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ORIGINAL ARTICLE

Does the site of platelet sequestration predict the response to splenectomy in adult patients with immune thrombocytopenic purpura?

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Abstract

Splenectomy is the only potentially curative treatment for chronic immune thrombocytopenic purpura (ITP) in adults. However, one-third of the patients relapse without predictive factors identified. We evaluate the predictive value of the site of platelet sequestration on the response to splenectomy in patients with ITP. Eighty-two consecutive patients with ITP treated by splenectomy between 1992 and 2013 were retrospectively reviewed. Platelet sequestration site was studied by ^{111}Indium-oxinate-labeled platelets in 93% of patients. Response to splenectomy was defined at last follow-up as: complete response (CR) for platelet count (PC) $\geq 100 \times 10^9$/L, response (R) for PC$\geq 30 \times 10^9$/L and $<100 \times 10^9$/L with absence of bleeding, no response (NR) for PC$<30 \times 10^3$/L or significant bleeding. Laparoscopic splenectomy was performed in 81 patients (conversion rate of 16%), and open approach in one patient. Median follow-up was 57 months (range, 1–235). Platelet sequestration study was performed in 93% of patients: 50 patients (61%) exhibited splenic sequestration, 9 (11%) hepatic sequestration and 14 patients (17%) mixed sequestration. CR was obtained in 72% of patients, R in 25% and NR in 4% (two with splenic sequestration, one with hepatic sequestration). Preoperative PC, age at diagnosis, hepatic sequestration and male gender were significant for predicting CR in univariate analysis, but only age (HR = 1.025 by one-year increase, 95% CI [1.004–1.047], $p = 0.020$) and pre-operative PC (HR = 0.112 for > 100 versus <=100, 95% CI [0.025–0.493], $p = 0.004$) were significant predictors of recurrence-free survival in multivariate analysis. Response to splenectomy was independent of the site of platelet sequestration in patients with ITP. Pre-operative platelet sequestration study in these patients cannot be recommended.

Keywords

Immune thrombocytopenic purpura, platelet sequestration study, predictive factors, splenectomy

History

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Introduction

Immune thrombocytopenic purpura (ITP) is an immune-mediated acquired disease characterized by a decrease of the platelet count (PC) (transient or persistent), in which auto-antibodies cause platelet destruction and suboptimal platelet production. The incidence of ITP in adults is estimated at approximately 1.6–3.9 per 10^5 person/year [1–3].

Corticosteroids (CS) and intravenous immunoglobulins (IVIg) are the standard first-line therapies and yield a rapid increase of PC in patients with severe thrombocytopenia. But they do not often provide a durable response, they have long-term side effects, and are costly [4, 5]. Sixty-five to 70% of patients obtain a good platelet response, but only 15% have a durable remission after treatment. Thombopoietin (TPO) mimetics are a new therapeutic option increasing the rate of platelet production, with an efficacy as high as 88% of overall response rate in splenectomized and non-splenectomized patient, but must be administered as a long-term treatment for most patients [6]. No predictive factor of any response to medical treatments could be identified yet. Despite the availability of alternate medical therapies, such as rituximab, azathioprine, cyclosporine, mycophenolate or vinca alkaloids, splenectomy remains the treatment associated with the higher curative potential in patients with chronic disease [7].

More than 80% of patients have an excellent response rate to surgery, with a long-term stable response in approximately 60% [8, 9]. Identification of predictive factor of no response to splenectomy might be useful to avoid unnecessary surgical intervention with a significant morbidity rate. For many patients, spleen is the primary site of platelet sequestration (SPS), but sometimes hepatic destruction may be present or predominant. It was previously suggested that patients with splenic sequestration had better outcome after splenectomy than those with mixed or hepatic sequestration [10, 11]. However, in the last 10 years, divergent reports were published and no conclusion has been drawn about the potential prognostic value of the SPS in ITP [5, 12, 13].

Therefore, the purpose of this retrospective study was to evaluate the efficacy of splenectomy in patients with ITP and a mixed or hepatic platelet sequestration, and additionally to identify factors which could predict response to splenectomy.

Methods

Between October 1992 and July 2013, all adult patients with ITP surgically treated at our institution were retrospectively reviewed. Diagnosis of ITP was based on the exclusion of other causes of

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thrombocytopenia. According to the American Society of Hematology guidelines, splenectomy was recommended for patients unresponsive to medical treatment (CS or IVIg) with persistent low PC and high bleeding risk, patients intolerant to medical treatment, or patients with frequent relapses of the disease [14].

