is a curable and preventable disease. Globally, the disease burden is about US $13 billion annually for prevention, diagnosis, treatment, and care. About a quarter of the global population is estimated to have been infected with TB, with variable clinical manifestations. Malaysia had a population of 34 million in 2022. However, TB data for 2022 versus 2015 show a dramatic rise of 80% in TB deaths and a 26% increase in TB incidence. In 2024, the incidence and mortality rates of TB in Malaysia are 76.88 and 7.58 per 100000 population (Malaysia Health Facts 2025). Smoking is the highest risk factor associated with TB, followed by alcohol use disorder, undernourishment, diabetes, and, lastly, HIV. The TB disease burden on Malaysia's economy in 2022 is estimated at US$16 million, with a rise of 2.3% compared to the previous year (1). TB is caused by M. tuberculosis, a human pathogen.

Humans are the only known reservoir of M. tuberculosis, although animals can be infected and zoonotic transmission can occur. TB is primarily transmitted through airborne droplets generated by coughing, sneezing, or speaking. TB commonly causes pulmonary tuberculosis, but it can also infect other organs (extrapulmonary TB). M. tuberculosis is an aerobic, non-spore-forming, non-motile bacillus with a high lipid content in the cell wall, which makes the bacilli acid-fast and likely contributes to immunomodulation and virulence. Its intracellular localization leads to subacute, progressive disease manifestations that can also remain dormant within infected cells.

## 2 CASE REPORT

An 80-year-old Chinese gentleman was admitted to a tertiary private hospital and presented with a chronic cough for two (2) weeks, without fever, weight loss, night sweats, family history of blood dyscrasia, or any thrombotic event. Full blood count (FBC) shows leukocytosis (white blood cells (WBC) count: 22.63 x 103/uL) with a predominant neutrophils (neutrophils count was 19.49 x 103/uL, and remarkable thrombocytosis (platelet count was 1858 x 109/L), Mean Platelet Volume (MPV) is 8.4/fL (normal 7.5 – 12/fL), Platelet Distribution Width (PDW) is 8.6/fL (normal 8.1 – 25.0/fL). Peripheral blood film (PBF) shows absolute leukocytosis with neutrophils, monocytosis, and basophilia. Left shift with band forms, myelocytes, and some dysplastic neutrophils. Red blood cells are microcytic and hypochromic, with acanthocytes and cigar cells observed. Severe thrombocytosis with circulating megakaryocyte fragments and platelet anisocytosis with small, large, and giant platelets. The differential diagnosis was essential thrombocytosis (ET) and severe infection. Iron study and liver function test were normal. Essential thrombocytosis was suspected due to persistent thrombocytosis (normal range 150–450 x 109/L) for 1 week during admission but was ruled out as mutation analysis for JAK2 was negative. Suspicion of pulmonary TB due to cough was confirmed via Gene-Xpert MTB/RIF sputum test (PCR). Computed tomography (CT) chest scan demonstrates features consistent with infection and shows generalized bronchiectasis in both lungs, calcification, cavitation, and nodules in all lobes except the right upper lobe. Subsequently, anti-tuberculosis therapy was initiated, to which the patient responded well. The patient's platelet count was closely monitored, and levels continued to decline without any VTE prophylaxis. The recovery was uncomplicated, and the thrombocytosis resolved.

## 3 DISCUSSION

Etiologies of secondary thrombocytosis can be easily remembered as "5 I's" - inflammation, ischemia, infection, infarction, and iron deficiency (2). Thrombocytosis is defined as a platelet count greater than 450 x 109/L, and extreme thrombocytosis (platelet count ≥ 1000 x 109/L) is uncommon and may indicate more than a reactive phenomenon (3). In a comparative cross-sectional study of 164 newly diagnosed tuberculosis patients in Ethiopia, 11.6% had thrombocytosis and 9.8% had thrombocytopenia, based on WHO-defined platelet count cut-offs (>450 ×10³/µL and <150 ×10³/µL) using automated complete blood count analysis (4). Thrombocytosis in TB will demonstrate significant correlation with Mean Platelet Volume (MPV) (5,6) as well as platelet count, and platelet distribution width (5). TB also causes thrombocytopenia, and some studies suggest that the role of platelets in the immunology of tuberculosis is not fully understood (7).

