Extreme Thrombocytosis in Refractory ITP Post-Splenectomy With Associated Fatal Thromboembolism

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ABSTRACT: Thrombopoietin (TPO)-receptor agonists have heralded a paradigm shift in the treatment of refractory immune thrombocytopenia (ITP). Reactive thrombocytosis has been described as a secondary effect of such therapies. However, the phenomenon of extreme thrombocytosis with morphology mimicking a myeloproliferative neoplasm (MPN) followed by fatal thromboembolism is unusual in this setting. Caution is required in the diagnosis of refractory ITP as well as TPO-receptor agonist dosing in such cases.

KEYWORDS: Purpura, thrombocytopenic, idiopathic, splenectomy, thrombocytosis, thromboembolism, receptors, thrombopoietin

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Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder defined by a platelet count of $<100 \times 10^9$/L, resulting from antibody-mediated platelet destruction as well as reduced megakaryocytic number and function secondary to the immune response.[1] Primary ITP is diagnosed in the absence of other possible causes of thrombocytopenia, and has the potential for significant morbidity and mortality associated with both the underlying disease process as well as required therapies.[1,2] First-line therapies include glucocorticoids and intravenous immunoglobulin (IVIg), with splenectomy recommended in those without a contraindication who fail initial therapy. Refractory ITP is defined as thrombocytopenia that persists or recurs after splenectomy, and requires treatment to reduce the risk of significant bleeding.[3] Thrombopoietin (TPO)-mimetics such as romiplostim have proven to be promising therapies in refractory cases.[4] We describe a case of extreme thrombocytosis with morphology mimicking a myeloproliferative neoplasm (MPN) in a patient with refractory ITP on romiplostim, followed by fatal thromboembolism. The importance of excluding other potential causes of thrombocytopenia in treatment-refractory ITP is emphasized. Also presented is a literature review analyzing the thrombotic risk associated with the post-splenectomy state and extreme thrombocytosis, as well as caveats relating to TPO-receptor agonist administration in ITP.

Case

An 82-year-old man presented with 2 months of hemoptysis and a lower limb rash developing over the preceding week. His background history included ischemic heart disease, bioprosthetic aortic valve replacement and hypertension. There was no significant family history or symptomatology suggestive of malignancy. He took no relevant regular medications apart from aspirin 100 mg daily. Physical examination was notable for oral blisters and a petechial rash over the lower extremities. His weight was 95 kg. Full blood count revealed a platelet count of 5×10^9/L, which was confirmed on blood film examination with no additional abnormalities. Initial workup including thyroid stimulating hormone, viral serologies, serum *H. pylori* immunoglobulin G antibody, hematinic studies, and hemolysis screen was unremarkable. Coagulation profile was normal and an autoimmune panel was negative. Bone marrow examination was unrevealing with adequate megakaryopoiesis and no significant dysplasia or abnormalities detected by flow cytometry or cytogenetic analysis.

A diagnosis of ITP was made and the patient's aspirin was withheld. Initial treatment with 4 days of oral dexamethasone 40 mg daily and IVIg at 2 g/kg incremented the platelet count to 433×10^9/L. Further investigations revealed the presence of a solitary left-sided pulmonary nodule that was fluorodeoxyglucose-avid on positron emission tomography (PET) scan. Bronchoscopy demonstrated a vascular endobronchial lesion in the left upper lobe. Bronchial biopsy and subsequent left upper lobectomy confirmed a low-grade, well-differentiated neuroendocrine tumor with clear resection margins. Further definitive management was not required given the absence of local or metastatic spread.

The patient experienced a number of glucocorticoid-responsive relapses of his ITP with marked thrombocytopenia and he subsequently underwent a splenectomy at 4 months following initial diagnosis. Despite a good initial response, the platelet count significantly reduced to 8×10^9/L on surveillance blood testing at 2 months post-splenectomy. This prompted reassessment of the diagnosis of ITP and repeat testing for other possible causes of thrombocytopenia, which was again unremarkable. A follow-up PET scan excluded

recurrence of neuroendocrine tumor as a possible cause of ITP relapse. Subcutaneous romiplostim was commenced at 100 μg (~1 μg/kg). A second dose of 150 μg was given the following week due to ongoing marked thrombocytopenia, resulting in an increase in platelet count to 1131×10^9/L. Romiplostim was withheld for 2 weeks with resolution of the thrombocytosis. The chronology of subsequent romiplostim dosing and associated platelet count changes is illustrated in Figure 1.

Ten days following a romiplostim dose of 250 μg, the patient presented with a 2-day history of frank hemoptysis and was noted to have a peak platelet count of 2365×10^9/L. Blood film examination confirmed extreme thrombocytosis with numerous large and giant platelets, anisochromasia, and megakaryocyte fragments, as well post-splenectomy red cell changes (Figure 2). Computed-tomography pulmonary angiogram showed no pulmonary embolism or other causes for hemoptysis. Screening for an acquired von Willebrand syndrome was unremarkable. Next-generation-sequencing (NGS) using a targeted amplicon panel against genes implicated in MPN revealed no mutations. The patient underwent 1 plateletpheresis procedure with whole blood, following which his hemoptysis settled and platelet count decreased but still remained markedly elevated.

