

Extreme Reactive Thrombocytosis Caused by Obstructive Nephrolithiasis and Pyelonephritis

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Platelet counts in reactive thrombocytosis rarely exceed $1000 \times 10^9/L$. We present the case of a male patient, aged 80 years, with quiescent rheumatoid arthritis who was found to have a platelet count of $1011 \times 10^9/L$ on routine laboratory testing. The patient was initially asymptomatic but developed leukocytosis to $23.1 \times 10^9/L$ on hospital day 2. Diagnostic work-up revealed obstructive nephrolithiasis and pyelonephritis, and the thrombocytosis and leukocytosis gradually resolved with empiric antibiotic treatment and ureteral stent placement. Tests for myeloproliferative disorders, including JAK-2V617F mutation, BCR-ABL for chronic myeloid leukemia and acute lymphocytic leukemia, and myeloproliferative neoplasms (MPL/CALR), were negative. Physicians should be aware that in rare cases reactive thrombocytosis can exceed $1000 \times 10^9/L$, and that markedly elevated platelet counts in the setting of urinary tract infections may be an early sign of obstructive uropathy.

Keywords: Reactive thrombocytosis; Urinary tract infection; Obstructive uropathy; Geriatrics; Hematology

Thrombocytosis can be caused by either reactive or autonomous processes. The mechanism of reactive thrombocytosis secondary to infection and inflammation has been well documented. Platelet production can be driven by interleukin-6, cytokines, and catecholamines in infectious and inflammatory states.¹ In particular, interleukin-6 stimulates hepatic production of thrombopoietin, which thereby directly stimulates megakaryocyte proliferation. Moreover, evidence suggests that platelets play a role in amplification of inflammatory and immune responses in chronic inflammation.² However, infection is not necessarily accompanied by thrombocytosis. A 2019 retrospective study of 421 patients hospitalized with acute infections revealed thrombocytosis occurred in approximately 8% of patients presenting for acute community-acquired pneumonia, urinary tract infections (UTIs), and skin and soft tissue infections, with platelet counts ranging from $401-917 \times 10^9/L$.³ We report a case of extreme reactive thrombocytosis with initial platelet count $> 1000 \times 10^9/L$ in a patient with obstructive nephrolithiasis and pyelonephritis.

Case Report

A man, aged 80 years, with a history of rheumatoid arthritis on methotrexate, prostate cancer previously treated with external-beam radiation therapy, and osteoarthritis status post bilateral knee arthroplasties, was referred to the emergency room by his outpatient rheumatologist for a platelet count of $1011 \times 10^9/L$ (up from 348×10^9 2 months before admission), worsening anemia, and mild acute kidney injury noted on routine laboratory testing. On arrival, the patient was asymptomatic except for his chronic and stable right thigh pain. He had no hand or wrist joint swelling, and less than 30 minutes of morning stiffness. He had self-discontinued the methotrexate 3 weeks prior to admission. On physical examination, vital signs were temperature $98.0^\circ F$, respiratory rate 15 breaths per minute, heart rate 83 beats per minute, blood pressure 130/75 mmHg, with no focal findings to suggest infection and no synovitis, lymphadenopathy, or costovertebral angle tenderness. Laboratory results were notable for platelet count $1011 \times 10^9/L$, white blood cell count (WBC) $12.6 \times 10^9/L$ with immature neutrophils on peripheral smear (6 bands, 8

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metamyelocytes, 6 myelocytes, and 2 promyelocytes), and hemoglobin 9.3 mg/dL (down from 12.9 mg/dL 2 months before admission) with mean corpuscular volume 95 and red cell distribution width 16.6. The ferritin was 592 ng/mL, and iron studies were consistent with anemia of chronic disease. The reticulocyte count was 1.05%, and markers for hemolysis (total bilirubin, lactate dehydrogenase, and haptoglobin) were normal. Erythrocyte sedimentation rate was 55 mm/hr, blood urea nitrogen 28 mg/dL, creatinine 1.8 mg/dL (baseline 1.3 mg/dL), and carbon dioxide 16 mmol/L. Tests for myeloproliferative disorders, including JAK-2V617F mutation, BCR-ABL for chronic myelogenous leukemia and acute lymphocytic leukemia, and myeloproliferative neoplasms (MPL/CALR), were negative. On hospital day 2 the patient developed worsening leukocytosis (WBC $23.1 \times 10^9/L$). Urinalysis was notable for positive leukocyte esterase and 32 WBC/HPF; blood and urine cultures were negative. The patient was started on empiric vancomycin and piperacillin-tazobactam for a possible urinary tract infection. Computed tomography scan of the abdomen and pelvis revealed evidence of left sided pyelonephritis with obstructive uropathy from a 9.8 mm left mid-ureteral stone. The patient then developed gross hematuria with passage of clots, and eventually underwent cystoscopy with clot evacuation and fulguration, laser lithotripsy, and left ureteral stent placement. His platelet count gradually downtrended to the 400-500 $\times 10^9$ range (Figure 1), and his leukocytosis resolved.

