

# Romiplostim as a Viable and Long-term Remedy for Refractory Immune Thrombocytopenia and Concomitant Small B-Cell Lymphoma

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## Abstract

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by immune-mediated destruction of otherwise normal platelets and can be either primary, without obvious initiating or underlying cause, or secondary ITP due to an underlying disease or drug exposure.

The goals of therapy for ITP include achieving an adequate platelet level for hemostasis and minimizing toxicities with current options including: corticosteroids, rituximab, splenectomy, intravenous gamma globulin (IVIG), Anti-D, and thrombopoietin receptor agonists (TPO) like romiplostim and eltrombopag.

TPO mimetics like romiplostim have emerged as viable and practical option in relapsed and refractory ITP. We present a 70-year-old Caucasian male patient with chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) related secondary ITP who had been maintained for nearly a decade on romiplostim after failing all other options of therapy. We report this case to demonstrate the efficacy and sustainability of romiplostim use in the relapse/refractory ITP in such a patient who failed to respond to other therapeutic options.

**Keywords:** Immune thrombocytopenia; Lymphoid neoplasm; Thrombosis

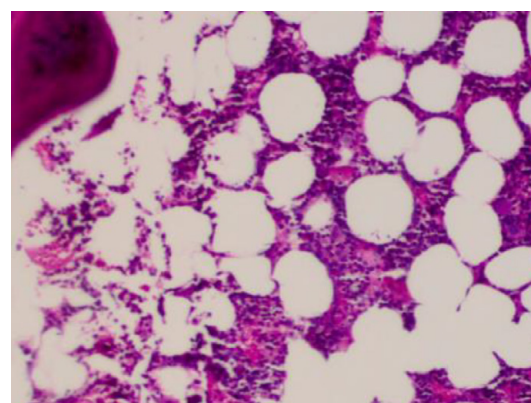
## Introduction

Clinically significant ITP is noted in 2 to 5 percent of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [1]. Nearly one third of these patients will have a concurrent autoimmune hemolytic anemia presenting as Evan's syndrome. Common causes of thrombocytopenia such as bone marrow failure or hypersplenism must be ruled out, and the rapid drop in the platelet count must be otherwise unexplainable to consider the diagnosis of ITP. Once ITP is diagnosed in the context of CLL/SLL, the treatment of these patients is similar to those without a lymphoid neoplasm. Approximately half of these patients will respond to initial therapy, and 20 percent will have refractory disease despite trials of several agents [2-4]. The most commonly employed treatment options for ITP include corticosteroid, IVIG, rituximab, and splenectomy. More recently, the use of TPO mimetics have become an established option for patients who have refractory ITP. Our case demonstrates the long-term stabilization of a refractory ITP patient on romiplostim.

## Case Report

The patient was a 70-year-old Caucasian man with multiple comorbidities including hypertension, coronary artery disease status post coronary artery bypass grafting, severe COPD with ongoing active smoking, and chronic back pain from degenerative disc disease associated with a remote history of motor vehicle accident with multiple fractures. He was diagnosed with ITP in 2009 associated with an otherwise asymptomatic CLL/SLL after a bone marrow biopsy (Figure 1) was performed to evaluate the thrombocytopenia which confirmed the diagnosis. The platelet count failed to rise despite multiple lines of therapy including corticosteroids, IVIG infusions, and rituximab therapy. His platelet counts increased transiently following a laparoscopic splenectomy. Pathologic evaluation of the spleen revealed changes consistent with lymphomatous involvement (Figures 2-4), and post-operative imaging failed to demonstrate any sign of accessory spleens. At that point, therapy was initiated on romiplostim 1mcg/kg/week, which was not yet approved at that time, with slow

dose escalation to a target of a platelet count of 100,000. He had been maintained on romiplostim for nearly seven years before the patient began to notice drenching night sweats, diffuse lymphadenopathy, and weight loss. Further work up that included computerized tomography (CT) of the chest, abdomen and pelvis and a repeat bone marrow biopsy with cytogenetics and fluorescent in situ hybridization confirmed symptomatic CLL/SLL without cytogenetic or karyotypic



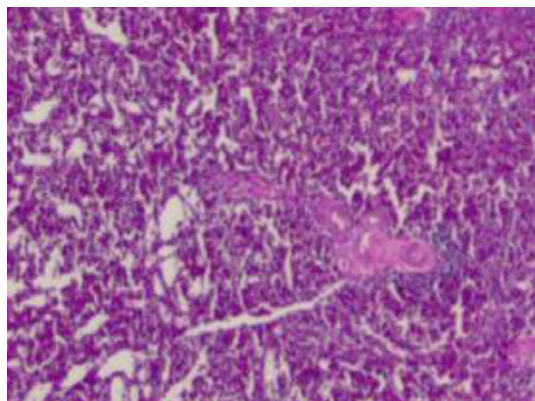
**Figure 1:** Highlights bone marrow involvement of approximately five percent by mature neoplastic cells (H&E, 100x magnification).

