Idiopathic Thrombocytopenic Purpura and Radiotherapy: A Case Report and Review of the Literature

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Abstract

Idiopathic thrombocytopenic purpura is an acquired immune disorder characterized by immune-mediated destruction of platelets and their precursors, megakaryocytes. Bleedings are the main risks, and it results in a lower quality of life. A 45-year-old man presenting with idiopathic thrombocytopenic purpura received successive treatments. However, he became resistant to medical treatments, and he required a splenectomy. Two years later, the patient relapsed, and despite the use of thrombopoiesis stimulating agents, the improvement was transitory. A CT scan showed an accessory spleen that could explain this refractory idiopathic thrombocytopenic purpura. Splenectomy was contra-indicated, and irradiation at the dose of 10 Gy in 10 daily fractions was refused, and the patient relapsed, and despite the use of thrombopoiesis stimulating agents, the improvement was transitory. A CT scan showed an accessory spleen that could explain this refractory idiopathic thrombocytopenic purpura.

Keywords: Idiopathic thrombocytopenic purpura • Accessory spleen • Splenic irradiation

Introduction

Idiopathic Thrombocytopenic Purpura (ITP) is a hematological autoimmune disease characterized by platelets and megakaryocytes destruction due to acquired auto-antibodies [1,2]. The result of a low platelet count is an increase of bleeding risk manifested by petechiae, purpura, mucosal bleeding in the urinary tract, gastrointestinal tract and oral cavities, including epistaxis, and reduced quality of life. In 0.2% of cases, fatal intracranial hemorrhages can occur [3,4].

Prevalence and incidence of primary ITP, defined as acquired ITP in the absence of co-existing disorders, reach up to 9.5/100,000 and 3.3/100,000 adults per year, respectively, increasing with age, with a slight overall female predominance [2-4]. ITP is classified as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months) [5].

The primary aim of treatment is the restoration of platelet counts compatible with sufficient hemostasis rather than achieving physiological platelet counts [4,6]. Glucocorticoids are the standard first-line treatment to achieve an initial response. However, the rate of long-term remission is low, and multiple lines of therapy are often required [3]. Among them, there is surgery with splenectomy.

Patients who are ineligible or relapse after splenectomy and have severe ITP or have a risk of bleeding that requires therapy are considered to develop refractory ITP [5]. In some patients, relapse is due to the presence of an accessory spleen [7]. When a second splenectomy is not feasible, splenic irradiation may be an alternative.

The current report describes the case of a man with a refractory ITP after splenectomy caused by an accessory spleen, who was treated by radiotherapy because not operable.

Case Report

A 45-year-old man was referred to the radiotherapy department for splenic irradiation in the context of an ITP. The diagnosis had been made in September 2008, because of petechiae, spontaneous hematomas, and a platelet count at 3 × 10⁹/L, the patient was initially treated exclusively by corticosteroids 160 mg per day followed by a gradual decrease until 40 mg per day. The platelet count increased up to 77 × 10⁹/L.

In November 2008, the platelet count decreased at 36 × 10⁹/L, and intravenous immunoglobulins were recommended in addition to the corticosteroid treatment. Platelets temporarily reached a maximum count of 130 × 10⁹/L.

In December 2008, because the patient relapsed again, weekly rituximab infusions were started for four consecutive weeks, combined with corticosteroids, but failed to improve his condition with platelet count less than 120 × 10⁹/L.

The 05/02/2009, five months after the diagnosis, a splenectomy was performed, secured by platelet transfusions. The platelet count increased to 447 × 10⁹/L, and then gradually decreased.

In January 2011 and April 2012, the patient presented two severe thrombocytopenia episodes (<20 × 10⁹/L). The former was treated by corticosteroids 80 mg per day and weekly 500 μg of romiplostim subcutaneous infusion (Nplate®), a thrombopoiesis stimulating agent, and the latter by eltrombopag (Revolade®), one tablet of 50 mg per day. Eventually, for six years, the two thrombopoiesis stimulating agents were alternatively prescribed when the patient relapsed, to obtain approximately 150 × 10⁹/L platelets.

In May 2015, while platelet count less than 10 × 10⁹/L, additional treatment was done with intravenous immunoglobulin allowing for a transitional increase to 346 × 10⁹/L for about two weeks (Figure 1). After ten-year follow-up, the patient suffered from refractory thrombocytopenia at 5 × 10⁹/L. In May 2018, an abdominal ultrasound showed a 24 mm nodule in the splenectomy area. CT scan revealed an accessory spleen attached to the pancreatic tail (Figure 2).