Discussion

Platelet counts $> 1000 \times 10^9/L$ are traditionally thought to be caused by autonomous processes (i.e., myeloproliferative diseases such as essential thrombocytosis) rather than reactive processes such as infection or inflammation. A few cases of

severe thrombocytosis with platelet counts $> 1000 \times 10^9/L$ have been documented in the setting of iron deficiency anemia and pelvic inflammatory disease,^{4,5} and in rheumatoid arthritis,⁶ but there are no previous reports of platelet counts $> 1000 \times 10^9/L$ in patients with urinary tract infections. In Schattner's retrospective study, approximately of 8% of patients admitted with acute infection had reactive thrombocytosis (ranging from $401-917 \times 10^9/L$), and these patients had more suppurative complications, more bacteremia, increased length of hospital stay, and increased mortality compared with the majority of patients who did not have reactive thrombocytosis.³ Obstructive uropathy without infection would not be expected to induce the systemic inflammatory response necessary to trigger reactive thrombocytosis. However, UTIs that are caused or complicated by obstructive uropathy can be virulent and rapidly progressive, especially in the elderly, and therefore more likely to cause reactive thrombocytosis. Interestingly, in the setting of UTIs, thrombocytosis may be an early sign of serious obstructive complications. Gofrit et al.⁷ found 83 patients with upper urinary tract infections and thrombocytosis (mean platelet count $593 \times 10^9/L$; range, $501-949 \times 10^9/L$), in comparison to a control group of patients with upper urinary tract infections without thrombocytosis, had a significantly higher incidence of obstructive nephropathy (65% vs 18%, P value < 0.00001) and perinephric abscesses (8% vs 0%, P value < 0.003). The finding of thrombocytosis preceded the diagnosis of UTI by a median of 3 days, suggesting thrombocytosis may be an early marker for obstruction and perinephric abscess in the setting of urinary tract infection. This may be especially important in geriatric patients who often present with no fever and atypical symptoms, such as delirium, confusion, and drowsiness, that could make it difficult for them to report classic urinary symptoms.⁸

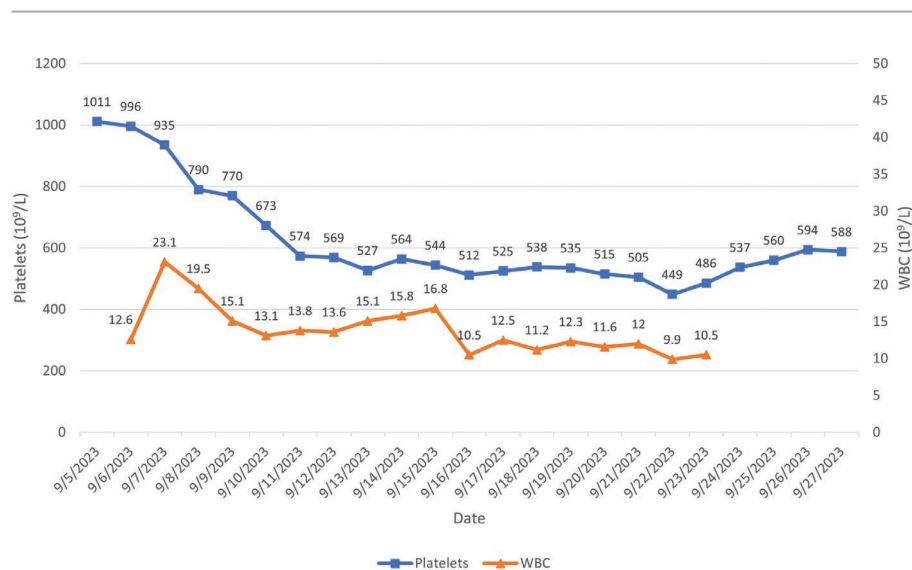


Figure 1. Clinical course in a man, aged 80 years, with reactive thrombocytosis caused by obstructive nephropathy and pyelonephritis.