The patient was discharged but re-presented 3 days later following a syncopal episode with no associated neurocardiogenic symptoms. Blood glucose level, postural blood pressures and cardiac telemetry were unremarkable apart from sinus tachycardia. The platelet count had reduced to 1563×10^9/L. A 1-day history of worsening pleuritic chest pain, dyspnea, and hypoxia was noted during his admission in the context of a normal chest radiograph. Serial troponin levels were slightly elevated but without a progressive rise, thereby excluding myocardial infarction. Transthoracic echocardiogram demonstrated findings consistent with right heart strain, including dilated right atrium and ventricle with impaired systolic function and elevated right ventricular systolic pressure. The patient subsequently died following an asystolic cardiac arrest despite resuscitation and thrombolysis for presumed pulmonary embolism. A large saddle pulmonary embolus was confirmed on a limited post-mortem examination.

Discussion

Accurate diagnosis of primary ITP requires consideration of the patient-specific context and careful exclusion of both thrombocytopenia due to non-immune causes as well as secondary causes of ITP. This patient-centric approach is not only crucial at initial presentation but also during the disease course where relapses are frequent. In this case, it was pertinent to exclude recurrence of neuroendocrine tumor as a potential mimic of refractory ITP given the reported association between solid organ malignancy and thrombocytopenia.[5] Although not typical, ITP is a rare paraneoplastic phenomenon associated with neuroendocrine tumors. Interestingly, such cases of ITP are resistant to conventional treatments such as glucocorticoids and splenectomy but respond dramatically to tumor-directed therapy.[5,6] This highlights the importance of reviewing the diagnosis of ITP in challenging and refractory cases prior to considering second-line treatments such as TPO mimetics.

Romiplostim typically requires previous splenectomy or a contraindication to splenectomy to qualify for treatment. Subcutaneous romiplostim is usually commenced at an initial dose of 1 μg/kg with weekly increments of 1 μg/kg thereafter, depending on platelet count response.[4] However, marked variation in effective romiplostim doses between patients makes dose adjustment challenging. This heterogeneous response is amplified following splenectomy and during intercurrent illness.[7] Significant fluctuations in platelet count, including both thrombocytosis and rebound thrombocytopenia, have been well-described due to the lag time between change in romiplostim dose and its maximal effect, with an average of 14 days (range 12-16 days).[4,7] Given this delayed marrow response, frequent substantial changes in romiplostim dosing should be avoided particularly during times of drug commencement and disease relapse. Reflecting on the outcome in this case, lower dose increments of 0.5 μg/kg/week for persistent thrombocytopenia may be safer.

There are conflicting data on the thrombotic risk associated with thrombocytosis alone post-splenectomy; overall, the risk appears greatest in those with a primary etiology such as MPN, compared to those with secondary thrombocytosis.[8,9] In cases of extreme thrombocytosis, defined as a platelet count $>1000 \times 10^9$/L, the risk of thrombotic complications again appears to be higher in those with an underlying MPN.[10,11] There are several reported cases of extreme thrombocytosis post-splenectomy requiring plateletpheresis due to hemostatic alterations; however, in contrast to our patient, these cases were consistently reported only in the immediate post-operative period and associated with a lesser degree of thrombocytosis with no mention of specific morphological features.[12,13] Although thrombocytosis may accentuate the already heightened risk of thrombosis associated with the post-splenectomy state, romiplostim use in splenectomized patients is not clearly associated with increased thrombotic risk above baseline (6%-7%).[14] However, withholding romiplostim during times of intercurrent illness may be warranted to reduce the risk of extreme post-splenectomy thrombocytosis.[12,13,15]

An assortment of anomalies pertaining to platelet morphology have been described in MPN, including marked anisocytosis, large or giant platelets, hypogranular or agranular platelets, circulating megakaryoblasts and megakaryocyte fragments.[16] A majority of these striking peripheral blood morphological features mimicking MPN were observed in our case but have not been previously described in association with romiplostim use, raising the question of whether the effect of romiplostim on