M. tuberculosis are phagocytosed by macrophages after inhalation, which activate and recruit other immune cells like neutrophils, monocytes, natural killer cells and lymphocytes, particularly CD4+ T helper cells (8,9). Extravasation of platelet and its biogenesis as well as presence of megakaryocytes that escalate the platelet generation in response to specific stimuli, may explain why platelets are present in the site of TB. This patient shows atypical fragments of megakaryocytes in his PBF. It is proposed that platelet may sense M. tuberculosis via Toll Like Receptor (TLR) 2 and TLR 4 thus activated and granulate to release proinflammatory cytokines like IL-10 but decreased secretion of Interleukin-1**β** (IL-1**β**), Interleukin-6 (IL-6) and Tumour Necrosis Factor ά (TNFά) (8). Platelet-associated gene transcripts are upregulated with changes in its structure and function acting as a rapid innate immune response is seen in Tuberculosis patients (8). In a cohort study of newly diagnosed drug sensitive smear patients, platelet drive a pro-inflammatory condition, tissue degrading phenotype demonstrated by increased Platelet Factor 4 (PF4) on day 14 compared to day 60 of treatment, showing correlation of PF4 with the disease progression (9). In the same study, other markers such as matrix metalloproteinase-1 (MMP-1), platelet derived growth factor-BB (PDGF-BB), and RANTES were also increased. Platelet also encourage monocytes production of

IL-1β and Interleukin-10 (IL-10) in which the later inhibit both innate and adaptive pathway, inhibit phagosome in the monocyte, limiting the induction of T-helper cell type 1 lymphocytes and thus support M. tuberculosis survival in the lungs (10). Interleukin-6 (IL-6) promotes megakaryopoiesis in TB resulting in thrombocytosis in TB patients (11,12).

There are significant heamatological changes that occur in association in TB and the parameters are useful for predicting the severity, making the diagnosis and management along with monitoring of the disease progression (13, 14). Red blood cells (RBC) changes in TB includes low haemoglobin, RBC count, hematocrit and TB patient are usually anaemic (13,15). For RBC morphologically, 52% patients are microcytic hypochromic, 40% patients are normocytic normochromic and 8% are macrocytic hypochromic (13). Increased TNFά, interferon-ɣ (IFN-ɣ), and IL-6 in TB cause decreased erythropoiesis formation, leading to bone marrow suppression, along with poor iron transport and chronic inflammation, which could be the cause of anaemia (13,15). Leukocytosis and neutrophilia are manifestations of white blood cell (WBC) changes in TB. About 40.9% of patients had leukocytosis, but there was a low positive correlation between reactive thrombocytosis and WBC in TB (16). Monocyte and basophil counts are significantly higher in the TB control group (11). C-reactive protein (CRP) is synthesized in the liver, influenced by IL-6, and rapidly responds to infection, inflammation, trauma, tissue necrosis, and surgery (14). CRP is positive in 86.7% and negative in 13.3% of TB patients associated with thrombocytosis (14). Erythrocyte sedimentation rate (ESR) is not a specific test, as it is elevated in many diseases, and it is reported to be 98% positive in TB patients in India (16). Both markers of acute-phase reactants (ESR, CRP) are elevated in reactive thrombocytosis and may be useful indicators of TB disease, as they are easily available in many developing countries (17). All the common hematological abnormalities in pulmonary TB are reversible (18).

