



## Case Report

# Splenectomy in Primary Immune Thrombocytopenia (ITP)

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### Abstract

Splenectomy represents an effective second-line therapy for the treatment of primary immune thrombocytopenia (ITP). The objective of surgery is to stop the bleedings by eliminating the organ responsible for the clearance of antibody-coated platelets. We evaluate the efficacy of laparoscopic splenectomy versus open splenectomy for primary immune thrombocytopenia in patients with severe refractory thrombocytopenia. We studied 56 patients with ITP hospitalized in the Clinic of Hematology from Craiova (Romania) between 2003-2012. All patients were diagnosed with ITP, other causes of thrombocytopenia having been ruled out. All patients were initially treated with corticosteroids ± immunoglobulins as first line therapy and vinca alkaloids and splenectomy as second-line therapy. Indications for splenectomy were bleedings and low platelet count ( $<30 \times 10^9/l$ ) after corticosteroids/immunoglobulin/vincristine. Eleven patients from 56 had indications for splenectomy: Three patients received open splenectomy and eight laparoscopic splenectomy. Seven patients obtained a very good response after splenectomy, three patients obtained a good response and one no response after splenectomy. After three years from splenectomy, two patients relapsed (one due to accessory spleen). In conclusion, in our small cohort of patients, laparoscopic splenectomy seemed preferable to open splenectomy, reducing the level of patients discomfort, the postsurgical complications and the hospitalization period.

**Keywords:** Primary immune thrombocytopenia; Laparoscopic splenectomy; Open splenectomy

### Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune mediated disorder characterized by isolated immune mediated thrombocytopenia (ITP) with a peripheral blood platelet count less than  $100 \times 10^9/l$  in the absence of any obvious initiating and/or underlying causes of thrombocytopenia [1-3]. In ITP pathogenesis two mechanisms of thrombocytopenia are involved: increased platelet destruction immune-mediated by autoantibodies and

impaired platelet production. In the pathogenesis of disease dendritic cells, B cells, T helper cells and regulatory T cells are involved [4-6]. The activity of B cells and T helper cells is under control of regulatory T cells. The B cells that escape the T cells regulatory surveillance produce auto-antibodies directed against specific glycoproteins of platelet specific surface (GP IIb/IIIa and/or GP Ib-IX) and also against antigens present on megakaryocytes. The effects of these events are: early platelet destruction and phagocytosis by macrophages from spleen and liver and decreased platelet production. Deficiency of regulatory T cells probably determines the persistence of immune reaction [7].

The new consensus of the therapeutic modalities of ITP recommended as first line therapy at newly diagnosed patients with ITP are corticosteroids (prednisone, prednisolone, methylprednisolone, dexamethasone) which increase platelet count and have a direct effect on blood vessels, or high dose IV immunoglobulins. Second line therapy is surgical (splenectomy) or medical, including immunosuppressive/immunomodulatory agents (azathioprine, cyclophosphamide, vinca alkaloids, cyclosporine, rituximab) or thrombopoietin receptor agonist (romiplostin and eltrombopag). Third line therapy includes the thrombopoietin receptor agonist as the only salvage therapy single or in combination with chemotherapy, alemtuzumab or stem cell transplantation [8-13].

### Patients and Method

We studied 56 patients with ITP (informed consent obtained) hospitalized in the Clinic of Hematology from Craiova (Romania) between 2003-2012. All patients were diagnosed with ITP according to the guidelines of European/American Society of Hematology and other causes of thrombocytopenia were ruled out. Pseudothrombocytopenia (caused by EDTA dependent platelet agglutinines), drug-induced thrombocytopenia (patients with recurrent episodes of thrombocytopenia after drugs administration), HIV, hepatitis C infections, systemic lupus erythematosus, lymphoproliferative disorders (immune-mediated thrombocytopenia, positive specific tests), thrombotic thrombocytopenia purpura (absence of microangiopathic anemia, fever, neurological and renal symptoms), congenital/hereditary thrombocytopenia (young patients who did not respond to treatment of ITP) were excluded.

At all patients, there were determined: patient/family history, physical examination, complete blood count and reticulocyte count, peripheral blood smear, bone marrow examination, quantitative immunoglobulin level; tests for H.pylori, HIV, HCV, antiphospholipoid antibodies, antithyroid antibodies/thyroid function, antinuclear antibodies, bleeding time, serum complement were made.

All patients were initially treated with corticosteroids (prednisone 1 mg/kg/day for several days to several months or high-dose dexamethasone 40 mg/day  $\times$  4 days), two of them with high-dose intravenous immunoglobulin (IVIg) 1g/kg, 2 infusions over 2 days; one received Danazol orally at a dose of 200 mg three times daily; one received Azathioprine 150 mg/day and three slow perfusions with Vincristine.

