

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

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**Received** 05 June 2020; **Accepted** 22 June 2020; **Published** 29 June 2020

## 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 10Gy in 10 daily fractions of 1 Gy was performed. In the absence of platelets increase, we proposed second irradiation. This case of accessory spleen irradiation is the opportunity to review the role of radiotherapy in idiopathic thrombocytopenic purpura and discuss its place compared to the new efficient treatment.

**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 hematoma, and a platelet count at  $3 \times 10^9/L$ , 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  $77 \times 10^9/L$ .

In November 2008, the platelet count decreased at  $36 \times 10^9/L$ , and intravenous immunoglobulins were recommended in addition to the corticosteroid treatment. Platelets temporarily reached a maximum count of  $130 \times 10^9/L$ .

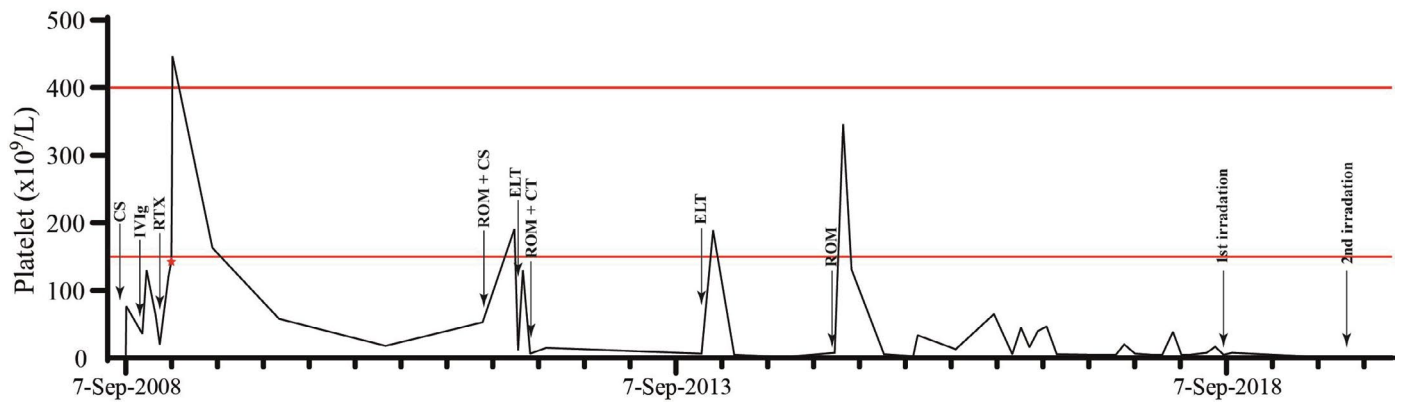
In December 2008, because the patient relapsed again, weekly rituximab infusions were started for four consecutive weeks, combined with corticosteroids, but failed to improve his condition with platelet count less than  $120 \times 10^9/L$ .

The 05/02/2009, five months after the diagnosis, a splenectomy was performed, secured by platelet transfusions. The platelet count increased to  $447 \times 10^9/L$ , and then gradually decreased.

In January 2011 and April 2012, the patient presented two severe thrombocytopenia episodes ( $<20 \times 10^9/L$ ). 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  $150 \times 10^9/L$  platelets.

In May 2015, while platelet count less than  $10 \times 10^9/L$ , additional treatment was done with intravenous immunoglobulin allowing for a transitional increase to  $346 \times 10^9/L$  for about two weeks (Figure 1).

After ten-year follow-up, the patient suffered from refractory thrombocytopenia at  $5 \times 10^9/L$ . In May 2018, an abdominal ultrasound showed a 24 mm nodule in the splenic area. CT scan revealed an accessory spleen attached to the pancreatic tail (Figure 2). After a multidisciplinary team meeting; a splenectomy was recommended but ultimately challenged due to a too low platelet count ( $1 \times 10^9/L$ ) despite platelet transfusions. Finally, localized radiation therapy at the dose of 10Gy 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 5mm 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  $1 \times 10^9/L$ . One month after radiotherapy, the platelet count had not increased, and a CT scan showed stability of the accessory spleen ( $13.3 \text{ cm}^3$  before versus  $12.6 \text{ cm}^3$  after irradiation). A Romiplostim subcutaneous infusion (Nplate®) was resumed.



CS : Corticosteroids ; IVIg : Intravenous immunoglobulins ; RTX : Rituximab ; ROM : Romiplostim ; ELT : Eltrombopag ; ★ : Splenectomy

Figure 1: Changes in the patient platelet count (red lines minimum and maximal normal counts).