TB is associated with a hypercoagulable state, hematological changes, and chronic inflammation, leading to uncommon venous thromboembolism (VTE) complications, including deep vein thrombosis (DVT) and pulmonary emboli (PE) (19). Kumarihamy reported a rare case of DVT in severe pulmonary TB, with superadded infections during treatment, that resulted in mortality (19) McKinnon also reported a case series of three patients with pulmonary TB who were on treatment and had complications related to pulmonary embolism (20). Stasis, endothelial lesions that release pro-coagulants such as kallikrein and activate the complement cascade, as well as lymph node enlargement causing direct venous compression are other possible mechanisms that cause the complication (20). Decreased antithrombin III and protein C, along with elevated factor VIII, plasminogen activator inhibitor I, and fibrinogen, as well as increased platelet aggregation and reactive thrombocytosis, also contribute to the hypercoagulable state. Some antitubercular drugs increase the risk of VTE. As such, Rifampicin and Isoniazid, with the former being a potent inducer of cytochrome P450 (CYP) enzymes and transporters, can significantly reduce the efficacy of anticoagulants and complicate the achievement of the target INR value in patients with VTE. It's important for clinicians to maintain a high index of suspicion for VTE complications among TB patients. Few studies have suggested antiplatelet therapy as an adjunct to anti-TB drugs. Kirwan proposed that antiplatelet agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and P2Y12 inhibitors (such as Ticagrelor and Clopidogrel), may inhibit platelets and exhibit direct anti-mycobacterial properties, thus preventing further collateral tissue damage in TB (8). Lee et al also conclude that better overall survival and lower 12 months mortality in pulmonary TB patients who received anti-tubercular and antiplatelet drugs (21) Aspirin administration in TB patients has also demonstrated irreversible inhibition of both cyclooxygenase (COX) enzymes, thereby preventing thromboxane A2 generation, which is a potent platelet activator (20) Aspirin provides anti-thrombotic effect at low dose and anti-inflammatory effect at higher dose (8).

## CONCLUSION

This is an extremely rare case of pulmonary TB with severe thrombocytosis in an elderly patient. Clinicians should consider TB in the differential diagnosis of respiratory illness and thrombocytosis, given its high endemicity in our region, before pursuing other aggressive diagnostic tests. Adjunctive antiplatelet therapy may hold promise as a host-directed intervention for TB but requires further clinical validation on a case-by-case basis. Earlier literature has shown that platelets are key players in the immunopathology of TB, warranting further efforts to develop interventions targeting inflammatory

responses in TB. Targeting platelets with antiplatelet agents is being considered as a potential host-directed therapy to limit tissue damage and improve treatment outcomes among TB patients.

**Table I.** Full Blood Count during admission

| Parameter | Result | Normal value |
|---|---|---|
| White blood cell (WBC) x $10^3$/uL | 22.63 | 4.00-10.00 |
| Red blood cell (RBC) x $10^{12}$/uL | 4.94 | 3.86-5.62 |
| Haemoglobin (Hb) / g/dL | 12.20 | 11.80-16.90 |
| Hematocrit (HCT) / % | 36.90 | 35.70-48.90 |
| Mean corpuscular volume (MCV) / fL | 74.70 | 80.60-95.50 |
| Mean corpuscular haemoglobin (MCH) / pg | 24.70 | 26.90-32.30 |
| Mean corpuscular haemoglobin concentration (MCHC) / g/dL | 33.10 | 31.90-35.30 |
| Platelet x $10^9$/L | 1868.00 | 142-350 |
| Red cell distribution width - standard deviation (RDW-SD) / fL | 45.80 | 37.50-48.10 |
| Red cell distribution width - coefficient of variant (RDW-CV) / % | 17.90 | 12.00-14.80 |
| Platelet distribution width (PDW) / fL | 8.60 | 10.10-16.10 |
| Mean platelet volume (MPV) / fL | 8.40 | 9.30-12.10 |
| Nucleated red blood cells (NRBC) / % | 0.00 | 0.00 |
| Neutrophils / $10^3$/uL | 19.49 | 4.00-10.00 |
| Lymphocyte / $10^3$/uL | 1.26 | 2.00-7.00 |
| Monocytes / $10^3$/uL | 1.71 | 1.00-3.00 |
| Eosinophils / $10^3$/uL | 0.06 | 0.20-1.00 |
| Basophils / $10^3$/uL | 0.11 | 0.00-0.10 |
| Immature granulocytes (IG) / % | 1.00 | 0.00-0.60 |
| Reticulocytes (Ret) / % | 1.58 | 0.43-1.36 |
| Immature reticulocytes fragments (IRF) / % | 12.10 | 2.00-16.10 |
| Low fluorescence ratio (LFR) / % | 87.90 | 82.47-97.99 |
| Medium fluorescence ratio (MFR) / % | 10.00 | 2.00-14.03 |
| Highly fluorescence reticulocytes (HFR) / % | 2.10 | 0.00-2.50 |
| Reticulocytes Haemoglobin Equivalent (Ret-He) / pg | 27.40 | |