In addition to his obstructive uropathy and pyelonephritis, our patient had rheumatoid arthritis, which also could have caused or contributed to his thrombocytosis. In a study of 75 patients with rheumatoid arthritis, Hutchinson et al.⁶ found 39 (52%) had platelet counts $> 450 \times 10^9/L$, and 8 (12.5%) had platelet counts $> 1000 \times 10^9/L$. Hutchinson also observed the height of the platelet count correlated with disease activity. Farr et al.⁹ noted the same correlation in another cohort of rheumatoid arthritis patients and, also found the rise in platelet counts corresponded with rises in erythrocyte sedimentation rate and C-reactive protein. Of note, our patient's platelet count was normal at $348 \times 10^9/L$ two months before hospital admission, and his rheumatoid arthritis symptoms were

quiescent at the time of admission. There was also no evidence of iron deficiency anemia; his iron studies were consistent with anemia of chronic disease, and the ferritin level was markedly elevated at 592 ng/mL. This suggests the primary cause of his severe reactive thrombocytosis was the proximal urinary tract infection caused by obstruction from a ureteral stone.

Conclusion

Platelet counts $> 1000 \times 10^9/L$ are traditionally thought to be caused by myeloproliferative diseases rather than reactive processes such as infection, inflammation, and iron deficiency anemia. In rare cases, however, reactive thrombocytosis can exceed $1000 \times 10^9/L$. Physicians should be aware that the presence of severe thrombocytosis in urinary tract infections may be an early marker for obstructive uropathy and warrants prompt imaging and intervention to treat the infection and relieve the obstruction.

References

1. Araneda M, Krishnan V, Hall K, Kalbfleisch J, Krishnaswamy G, Krishnan K. Reactive and clonal thrombocytosis: proinflammatory and hematopoietic cytokines and acute phase proteins. *South Med J*. 2001;94(4):417-420.
2. Senchenkova EY, Ansari J, Becker F, et al. Novel Role for the AnxA1-Fpr2/ALX Signaling Axis as a Key Regulator of Platelet Function to Promote Resolution of Inflammation [published correction appears in *Circulation*. 2019 Jul 23;140(4):e172. doi: 10.1161/CIR.0000000000000713]. *Circulation*. 2019;140(4):319-335. doi:10.1161/CIRCULATIONAHA.118.039345
3. Schattner A, Kadi J, Dubin I. Reactive thrombocytosis in acute infectious diseases: Prevalence, characteristics and timing. *Eur J Intern Med*. 2019;63:42-45. doi:10.1016/j.ejim.2019.02.010.
4. Bergmann K, Bergmann OJ. An unusual case of extreme thrombocytosis caused by iron deficiency. *BMJ Case Rep*. 2020;13(1):e231833. doi:10.1136/bcr-2019-231833.
5. Muhammed ZAE, Alfatih M, Babiker ASH, et al. Extreme thrombocytosis with severe anemia and infection in a Sudanese patient: A case report. *Ann Med Surg (Lond)*. 2022;84:104927. doi:10.1016/j.amsu.2022.104927.
6. Hutchinson RM, Davis P, Jayson MI. Thrombocytosis in rheumatoid arthritis. *Ann Rheum Dis*. 1976;35(2):138-142. doi:10.1136/ard.35.2.138.
7. Gofrit ON, Shapiro A, Rund D, et al. Thrombocytosis accompanying urinary tract infection suggests obstruction or abscess. *Am J Emerg Med*. 2006;24(1):118-121. doi:10.1016/j.ajem.2005.05.007.
8. Dutta C, Pasha K, Paul S, et al. Urinary Tract Infection Induced Delirium in Elderly Patients: A Systematic Review. *Cureus*. 2022;14(12):e32321. doi:10.7759/cureus.32321
9. Farr M, Scott DL, Constable TJ, Hawker RJ, Hawkins CF, Stuart J. Thrombocytosis of active rheumatoid disease. *Ann Rheum Dis*. 1983;42(5):545-549. doi:10.1136/ard.42.5.545.

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