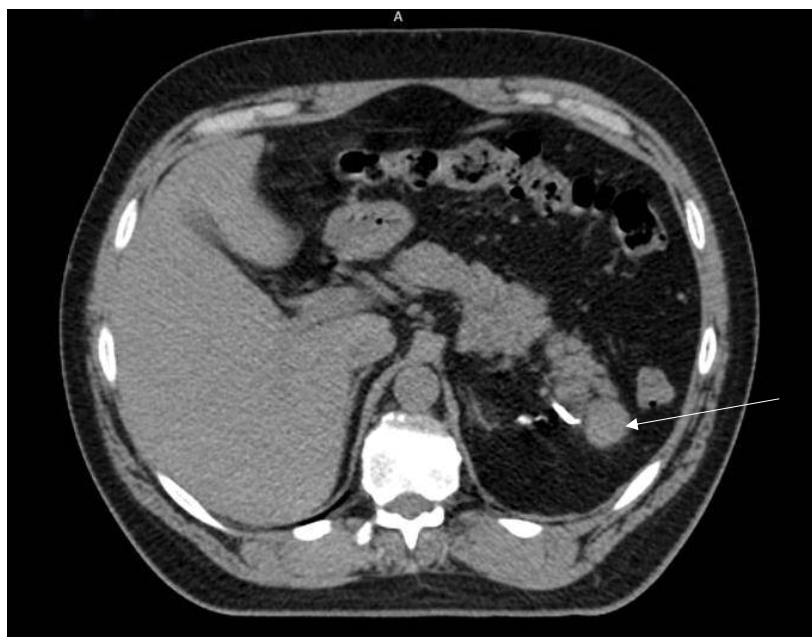


Figure 2. CT scan imaging of the accessory spleen attached to the pancreatic tail.

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 ( $2 \times 10^9/L$ ).

## 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- $\gamma$ , IL-2, and IL-17) and a decrease in anti-inflammatory cytokines (IL-10, TGF- $\beta$ , 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)  $\alpha IIb\beta 3$  (GPIIb/IIIa) and GPIb-IX-V. Macrophages bearing Fc $\gamma$ -receptors (Fc $\gamma$ R) 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].

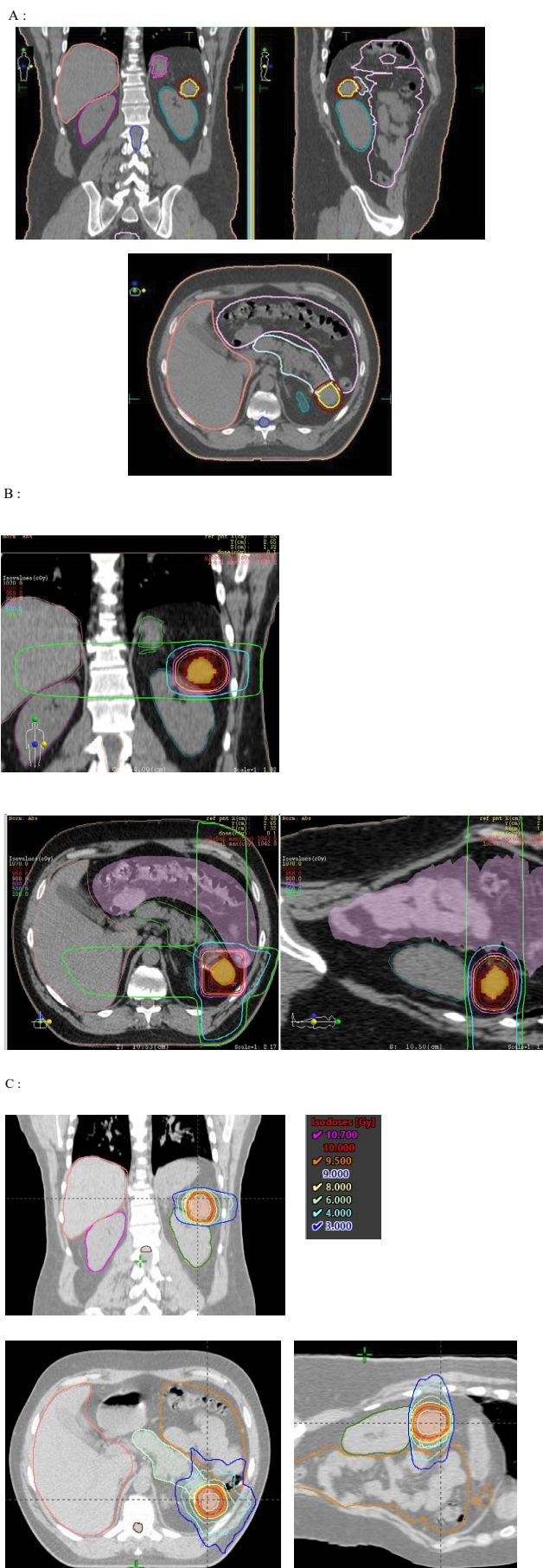
Features of ITP-spleen histology was not explicitly described in the literature. Two studies have shown that ITP spleens had significantly

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 low 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  $30 \times 10^9/L$  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, long-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.