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The majority of patients responded to medical treatment, but 12 of them had refractory ITP. For the patients with bleedings (recurrent epistaxis, genitourinary hemorrhage, melena, gingival hemorrhage, ecchymoses) and low platelet count (< 30×10<sup>9</sup>/l) after corticosteroids/immunoglobulin/vincristine therapy indicated the need for splenectomy. One patient with ITP and diabetes mellites received eltrombopag 50 mg/day. Three patients received open splenectomy and eight laparoscopic splenectomy. At least 2-4 weeks before surgery the patients received prophylactic polyvalent vaccines and oral high dose dexamethasone (40 mg/day for 4 days). The response after splenectomy was measured by the platelet count as following: very good response: platelet count >150×10<sup>9</sup>/l, good response: platelet count between 150 - 50×10<sup>9</sup>/l; no response: platelet count < 50×10<sup>9</sup>/l. After discharge from surgical clinic, the patients were follow-up in the Clinic of Hematology.

### Results

Of the 56 patients with ITP hospitalized in the Clinic of Hematology from Craiova, 11 patients (19,64%) were splenectomized; mean age was 36 years, F/M ratio = 2,66 (Table 1). Five patients had associated diseases: diabetes mellites (two cases), ischemic heart disease (one case), arterial hypertension (two cases). All patients presented bleedings: recurrent epistaxis (four patients), genitourinary hemorrhage (two patients), melena (two patients), gingival hemorrhage (two patients), ecchymoses (one patient). The mean platelet count was 18 ×10<sup>9</sup>/l. All patients received corticosteroids (prednisone/high-dose dexamethasone); in addition, two patients received IVIg and three vincristine, with no response. The patients with platelet count < 20 ×10<sup>9</sup>/l received peripheral platelet transfusions. Three patients had undergone open splenectomy and eight laparoscopic splenectomy. Response after splenectomy was: very good in 7 cases (63,63%), good in 3 cases (27,27%) and no response in one case (9,10%). Two patients had postoperative complications: one - urinary tract infection (with open splenectomy) and one subphrenic abscess (with laparoscopic splenectomy). After a period of 2-4 years, two patients with splenectomy (18,18%) relapsed (one due to accessory spleen).

### Discussion

Splenectomy represents an effective second-line therapy for the treatment of ITP with a rate of 70-90% of hematologic response at patients with refractory ITP [14-16]. The response is sustained in 66% for the patients without additional therapy for at least five years, some

patients have a partial or transient response, 14% are non responders and approximately 20% of responders relapsed after weeks, months or years. Splenectomy stopped or prevented the bleedings by eliminating the organ responsible for the clearance of antibody-coated platelets.

In our study, we obtained a very good response in 7 cases, a good response in 3 cases and no response in one case.

The complications after splenectomy vary considerably and may be greater at patients over 65 years and are represented by uncontrolled infections (with a poor outcome from Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae), intraoperative bleedings, posthaemorrhage anemia, fluid/blood collections [13,17]. The laparoscopic splenectomy reduces the level of the patient's discomfort, the number of hospital days and decreases intra - and postsurgical complications [18-20]. Open splenectomy is associated with a higher rate of postsurgical complications and an increased duration of hospitalisation.

In our study, only two patients had postoperative complications, both with open splenectomy: one had urinary tract infection and one subphrenic abscess. The patients with laparoscopic splenectomy had no complications and no transfusions were needed; they had a shorter hospital stay (median three days, versus eight days at patients with open splenectomy) and very good remission rates. Seven patients obtained a very good response after splenectomy (two after open splenectomy and five after laparoscopic splenectomy), three patients obtained a good response after splenectomy (one after open splenectomy and two after laparoscopic splenectomy); one did not respond after laparoscopic splenectomy.

At three years after splenectomy, eight patients showed a complete response (six with laparoscopic splenectomy and one with open splenectomy), one had a partial response (after open splenectomy), two patients relapsed (one after laparoscopic splenectomy and one after open splenectomy) and one no response (after laparoscopic splenectomy). In one case with relapse, surgical reintervention was made and an accessory spleen was discovered; in another case the patient received thrombopoietin receptor agonist with a favourable evolution.

In conclusion, the splenectomy should be considered a second line therapy in patients with refractory ITP at medical treatment. In our small cohort of patients, laparoscopic splenectomy seemed to be preferable to open splenectomy because it decreased blood loss, the

Table 1: Characteristics of patients splenectomized for refractory ITP.