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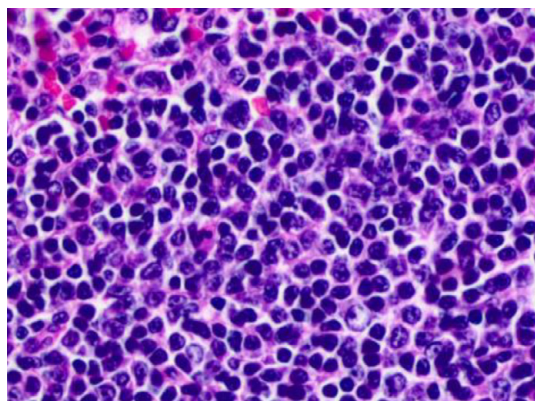
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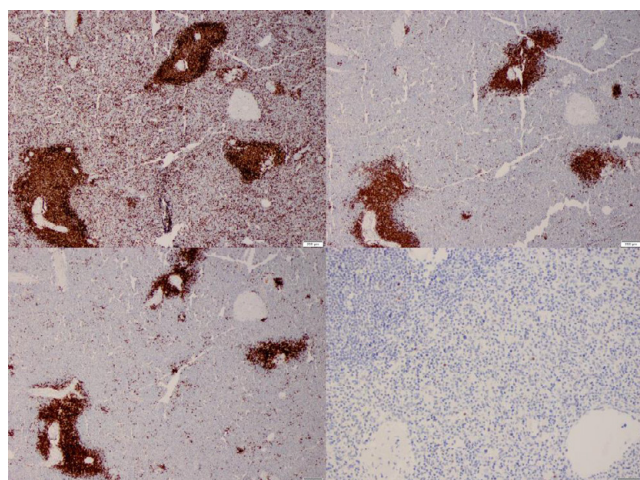
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**Figure 2:** Low power view of the patient's spleen demonstrating expanded lymphoid areas by monotonous small lymphocytes (H&E, 20x magnification).



**Figure 3:** Highlights expanded lymphoid areas in the spleen consisting predominantly of small, mature, neoplastic, homogenous lymphocytes (H&E, 400x magnification).



**Figure 4:** Top left (CD5, 40x magnification), top right (CD20, 40x magnification), and bottom left (CD23, 40x magnification) highlight the neoplastic cells in both the lymphoid areas and the red pulp. Bottom right (Ki-67, 200x magnification) highlights the low cellular proliferation (<10%) of the neoplastic cells.

abnormalities. Due to his multiple comorbidities and frailty, treatment was initiated with chlorambucil and obinotuzumab, but he could only tolerate the treatment for only two cycles with partial improvement in his symptoms and lymphadenopathy. During the course of treatment with this regimen, he experienced an allergic reaction to obinotuzumab nearly causing anaphylactic shock and cardiac arrest.

Of note, he had had multiple hospital admissions for recurrent symptomatic gastrointestinal (GI) bleeding from small bowel arteriovenous malformations (AVMs), which were managed with supportive care, transfusions as needed, and cauterization/clippings/embolization of the aberrant vasculature. Extensive work up including repeated upper and lower GI endoscopies, as well as capsule endoscopies and push-enteroscopies failed to identify any other source of the GI bleeding (other than the AVMs), and no permanent strategy could be found to successfully manage the recurrent GI bleeding.

Ultimately, the patient died of intractable bleeding nearly a decade after his initial diagnosis of CLL/SLL related chronic refractory ITP. His platelet count was maintained in the 50,000/mm<sup>3</sup> range at the time of death. Of note, the patient had undergone several major invasive procedures over the years, including an open reduction internal fixation following a traumatic hip fracture, multiple endoscopies with biopsies and cardiac catheterization while he had been maintained on romiplostim.

The long-term maintenance of the patient's platelet count after failing multiple lines of therapy illustrates a viable option for treatment of CLL/SLL related refractory ITP unresponsive to other standard therapeutic measures.

## Discussion and Conclusions

For patients with ITP who experience clinically relevant bleeding despite first-line therapy with glucocorticoids or patients who are unable to maintain platelet count of 20,000 or more, there are several second line options that can be used to treat the ITP. These include the use of rituximab, splenectomy, and TPOs. TPOs are usually reserved for patients who have persistent severe thrombocytopenia despite splenectomy and rituximab as they will require continuous maintenance administration and usually do not induce permanent remission leading to severe financial burden. The two most commonly used TPOs, romiplostim, a once weekly subcutaneous injection, and eltrombopag, a once daily oral tablet have similar efficacy and toxicity. Several studies have demonstrated the efficacy of romiplostim in raising platelet counts in approximately 80 percent of patients [5-8].

Romiplostim is generally well tolerated with potential short-term adverse reactions including thrombocytosis, thrombosis, and minor reactions like headache and gastrointestinal symptoms. In a 2015 meta-analysis from 14 trials involving 1059 patients with ITP treated with romiplostim versus placebo (standard of care) for up to five and a half years, there were comparable rates of hemorrhage, thrombosis, myelodysplasia and other hematologic and non-hematologic neoplasms [9]. In addition, romiplostim has no sequence homology to thrombopoietin and therefore is not expected to result in the formation of inhibitory antibodies. It also has very few drug interactions.

In conclusion, TPO mimetics should be considered in the treatment armamentarium of patients with chronic phase CLL/SLL who present with refractory ITP and fail other treatment options including steroids, IVIG, rituximab or splenectomy. Romiplostim offers a safe and long-term option to maintain an adequate platelet count even in patients

who have multiple comorbidities and are not eligible for aggressive treatment of their CLL/SLL.

## Statement of Ethics

The authors have no ethical conflicts to declare.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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