**Cite this article:** Chambrelant I, et al. Idiopathic Thrombocytopenic Purpura and Radiotherapy: A Case Report and Review of the Literature. Oncol Cancer Case Rep, 2020, 06 (2), 001-006.



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-RAs (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 hyposplenism 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 remained heterogeneous [20-22]. Reasons to irradiate patients are also variable: some patients may not be suitable to undergo a splenectomy because of medical comorbidities, particularly elderly patients, or surgery refusal [14-21]. In our case, the platelet count was too low to perform further splenectomy. By combining the results of two retrospective series, 10/18 (55.6%) patients with primary ITP presented an excellent early response with a rise in the platelet count  $\geq 50 \times 10^9/L$  (Table 1) [20,21]. Responses lasted for more than six months for seven patients, and two patients responded late.

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 ( $>50 \times 10^9/L$ ) and 63.6% (7/11 patients). This discrepancy may be explained by the protection of the left kidney in the Caulier's study, leaving 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  $18 \times 10^9/L$  to  $110 \times 10^9/L$ , 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

Patient	Age/ Sexe	Variables			Platelet count ( $\times 10^9/L$ )									Second course of Radiation treatment
		Disease duration (Months)	Concurrent treatment	Total irradiation dose (Gy)	Before irradiation	End of irradiation	After end of irradiation							
							1 month	2 months	3 months	6 months	12 months	24 months		
1 Calverley	80/F	NA	NA	10	15	NA	NA	150	NA	75	NA	NA	NA	No
2 Calverley	74/M	NA	NA	13.7	5	NA	NA	65	NA	60	NA	NA	NA	No
3 Calverley	91/M	NA	NA	5	20	NA	NA	140	NA	NA	NA	NA	NA	No
4 Calverley	92/M	NA	NA	6	10	NA	NA	210	NA	235	NA	NA	NA	Yes
5 Calverley	65/F	NA	NA	6	10	NA	NA	45	NA	40	45	NA	NA	No
6 Calverley	82/F	NA	NA	8	25	NA	NA	15	NA	NA	NA	NA	NA	No
7 Calverley	80/F	NA	NA	5.94	20	NA	NA	260	NA	130	NA	NA	NA	No
8 Calverley	84/M	NA	NA	6	30	NA	NA	100	NA	65	NA	NA	NA	No
9 Calverley	83/M	NA	NA	6	10	NA	NA	35	NA	70	NA	NA	NA	Yes
10 Calverley	65/M	NA	NA	6.08	30	NA	NA	NA	NA	50	NA	NA	NA	Yes
11 Calverley	78/F	NA	NA	6	10	NA	NA	135	NA	195	NA	NA	NA	No
1 Caulier	86/M	60	Prednisolone	15	29	NA	60	NA	55	55	55	50	50	No
2 Caulier	81/F	7	No	15	7	155	95	NA	NA	46	NA	NA	NA	Yes
3 Caulier	81/F	38	No	15	18	19	21	NA	40	45	45	40	40	No
4 Caulier	63/F	17	No	15	38	35	39	NA	48	33	36	NA	NA	No
5 Caulier	62/F	78	No	15	20	31	16	NA	27	32	32	NA	NA	No
6 Caulier	65/F	28	No	15	47	143	150	NA	56	38	NA	NA	NA	Yes
7 Caulier	82/F	6	No	15	21	12	4	NA	NA	NA	NA	NA	NA	No
1 Callis	23/M	132	NA	15	18	110	NA	NA	NA	NA	NA	NA	NA	No
1 ICANS	45/M	120	No	10	1	1	1	2	1	1				Yes

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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 Caulier 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 Caulier 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 Caulier'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  $^{111}\text{In}$ -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.

