

RESEARCH ARTICLE

Clinical course and short-term outcome of postsplenectomy reactive thrombocytosis in children without myeloproliferative disorders: A single institutional experience from a developing country

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Abstract

Objectives

To evaluate the clinical outcome and complications in the pediatric population who had splenectomy at our institution, emphasizing the incidence of postsplenectomy reactive thrombocytosis (RT) and its clinical significance in children without underlying hematological malignancies.

Materials and methods

The medical records of pediatric patients undergoing splenectomy were retrospectively reviewed for the period 1999–2018. The following variables were analyzed: Demographic parameters (age, sex), indications for surgery, operative procedures, preoperative and postoperative platelet count (postsplenectomy RT), the use of anticoagulant therapy, and postoperative complications. The patients were divided into two groups according to indications for splenectomy: The non-neoplastic hematology group and the non-hematology group (splenectomy for trauma or other spleen non-hematological pathology).

Results

Fifty-two pediatric (37 male and 15 female) patients who underwent splenectomy at our institution were reviewed. Thirty-four patients (65%) were in the non-hematological group (splenic rupture, cysts, and abscess) and 18 patients (35%) in the non-neoplastic hematology group (hereditary spherocytosis and immune thrombocytopenia). The two groups did not differ significantly in regards to the patients' age, sex, and preoperative platelet count ($P > 0.05$ for all variables). Forty-nine patients (94.2%) developed postsplenectomy RT. The percentages of mild, moderate and extreme thrombocytosis were 48.9%, 30.7%, and 20.4%, respectively. The comparisons of RT patients between the non-neoplastic

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Abbreviations: AML, Acute myelogenous leukemia; CML, Chronic myeloid leukemia; HS, Hereditary spherocytosis; IL, Interleukin(s); INR, International normalized ratio; ITP, Immune thrombocytopenia; PSVT, Portal splenic vein thrombosis; RT, Reactive thrombocytosis; SW test, Shapiro-Wilk test.

hematology and the non-hematology group revealed no significant differences in regards to the patients' age, sex, preoperative and postoperative platelet counts, preoperative and postoperative leukocyte counts, and the average length of hospital stay ($P>0.05$ for all variables). None of the patients from the cohort was affected by any thrombotic or hemorrhagic complications.

Conclusions

We confirm that RT is a very common event following splenectomy, but in this study it was not associated with clinically evident thrombotic or hemorrhagic complications in children undergoing splenectomy for trauma, structural lesions or non-neoplastic hematological disorders.

Introduction

Reactive thrombocytosis (RT) refers to thrombocytosis in the absence of a chronic myeloproliferative disease or myelodysplastic disorder. RT is associated with various medical conditions including infections, inflammation, hemorrhage, trauma, or surgery [1]. RT can be either transient or sustained and is driven by increased production of thrombopoietin, catecholamines, and various interleukins (e.g. IL-6 and IL-11) [2].

Postsplenectomy RT is a very common event affecting 75–90% patients undergoing the splenectomy [3, 4]. The platelet counts after splenectomy usually increase 30–100%, with the highest values in the period between 10 to 20 days postoperatively [5]. Thrombocytosis may persist over the next 2–3 months in most cases but in a few patients, thrombocytosis persists indefinitely [6].

Although it is well established that the size and function of platelets in RT are normal and that their interactions with blood vessels remain qualitatively normal [1], RT has been occasionally associated with an increased risk of thrombotic and hemorrhagic events in patients undergoing splenectomy [7, 8]. The thrombogenic potential of RT following splenectomy in children without underlying hematological malignancies (myeloproliferative disorders or myelodysplastic syndromes) are still not clearly defined.

To clarify the incidence and short-term clinical course and possible complications related to RT following splenectomy in the absence of hematological malignancies, we provide a single institution experience with RT in the pediatric population undergoing elective or emergency splenectomy.

Patients and methods

Patients and selection criteria

The data of all patients who underwent total splenectomy (urgent or elective) at our pediatric surgical department between January 1999 and December 2018 were retrospectively reviewed. The following data were analyzed: Demographic parameters (age, sex), indications for surgery, operative procedures, preoperative and postoperative platelet count, the use of anticoagulant therapy, and postoperative complications. The patients were followed over the first three weeks postoperatively. According to indications for splenectomy and RT, the patients were divided into the non-neoplastic hematology group and the non-hematology group.