Diagnosis and pre-operative evaluation of ITP were made by plasmatic platelet count, bone marrow biopsy, abdominal computed tomography (CT) to identify accessory spleens, and/or ^{111}Indium-oxinate-labeled platelet sequestration study. Operative risk and comorbidities were evaluated according to the American Society of Anaesthesiology (ASA) physical score [15].

All patients underwent successful splenectomy, either laparoscopic or open using standard technique. Surgical complications were graded according to the Clavien-Dindo classification: grade I includes minor complications that can be treated with routine medications; grade II includes conditions that require major pharmacological intervention; grade III includes any complication requiring a surgical, endoscopic or radiological intervention; grade IV includes patients with life-threatening complications requiring intensive care; and grade V includes death in the post-operative period [16].

During follow-up platelet counts were measured at each visit with the surgeon or the hematologist (at 1 week, 1 month, and 3, 6 and 12 months, and even more). Abdominal CT and ^{69m}Technetium heat-damaged red blood cell scintigraphy were performed routinely in patients with recurrent thrombocytopenia to exclude residual accessory spleen.

Response to splenectomy (and if necessary accessory splenectomy) was defined according to the recommendations of the International Working Group [17]. A complete response (CR) corresponding to a PC $\geq 100 \times 10^9$/L and absence of bleeding, response (R) consisted of a PC $\geq 30 \times 10^9$/L and $< 100 \times 10^9$/L, doubling from baseline with absence of bleeding, and no response (NR) defined as refractory ITP with a PC $< 30 \times 10^3$/L or less than doubling from baseline or presence of bleeding required further treatments. Response was assessed at last follow-up, and presence of residual accessory spleen(s) was excluded before qualifying it.

All statistical analyses were carried out using SAS v.9.3 (SAS Institute Inc., Cary, North Carolina). Categorical data were compared using chi-squared test. Continuous variables were compared using either Kruskall–Wallis or Mann–Whitney tests as appropriate. The Cox proportional hazards regression model was applied in order to identify independent prognostic factors associated with recurrence-free survival following surgery. The variables associated with a p value < 0.20 at univariate analysis were entered into a multivariate analysis performed using backward Cox' regression. The significance level was set at 0.05.

Results

The study cohort consisted of 82 patients (56 females, 26 males). Mean age at surgery was 45.5 years (range, 15–86 years). Twenty patients (24%) had an ASA score of III–IV. Median pre-operative platelet count was measured at 93×10^3/μL (range, 4–323) (Table I). Indication for surgery was non-response to medical treatment for 48% of patients, frequent relapses of the disease in 41%, and intolerance to first-line treatment in 11%. The day before surgery, 13 patients had a platelet transfusion (16%), nine were infused by IVIg (11%), and 15 received both treatments (18%).

Laparoscopic splenectomy was performed in 81 patients, with a conversion rate of 16%; open surgery was performed in one patient. Mean operative time of 126 minutes (range, 60–270). Thirteen of the 15 accessory spleens detected at CT scan were confirmed at laparoscopic exploration, and three were discovered intraoperatively; all visualized spleens were removed.

Table I. Patients' characteristics.

	N (% included patients)
Demographics	
Patients, *n*	82
Gender, *female/male*, *n*	56/26 (68/32%)
Mean age at surgery, *y* (range)	45.5 (15–86)
Operative risk, *n*	
- ASA score I & II	62 (76%)
- ASA score III & IV	20 (24%)
Median disease duration, mo (range)	9.5 (1–588)
Pre-operative parameters	
First-line treatment, *n*	
- Immunoglobulins	55 (67%)
- Corticosteroids	78 (95%)
Median preoperative (*d* - 1) PC, $\times 10^3$/μL (range)	93 (4–323)
Intra-operative parameters	
Accessory spleen, *n*	
- Detected at CT scan	15 (18%)
o Confirmed at surgery	o 13 (16%)
- Detected only at laparoscopy	3 (4%)
Post-operative parameters	
Median PC at day 2, $\times 10^3$/μL (range)	201 (4–766)
Median hospital stay, *d* (range)	4 (2–20)
Complications, *n* (%)	10 (12%)
- Dindo-Clavien of II	– 6 (7%)
- Dindo-Clavien of III, IV	– 4 (5%)
Median follow-up, mo (range)	57 (1–235)