## References

1. Arai Y., et al. "Comparison of treatments for persistent/chronic immune thrombocytopenia: A systematic review and network meta-analysis". *Platelets* 30.8 (2019): 946-956.
2. Li J., et al. "Pathophysiology of immune thrombocytopenia". *Curr Opin Hematol* 25.5 (2018): 373-381.
3. Bohn J.P. et al. "Current and evolving treatment strategies in adult immune thrombocytopenia". *Memo* 11.3 (2018):241-246.
4. Zufferey A., et al. "Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP)". *J Clin Med* 6.2 (2017):16.
5. Neunert C., et al. "The American society of hematology 2011 evidence-based practice guideline for immune thrombocytopenia". *Blood* 117.16 (2011):4190-4207.
6. Bylsma, L., et al. "Systematic literature review of treatments used for adult immune thrombocytopenia in the second-line setting". *Am J Hematol* 94.1 (2019):118-132.
7. Choi, Y., et al. "Laparoscopic accessory splenectomy for recurrent idiopathic thrombocytopenic purpura". *JSLs* 12.3 (2008):314-317.
8. Aster R.H., et al. "Sites of platelet destruction in idiopathic thrombocytopenic purpura". *Br J Haematol* 16.1 (1969):61-73.
9. Rossi G., et al. "Platelet kinetic study in patients with idiopathic thrombocytopenic purpura (ITP) refractory or relapsing after corticosteroid treatment". *Hematol J Off J Eur Haematol Assoc* 3.3 (2002):148-152.
10. Sarpatwari A., et al. "Autologous  $^{111}\text{In}$ -labelled platelet sequestration studies in patients with primary Immune Thrombocytopenia (ITP) prior to splenectomy: A report from the United Kingdom ITP Registry". *Br J Haematol* 151.5 (2010):477-487.
11. Furudōi A., et al. "Adult Primary immune thrombocytopenia: Spleen histology findings and outcomes according to rituximab use based on analysis of 41 cases". *Am J Surg Pathol* 42.3 (2018):401-412.
12. Audia S., et al. "Splenic TFH expansion participates in B-cell differentiation and antiplatelet antibody production during immune thrombocytopenia". *Blood* 124.18 (2014):2858-2866.
13. Cohen Y.C., et al. "The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts". *Arch Intern Med* 160.11 (2000):1630-1638.
14. Huber M.R., et al. "Treatment advances in adult immune thrombocytopenic purpura". *Ann Hematol* 82.12 (2003):723-737.
15. Yang R., et al. "Therapeutic options for adult patients with previously treated immune thrombocytopenia- A systematic review and network meta-analysis". *Hematol Amst Neth* 24.1 (2019):290-299.
16. Kuter D., et al. "Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: A double-blind randomised controlled trial". *Lancet* 371. 9610 (2008):395-403.
17. Saleh M., et al. "Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: Results of the long-term, open-label EXTEND study". *Blood* 121.3 (2013):537-545.
18. Togasaki E., et al. "Long-term efficacy of partial splenic embolization for the treatment of steroid-resistant chronic immune thrombocytopenia". *Ann Hematol* 97.4 (2018):655-662.
19. Junus K., et al. "Accessory spleen embolization: An option for refractory idiopathic thrombocytopenic purpura (ITP)". *Diagn Interv Imaging* 101.2 (2020): 117-118.
20. Calverley D.C., et al. "Splenic radiation for corticosteroid-resistant immune thrombocytopenia". *Ann Intern Med* 116.12 (1992):977-981.
21. Caulier M., et al. "Splenic irradiation for chronic autoimmune thrombocytopenic purpura in patients with contra-indications to splenectomy". *Br J Haematol* 91.1 (1995):208-211.
22. Callis M., et al. "Splenic irradiation as management of ITP". *Br J Haematol* 105.3 (1999):843-844.
23. Targarona E.M., et al. "Residual splenic function after laparoscopic splenectomy: A clinical concern". *Arch Surg* 133.1 (1998):56-60.
24. Vikse J., et al. "The prevalence and morphometry of an accessory spleen: A meta-analysis and systematic review of 22,487 patients". *Int J Surg* 45 (2017):18-28.

25. Leo C.A., et al. "Postsplenectomy recurrence of idiopathic thrombocytopenic purpura: Role of laparoscopic splenectomy in the treatment of accessory spleen". *Il G Chir* 36.4 (2015):153-157.
26. Szold A., et al. "Laparoscopic accessory splenectomy for recurrent idiopathic thrombocytopenic purpura and hemolytic anemia". *Surg Endosc* 14.8 (2000):761-763.
27. Morris K., et al. "Laparoscopic management of accessory spleens in immune thrombocytopenic purpura". *Surg Endosc* 13.5 (1999):520-522.
28. Velanovich V., et al. "Laparoscopic excision of accessory spleen". *Am J Surg* 180.1 (2000):62-64.
29. Al-Shammari A., et al. "Laparoscopic intrapancreatic accessory splenectomy: A case report of recurrent immune thrombocytopenia in a 33 years old male patient after 6 years of splenectomy". *Int J Surg Case Rep* 60 (2019):168-170.
30. Woo J., et al. "Postsplenectomy recurrence of thrombocytopenia with an accessory spleen". *Korean J Intern Med* 19.3 (2004):199-201.
31. Stanek A., et al. "Accessory spleens: Preoperative diagnostics limitations and operational strategy in laparoscopic approach to splenectomy in idiopathic thrombocytopenic purpura patients". *Langenbecks Arch Surg* 390.1 (2005):47-51.
32. Palandri F., et al. "The choice of second-line therapy in steroid-resistant immune thrombocytopenia: Role of platelet kinetics in a single-centre long-term study". *Am J Hematol* 89.11 (2014):1047-1050.