The inclusion criteria for both groups were (1) Patients aged < 16 years; (2) Patients undergoing total splenectomy; (3) Development of postsplenectomy thrombocytosis with platelet count > 500,000/ μ L; (4) Patients without neoplastic (myeloproliferative and myelodysplastic) hematological disorders.

All the clinical records were fully anonymized prior to the study. The Ethics Committee (Institutional Review Board) of University Clinical Center Sarajevo approved the study and waived informed consent request from the patients and their families (the number of approval: #10-01-2-123/19).

Definitions and classifications

Total splenectomy was defined as a complete surgical removal of the spleen. Myeloproliferative disorders were defined as any of several hematologic malignancies marked by the excess of one or more types of white blood cells [9]. These disorders include polycythemia vera, essential thrombocytosis, chronic myeloid leukemia (CML), and idiopathic myelofibrosis [9]. Myelodysplastic syndromes were defined as any of a broad group of bone marrow disorders that are characterized by an abnormal reduction in one or more lineages of circulating white blood cells due to defective growth and maturation of blood-forming cells in the bone marrow with a potential to progress to acute myelogenous leukemia (AML).

Thrombocytosis was defined as a platelet count >500,000/ μ L. Mild thrombocytosis was defined as a platelet count >450,000/ μ L and <600,000/ μ L, moderate thrombocytosis a platelet count >600,000/ μ L and <1,000,000/ μ L, and extreme thrombocytosis as a platelet count >1,000,000/ μ L. The platelets were consecutively measured first ten postoperative days after which three additional measurements (11th, 14th and 21st postoperative day) were done.

In an attempt to determine whether an association exists between RT and thrombotic or hemorrhagic complications, one month after hospital discharge all the patients were contacted for further investigations.

All platelet counts were performed on ABBOTT CELL DYN 3700 (Chicago, Illinois, USA) counter, using EDTA anticoagulated fresh blood. The normal range of platelet counts for this machine is 150,000 to 450,000/ μ L.

Statistical analysis

To evaluate the normality of the distribution of continuous variables, we used the Shapiro-Wilk (SW) test. The student's t-test was used to compare independent continuous variables that followed the normal distribution. The Wilcoxon signed-rank test was used to test the differences of paired data without the normal distribution. *P*-values < 0.05 were considered significant. All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) IBM Version 26 (SPSS) (UNICOM Systems, Inc.).

Results

The characteristics of the cohort are summarized in [Table 1](#).

Fifty-two children with a mean age of 9.2 years (range, 0.6–14.5 years) had splenectomy at our institution in the period 1999–2018. All patients were treated with an open splenectomy approach and all received prophylactic antibiotics and pneumococcal vaccine. Among the splenectomy children, 37 (71%) were male and 15 (29%) female patients (male/female ratio of 2.5:1). Severe spleen trauma (rupture) was the most common indication for splenectomy (29 patients, 55.8%), followed by non-neoplastic hematological disorders (18 patients, 34.6%). Three patients (5.8%) had splenectomy for splenic hydatid cysts, and two (3.8%) had splenectomy for multiple splenic abscesses. Among the patients with non-neoplastic hematological

Table 1. The patients' demographics, their perioperative characteristics, and indications for splenectomy.

Variable	Overall	Indications for splenectomy		P-value
		Non-neoplastic hematology group	Non-hematology group	
The number of patients no. (%)	52 (100%)	18 (34.6%)	34 (65.4%)	-
Mean age at surgery (yr)	9.0±1.84	9.2±1.22	8.6±2.08	0.12
Sex (% male)	37 (71%)	30 (81%)	7 (19%)	0.09
Preoperative platelet count	324 K/ μ L	332.5 K/ μ L	317.5 K/ μ L	0.98
Short-term adverse events (\leq 3 weeks) (wound infection, wound hematoma and splenic fossa collection)	4 (7.7%)	1 (5.6%)	3 (8.8%)	-

K/ μ L, kilo per microliter.