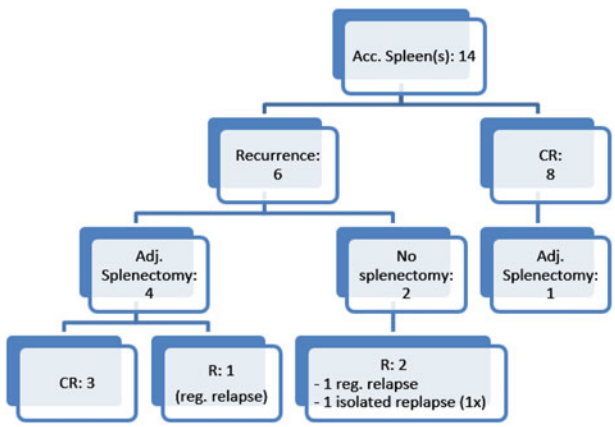

Figure 1. Outcomes of patients with accessory spleen(s). Acc. Spleen(s): accessory spleen(s); Adj. Splenectomy: adjuvant splenectomy; reg. relapse: regular relapse.

Median post-operative platelet count at day 2 was at 201×10^3/μL (range, 4–766), and was less than or equal to 100×10^3/μL in 15% of patients. Complications were observed in 10 patients (12%) (Table I). Minor complications like urinary infection, pancreatic fistula, pneumonia, pulmonary embolism and cellulitis were observed in six patients (Dindo-Clavien of II). Four patients presented major complications including myocardial infarction, medullar hematoma or hemorrhage (Dindo-Clavien of III, IV). Mortality rate was 1% ($n = 1$, myocardial infarction).

Median follow-up was 57 months (range, 1–235). Fourteen patients had a residual accessory spleen detected at post-operative assessment; six of them relapsed after an initial response to the first surgery (Figure 1). Four of the patients relapsing had adjuvant splenectomy: three had CR, and one frequently recurred from thrombocytopenia treated once in 13 years by IVIg. One patient relapsing refused another surgery and frequently recurred as bruises, treated by TPO mimetics twice in 3 years of follow-up.

Table II. Response to splenectomy according to the site of platelet sequestration.

Site of platelet sequestration	*N*	Splenic	Hepatic	Mixed	Normal or unknown	*p* Value
	82	50	9	14†	9	
Complete response	58	39 (78%)	4 (44%)	8 (57%)	7	
Response	20	9 (18%)	4 (44%)	5 (36%)	2	
No response	3	2 (4%)	1 (11%)	0	0	0.616

†One patient could not be classified due to perioperative death.

Table III. Univariate and multivariate analysis of predictive factors of complete response to splenectomy in patients with idiopathic thrombocytopenic purpura.

	Univariate analysis		Multivariate analysis	
Factors	HR	*p* Value	HR	*p* Value
Sex (male)	0.379	**0.0186**	–	–
Age at diagnosis (yrs)	1.040	**0.0003**	1.025	**0.0196**
Age >70 yrs	4.195	**0.0008**	–	–
Age >45 yrs	3.653	**0.0044**	–	–
ASA score >II	2.247	0.0653	–	–
Disease duration >12 months	1.375	0.4373	–	–
Corticotherapy pre-operatively	0.603	0.4947	–	–
IVIg pre-operatively	1.114	0.8107	–	–
Preoperative PC (10^3/μL)	0.985	**0.0002**	–	–
Preoperative PC >100	0.079	**0.0006**	0.112	**0.0038**
Hepatic SPS†	3.707	**0.0166**	–	–
Mixed SPS†	2.412	0.0855	–	–

Bold Values = significant predictors of recurrence-free survival
†Splenic sequestration was considered as the reference level

And the last one relapsed once in 5 years, 2 months after initial splenectomy and did not have accessory splenectomy.

SPS study was investigated in 93% of included patients, showing that 50 (61%) exhibited splenic or predominantly splenic sequestration, nine (11%) had hepatic or predominantly hepatic sequestration, and 14 (17%) had mixed sequestration (Table II). Comparing site of sequestration, CR was obtained in 78, 44 and 57% of patients with splenic, hepatic and mixed patterns, respectively ($p = 0.616$). Overall, CR was obtained in 72% of patients, R in 25% and NR in 4% (two with splenic sequestration, one with hepatic sequestration).

Pre-operative PC (either as continuous or according to a cut-off set at 100), age at diagnosis (either as continuous or as >45 or >70 years old), hepatic sequestration (taking as reference for the splenic pattern) and male gender were significant predictors of recurrence-free survival (RFS) in univariate analysis, but only age (HR = 1.025 by one-year increase, 95% CI [1.004–1.047], $p = 0.020$) and pre-operative PC (HR = 0.112 for >100 versus ≤100, 95% CI [0.025–0.493], $p = 0.004$) were significant predictors of RFS in multivariate analysis (Table III).