A multidisciplinary team meeting, a splenectomy was recommended but ultimately challenged due to a too low platelet count (1 × 10⁹/L) despite platelet transfusions. Finally, localized radiation therapy at the dose of 10 Gy in 10 daily fractions of 1 Gy was delivered. 2.5 cm slices CT scan was used for delineation and treatment planning (Figure 3). Target volume included accessory spleen. The planning target volume contained the target volume with a 5 mm margin was irradiated by 3D-conformational radiotherapy. The treatment outcome was evaluated on the increased platelet count. At the end of the irradiation, the platelet count remained at 1 × 10⁹/L. One month after radiotherapy, the platelet count had not increased, and a CT scan showed stability of the accessory spleen (13.3 cm² before versus 12.6 cm² after irradiation). A Romiplostim subcutaneous infusion (Nplate®) was resumed.
At nine-month follow-up, in the absence of conclusive results, we proposed to the patient a second radiation therapy at the dose of 10 Gy in 2 fractions of 5 Gy on alternate days, delivered within intensity-modulated radiotherapy (Figure 3). However, the platelet count remained low six months later (2 × 10^9/L).

**Discussion**

Pathophysiology of ITP is not well understood, but it is established that auto reactive antibodies associated with altered T and B cells are involved in the platelet's destruction and the impairment in thrombopoiesis and megakaryopoiesis. The imbalance between an increase of pro-inflammatory cytokines (IFN-γ, IL-2, and IL-17) and a decrease in anti-inflammatory cytokines (IL-10, TGF-β, and IL-4) induced autoantibody development and a central deficiency of immune tolerance [4]. The IgG autoantibody target two of the most abundantly expressed platelet surface antigens: glycoprotein (GP) αIIbβ3 (GPIIbIIIA) and GPIb-IX-V. Macrophages bearing Fcγ-receptors (FcyRs) recognized platelet-bound antibodies inducing antibody-mediated platelet phagocytosis and destruction primarily in the spleen, but also possibly in the liver and diffusely in the reticuloendothelial system [2,4]. The platelet destruction area can influence the decision to perform a splenectomy [8-10].

Features of ITP-spleen histology was not explicitly described in the literature. Two studies have shown that ITP spleens had significantly more follicular helper T cells localized in their reactive follicles than controls (post-trauma splenectomy), which leads to B-cell proliferation and differentiation into plasma cells which secrete anti-platelet autoantibody [11,12].

ITP is a benign and rarely fatal disease, but the prognosis darkens when a low platelet count persists [13]. Moreover, patients often present allow quality of life due to recurrent bleeding events or anxiety of potential hemorrhage [1]. Platelet counts do not necessarily correlate with bleeding risk, but the threshold of 30 × 10^9/L was a limit below which there is a higher risk of bleeding. Other parameters leading to introduce treatment could be the severity of previous bleeding, a risk life behaviour (fighting sport, violent relationship...), side effects of treatment, and patient preferences [5].

The purpose of first-line treatment is the inhibition of autoantibody production and platelet degradation. Corticosteroids were most administered with an immediate response in 80% of cases. However, along-term response was achieved in only 20% of patients, with potentially severe side effects [2,4]. Intravenous immunoglobulin (IVIg) and anti-D can be used alone in case of corticosteroids contraindication or combined with them if a faster result is required to counteract severe bleeding or before a splenectomy [3-14].

Nevertheless, 60% to 70% of patients require further additional treatment [15]. Because the spleen is the primary site for platelet
Figure 3. Radiotherapy planning for an accessory spleen: A: Planning CT scan, clinical target volume in yellow and planning target volume in red; B: Dosimetric plan of first irradiation; C: Dosimetric plan of second irradiation.
destruction in ITP, a laparoscopic splenectomy was also performed for decades with good response (around 80%) [2]. Recent studies have shown medical alternatives to lower inherent complications like infection or thrombosis [3].

The second-line treatments include Rituximab (RTX) and thrombopoietin receptor agonists (TPO-RA) [2]. Many systematic reviews showed that TPO-RA (eltrombopag and romiplostim) had a superior overall response compared with RTX or placebo, with best safety and tolerance over more extended periods of exposure [1-17]. TPO-RAs stimulate megakaryopoiesis and platelet production from the bone marrow, with overall response rates around 80% [2]. In the Yang et al. systematic review, romiplostim appears to be the most suitable treatment in terms of overall response (87.6%) compared to eltrombopag (65%) [15]. The lack of cross-resistance between both drugs led to propose the latter drug to the unresponsive patients at the former drug [3]. TPO-Ras induced a few side effects, but the most severe complications were thromboembolism and hepatotoxicity [16, 17].

Splenic artery embolization and splenic radiation are other possible strategies to try to eradicate splenic tissue [14-19]. Spleen irradiation is a standard treatment of ITP. Literature is sparse about spleen anatomical pathology examinations to determine the effect of the radiation on the spleen and the tissue architecture.