No	Age/sex [years]	Duration of disease [months]	First therapy	Plt count before splenectomy [×10 <sup>9</sup> /l ]	Bleedings	Type of splenectomy	Response after splenectomy	Complications	Response at 3 years
1.	26/F	8	P, Dex	28	RE	laparoscopic	very good	-	CR
2.	38/F	24	P, Dex	20	RE	laparoscopic	very good	-	CR
3.	21/F	5	P, Dex , Vin	8	GUH	laparoscopic	no response	-	no response
4.	45/M	27	P, Dex	26	M	open	good	UTI	PR
5.	31/F	14	P, Dex , Vin	8	RE	laparoscopic	very good	-	CR
6.	35/M	27	P,Dex, Ig	15	RE	laparoscopic	very good	-	CR
7.	61/F	9	P, Dex	20	GH	open	very good	SA	CR
8.	48/M	4	Dex, P	5	M	open	good	-	relapse
9.	23/F	6	P, Dex	10	GUH	laparoscopic	very good	-	CR
10.	29/F	11	P, Dex, Vin	30	Ech	laparoscopic	very good	-	CR
11.	39/F	23	Dex, P, Ig	28	GH	laparoscopic	good	-	relapse

P:prednisone, Dex : Dexamethasone, Vin: vincristine; RE: Recurrent Epistaxis, GUH: Genito-Urinary Hemorrhage, M: Melena, GH: Gingival Hemorrhage, Ech: Ecchymoses; UTI: Urinary Tract Infection, SA: aubphrenic abscess; CR: Complete Response, PR: Partial Response.

level of patients' discomfort, the postoperative complications and the hospitalization period.

#### References

1. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, et al. (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 113: 2386-2393.
2. Ruggeri M, Fortuna S, Rodeghiero F (2008) Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. *Haematologica* 93: 98-103.
3. British Committee for Standards in Haematology General Haematology Task Force (2003) Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 120: 574-596.
4. Chong BH (2010) ITP: Tregs come to the rescue. *Blood* 116: 4388-4390.
5. Bao W, Bussel JB, Heck S, He W, Karpoff M, et al. (2010) Improved regulatory T-cell activity in patients with chronic immune thrombocytopenia treated with thrombopoietic agents. *Blood* 116: 4639-4645.
6. McMillan R (2000) The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. *Semin Hematol* 37: 5-9.
7. Ling Y, Cao X, Yu Z, Ruan C (2007) Circulating dendritic cells subsets and CD4+Foxp3+ regulatory T cells in adult patients with chronic ITP before and after treatment with high-dose dexamethasone. *Eur J Haematol* 79: 310-316.
8. Stasi R, Brunetti M, Pagano A, Stipa E, Masi M, et al. (2000) Pulsed intravenous high-dose dexamethasone in adults with chronic idiopathic thrombocytopenic purpura. *Blood Cells Mol Dis* 26: 582-586.
9. Mazzucconi MG, Fazi P, Bernasconi S, De Rossi G, Leone G, et al. (2007) Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. *Blood* 109: 1401-1407.
10. Spahr JE, Rodgers GM (2008) Treatment of immune-mediated thrombocytopenia purpura with concurrent intravenous immunoglobulin and platelet transfusion: a retrospective review of 40 patients. *Am J Hematol* 83: 122-125.
11. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, et al. (2008) Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 371: 395-403.
12. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, et al. (2011) Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 377: 393-402.
13. Kojouri K, Vesely SK, Terrell DR, George JN (2004) Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood* 104: 2623-2634.
14. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, et al. (1996) Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 88: 3-40.
15. Wani NA, Parray FQ (2000) Therapeutic splenectomy in immune thrombocytopenic purpura. *World J Surg* 24: 92-94.
16. Kumar S, Diehn FE, Gertz MA, Tefferi A (2002) Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol* 81: 312-319.
17. Schattner E, Bussel J (1994) Mortality in immune thrombocytopenic purpura: report of seven cases and consideration of prognostic indicators. *Am J Hematol* 46: 120-126.
18. Lozano-Salazar RR, Herrera MF, Vargas-Vorácková F, López-Karpovitch X (1998) Laparoscopic versus open splenectomy for immune thrombocytopenic purpura. *Am J Surg* 176: 366-369.
19. Szold A, Schwartz J, Abu-Abeid S, Bulvik S, Eldor A (2000) Laparoscopic splenectomies for idiopathic thrombocytopenic purpura: experience of sixty cases. *Am J Hematol* 63: 7-10.
20. Bresler L, Guerci A, Brunaud L, Ayav A, Sebbag H, et al. (2002) Laparoscopic splenectomy for idiopathic thrombocytopenic purpura: outcome and long-term results. *World J Surg* 26: 111-114.