(Normal range source: Angeli Ambayya et. al., 2014. Hematologic Reference Intervals in a multiethnic population and reference range of Sysmex XE-2100)

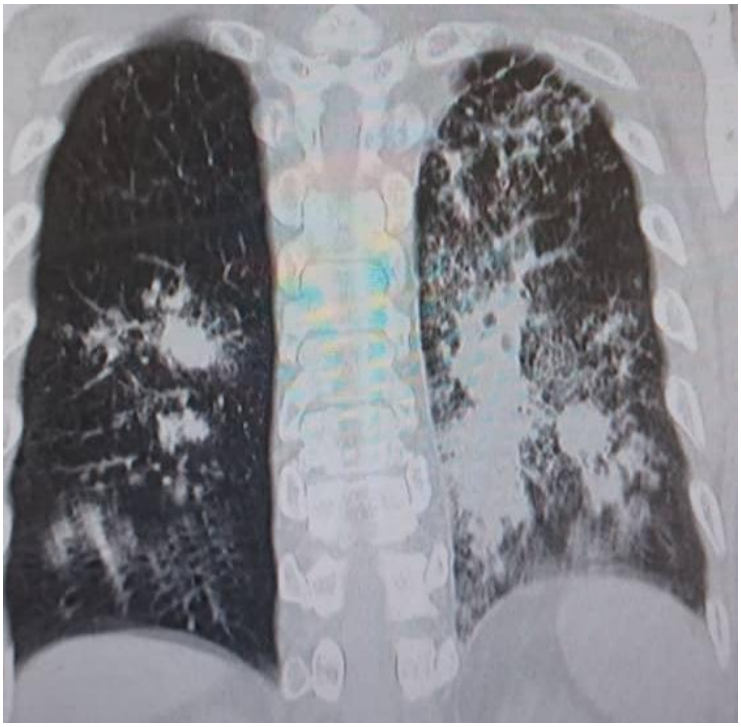

**Figure 1.** Computed tomographic (CT) chest scan (coronal view) during admission.


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## AUTHOR CONTRIBUTIONS

**Ashamuddin NA:** Conceptualization, Investigation, Data Curation, Writing – Original Draft.
**Tan JT, Tan EL, Mot YY:** Formal Analysis, Satistical analysis, Validation, Visualization.
**Mohd Yusoff N:** Supervision, Project Administration, Writing – Review & Editing

## AUTHORSHIP CLARIFICATION

Ashamuddin NA led in clinical design, patient data collection, and manuscript drafting, affiliated with Universiti Sains Malaysia. Tan JT & Tan EL handled hematological data analysis and diagnostic imaging interpretation at Sunway Medical Center. Mot YY offered methodological guidance and coordination at Asian Institute of Medical Science and Technology. Mohd Yusoff N supervised, managed, and validated the project at Universiti Sains Malaysia and Sunway Medical Center.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval for this case report was obtained from the relevant institutional committees. Permission to publish this clinical data was granted by the Director-General of Health, Ministry of Health Malaysia. The study was conducted in accordance with the Declaration of Helsinki.

## CONSENT FOR PUBLICATION

Approval and permission to publish this clinical study were granted by the Director-General of Health, Ministry of Health Malaysia, with additional acknowledgment from the Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia, and Sunway Medical Centre.

## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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