Discussion

Spleen is the main site of anti-platelet antibody production and platelet destruction in ITP. Splenectomy is therefore considered as an effective therapy in the management of the disease, with a CR obtained in 60 to 70% of adults at more than 5 years [18]. Our clinical experience of splenectomy for hematologic disease was previously reported [19–22].

Many studies have attempted to investigate predictive factors for success of surgical treatment, but results are equivocal. Patient age, previous response to steroids, disease duration before surgery, pre-operative PC and SPS are the most common factors with statistical significance [9, 23–25]. In the present study, pre-operative PC, pre-operative PC $>100 \times 10^3$/μL, patients' age, patients' age over >45 years old and over >70 years, hepatic sequestration and male gender were significant for predictive factors of RFS in univariate analysis, but only age and preoperative PC were significant predictors of RFS in multivariate analysis. So younger age, as well as a high platelet PC, were found to be associated with a more favorable prognosis (in terms of response to splenectomy), independently of the platelet sequestration.

^{111}Indium-labeled autologous platelet scanning to determine the SPS appears to be the most sensitive assessment in the literature to predict response to splenectomy, studies vary greatly by the technique used and the selected patients. When platelet destruction site is predominantly mixed or hepatic, efficacy of splenectomy remains controversial. In a systematic review of outcomes after splenectomy for ITP, Kojouri et al. concluded that there was no evidence for SPS as a predictive factor of good response to splenectomy with 0–75% of CR for patients with hepatic platelet sequestration [9–11, 26, 27]. However, it is noteworthy that the series of 15 heterogeneous studies using different clinical characteristics and techniques of platelet kinetic study cannot be considered as equivalent. Interestingly, Fenaux et al. [28] analyzed multiple variables in a multivariate model observing that splenic sequestration was not associated with response to splenectomy if age was included in the model. Moreover, Sarpatwari et al. [13] also concluded that platelet sequestration studies should be performed as an adjunct predictive tool prior to splenectomy for primary ITP with significantly better outcome in patients with splenic sequestration compared to hepatic or mixed sequestration.

Accessory spleen undetected during surgical exploration is the first cause to exclude after recurrence of thrombocytopenia following splenectomy. Post-operative red blood cell scintigraphy must be performed in case of recurrence of ITP, and repeated surgery should be considered for patients with accessory spleens. However, results about CR rates after excision of accessory spleens are variable (30–66% of patients) [29, 30]. The present study documents an accessory spleen in six patients with relapse. Three had CR remission after the second splenectomy, one frequently recurred despite excision of accessory spleen, and two did not have accessory splenectomy. Accordingly, Provan et al. [4] noted that in patients who never responded to initial splenectomy, response is extremely rare.

After failure of corticosteroids and splenectomy, other therapies can be used but their efficacy is widely variable. TPO mimetics offer a response rate ranging from 80 to 90% but durable response is observed only in 40–60% of patients. On the other hand, rituximab is effective in 40–60% refractory patients, but has a lower long-term response rate (20%) [31, 32]. Fewer than 30% of patients with refractory ITP remain unresponsive to all therapies. These patients had a significantly higher morbidity and mortality rates due to the disease and its treatment-related complications [33]. Unfortunately, no predictive factor of no response to medical treatments have been identified yet.

For patients with refractory ITP after splenectomy failure and resistant to all medical therapies, autoimmune disease or lymphoid malignancy should be excluded [34]. For these patients, treatment failure could thus be attributed to the associated disease rather than ITP itself. Regarding our three patients with ITP resistant to all therapies, one had autoimmune disease and another had pure red cell aplasia. Auto-immune disease and/or hematologic disease (genetic or malignant disease) was found at the initial presentation in 7/20 patients with R versus 5/58 with CR. These finding leads one to consider a common mechanism between those between those diseases and ITP.

The main limitations of this study were the retrospective nature of research and the absence of heterogeneity for the SPS due to unequal distribution but reflecting the reality**:** the number of patients with hepatic sequestration is limited compared with a larger group of patients with splenic sequestration. There was a selection bias due to the fact that some patients meeting the indications for splenectomy refused surgery.

Conclusion

Site of platelet sequestration was not significantly associated with recurrence-free survival in the present study. Younger patients with platelet count $>100 \times 10^3/\mu L$ should have a better response to splenectomy. The high incidence of associated auto-immune and hematologic disease especially in patients with treatment failure needs further investigation.

Declaration of interest

The authors report no declarations of interest.

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