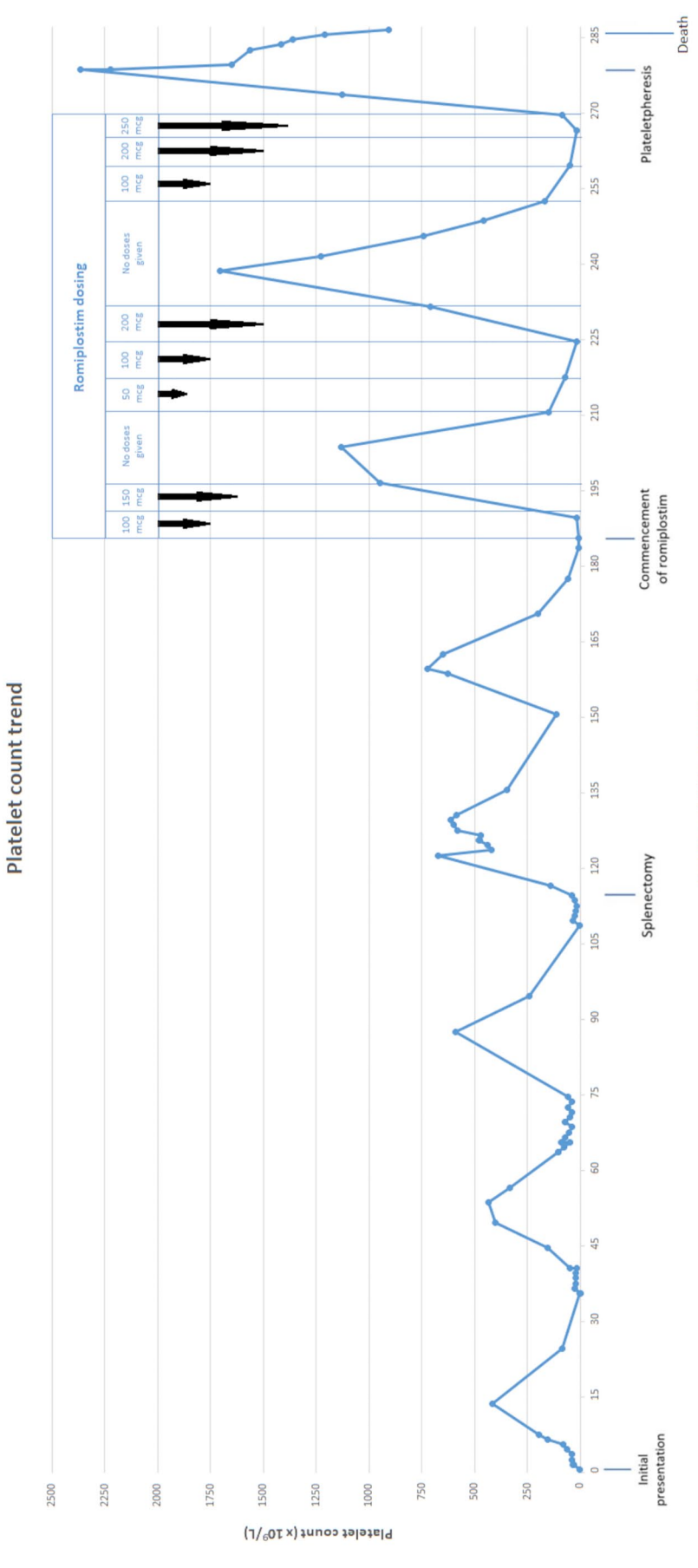

Figure 1. Platelet count trend and notable events over the disease course.

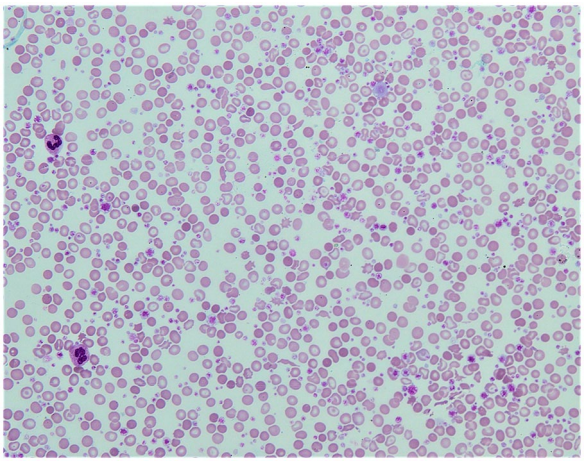

Figure 2. Extreme thrombocytosis and post-splenectomy blood film changes whilst on romiplostim.

megakaryocytic and platelet function results in a similar aetiopathogenesis to MPN. A study by Al-Samkari et al assessed platelet aggregometry in 15 patients with ITP receiving romiplostim and 7 healthy controls. They demonstrated that there was no evidence of spontaneous platelet aggregation, and no overall significant difference between patient groups apart from a mildly reduced response to low-dose ADP and epinephrine in the romiplostim group.[17] Nevertheless, further assessment of platelet function and global coagulation with platelet function testing and thrombin generation assays may further assist in delineating the physiological effects of TPO mimetic-associated thrombocytosis in future studies.

Conclusion

The diagnosis of refractory ITP requires prompt and thorough exclusion of other possible causes of thrombocytopenia. Marked fluctuations in platelet count are well-documented with romiplostim therapy for ITP, which may be further heightened by prior splenectomy. This case illustrates an extreme example of this phenomenon associated with fatal thromboembolism. Significant week-to-week changes in romiplostim dosing should ideally be avoided in such patients. Additionally, the unique platelet morphology raises the question of whether there is an increased thrombotic risk associated with the thrombocytosis seen with romiplostim therapy, similar to that described in MPN. Further studies are required to assess platelet function and coagulation status in this subset of patients, which may have significant implications for treatment.

Author Contributions

R. Nedumannil (first author) and E. Leitinger (second author) wrote the manuscript and performed the literature review. R. Nedumannil provided the figures with interpretation. S. Juneja (senior author) reviewed and revised the manuscript. All authors read and approved the final manuscript.

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