The morphological changes of erythrocytes (Howell-Jolly bodies, target cells, etc.), which were described after splenectomy, were not observed after irradiation, suggesting that only partial hypoplasmenia was achieved with radiation therapy [20,21]. However, it seems better to administer the pneumococcal vaccine before the irradiation and put on long-term antibiotherapy [21]. The review of the literature is deceiving because the number of reported cases is less than 20. Furthermore, the rationale for using radiation remains blurry. Efficient indicated doses seem low (5-15 Gy), but they leave 20-25% of the splenic volume undertreated [21].

Acute or long-term side-effects are uncommon with low-dose splenic irradiation since the radiation tolerance of the kidney and colon are well above the doses used [22].

The work of Callis et al. was based on these two studies to propose radiation therapy as a mean to prepare a risky candidate for a splenectomy. They delivered a total dose of 15 Gy in 5 fractions over five consecutive days. One week later, they obtained an increase of platelet count from 18 × 10^9/L to 110 × 10^9/L, allowing for splenectomy the following week [22].

Despite all these treatments, some patients relapse. Targarona et al. reported an accessory spleen in 33% of patients who did not show clinical improvement [23]. An accessory spleen is a part of splenic tissue that can be found in ectopic locations (splenic hilum, near or in the tail of pancreas, greater omentum), which might be potentially a cause of postoperative refractory ITP [24-29].

The accessory spleen may be a consequence of a benign variance during embryologic splenic development or the initial lack of total spleen resection, with subsequent hypertrophy or compensatory hypertrophy of small splenic residual [25].

It requires a new laparoscopic splenectomy with less 25% long-term remission [30]. Several exams are available to identify accessory spleen such as abdominal ultrasound, abdominal CT scan, MRI, or scintigraphy but with low sensitivity [7,25].

Therefore, surgeons should take extra care and carefully search for the presence of an accessory spleen in patients with ITP undergoing splenectomy [24,31].

Irradiation of accessory spleen has never been reported in the literature. Radiation doses varied between the series. Calverley et al. mainly used a 6 Gy total dose in six fractions over three weeks (2 fractions per week), whereas Caulier et al. used 15 Gy in 5 weeks (2 weekly 1.5 Gy doses) [20,21].

The results of Caulier et al. are slightly worse than those of Calverley et al., with respectively 42.8% (3/7 patients) of good responders (>50 × 10^9/L) and 63.6% (7/11 patients). This discrepancy may be explained by the protection of the left kidney in the Calvier’s study, leaving 20-25% of the splenic volume undertreated [21].

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<th>Variables</th>
<th>Platelet count (× 10^9/L)</th>
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<td>Age/ Sexe</td>
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literature. In our case, we decided to administer a total dose of 10 Gy in 10 fractions (5 weekly 1 Gy doses). Given that the prescribed doses agreed with those found in the literature, it seems to lack of efficiency in front of the still low platelet count after six months $(1 \times 10^9/L)$. Multiple reasons could explain this observation. First, the accessory spleen was diagnosed with abdominal ultrasound and a CT scan, but without histological evidence. Thus, the nodule may not be a splenic tissue, explaining that it is not sensitive to radiotherapy. Other medical treatments are also not efficient, and this confirms the hypothesis of histological resistance to radiotherapy and other therapy. Another explanation is that the patient suffers from another hematologic disease with deficient bone marrow, which was not explored because of the risk of bleeding with this low platelet count and the impossibility to correct it, even momentarily, with platelet infusions.

Finally, we used lower total doses and doses per fractions than Cauiller et al. and Callis et al. [21,22]. Our treatment plan may not be the most suitable, and we wonder about a second radiation course. Calverley et al. and Cauiller et al. reported respectively three and two cases of radiation performed twice, respectively, after transient response with the first irradiation. Four of the five patients responded again, transiently [20,21]. The two Cauiller's cases received a second similar irradiation course of 15 Gy, and the excellent response persisted after three months in both cases [21].

Despite the second treatment, we have not obtained any results after six months $(2 \times 10^9/L)$. The two-irradiation interval time is poorly described in the literature, but it could be a reason for this failing. Calverley et al. described approximately five months between the two treatments for one of their patients [20]. The interval time for our patient may be too long to obtain a positive result.

Woo J. et al. reported less than one-quarter long-term remission after the surgery of the accessory spleen. They attributed that to the increased destruction of platelets by another reticuloendothelial system than of the spleen [30], that can also explain the failure of the irradiation. To explore this hypothesis, it could have been interesting to perform a platelet kinetic study with $^{111}$In-Oxine-labeled autologous platelets that several teams used to determine the criteria of the short-term success rate of splenectomy [9-32].

Conclusion
A low dose of splenic irradiation may be a well-tolerated treatment in chronic ITP when splenectomy is contraindicated. However, the platelet count sometimes remains low. There is no consensus on the radiation course. Future studies are required to determine a reference total dose and fractionation. However, lots of unknown features of platelet destruction remain to optimize treatment management of patients with ITP.

Disclosure of Interest
The authors declare that they have no competing interests.

Informed Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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