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disorders, splenectomy was indicated for hereditary spherocytosis (HS) (n = 16) and immune thrombocytopenia (ITP) (n = 2). Four patients (7.7%) developed postoperative non-thrombotic complications including wound infection, wound hematoma and splenic fossa collection (Table 1). None of the patients developed thrombotic or hemorrhagic complications during the follow-up period. Neither postoperative death nor subsequent fatal infections were observed in the cohort. Forty-nine patients (94.2%) developed a postsplenectomy RT. The percentages of mild, moderate and extreme thrombocytosis were 48.9%, 30.7%, and 20.4%, respectively. The comparisons between RT patients in non-neoplastic hematology and non-hematology groups is shown in Table 2. In the non-neoplastic hematology group of patients, a gradual increase in platelet count was observed from the first to sixth day after splenectomy. After this period, the platelet count was gradually decreasing (Table 3). In the non-hematology group of patients, the platelet count decreased in the first two days after splenectomy, probably because of hemodilution but gradually increases starting at day three. From the sixth to the eleventh day, RT has been reported in this group of patients, followed by a gradual decrease in the platelet count, but RT persisted three weeks following splenectomy (Table 3). Although the recorded platelet counts were greater and lasted longer in the non-hematological group compared with the non-neoplastic hematological group, the difference was not significant

Table 2. The comparative analysis of various clinical parameters between the two groups of the patients affected by reactive thrombocytosis.

Variable	Overall	Postsplenectomy reactive thrombocytosis		P-value
		Non-neoplastic hematology group	Non-hematology group	
The number of patients no. (%)	49 (100%)	16 (32%)	33 (68%)	-
Mean age at surgery (yr)	9.0±1.9	9.3±1.3	8.6±2.11	0.85
Sex (% male)	35 (71%)	29 (82%)	6 (18%)	0.08
Preoperative leukocyte count	12.54x10 ⁹ /L	9.43 x 10 ⁹ /L	13.42 x 10 ⁹ /L	0.13
Preoperative platelet count	329	333	325	0.91
Postoperative leukocyte count (K/ μ L)*	12.21x10 ⁹ /L	11.4 x 10 ⁹ /L	12.48 x 10 ⁹ /L	0.52
Postoperative platelet count (K/ μ L)*	716	586	846	0.47
Mild thrombocytosis no. (%)	24 (48.9%)	10 (42%)	14 (58%)	-
Moderate thrombocytosis no. (%)	15 (30.7%)	4 (26%)	11 (74%)	-
Extreme thrombocytosis no. (%)	10 (20.4%)	2 (20%)	8 (80%)	-
Length of stay (day)	9.7	10.6	10.4	0.89

K/ μ L, kilo per microliter.

*The presented numbers are mean values that were recorded for these variables in the first 21 postoperative days.

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Table 3. The comparison of platelet counts between the non-neoplastic hematology vs. non-hematology group.

Variable	Postsplenectomy days													
	0	1	2	3	4	5	6	7	8	9	10	11	14	21
Platelet count in the non-neoplastic hematology group (K/ μ L)	294	347	384	448	479	609	675	502	505	511	497	485	460	420
Platelet count in the non-hematology group (K/ μ L)	343	314	322	378	376	497	619	749	951	974	985	992	760	665

K/ μ L, kilo per microliter.

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($p = 0.21$). Given that the international normalized ratio (INR) values were normal in all patients with extreme RT, the majority of the patients with extreme RT (80%) did not receive any antiplatelet or anticoagulant therapy. Only two patients received the treatment; one child received a low-dose aspirin (5 mg/kg) until their platelet counts fell to the reference values while the older pubertal child received a subcutaneous enoxaparin treatment.

Discussion

It is well known that the incidence of thrombocytosis shows an age-dependent pattern with the highest reported occurrence in infants aged up to 24 months [10, 11]. Specifically, during childhood, platelet counts greater than 500,000/ μ L may be seen in 13% of neonates at birth, 36% during the first month, particularly in low birth-weight infants, and 13% in 6 to 11 months of age [11]. The trend of a gradual decrease in platelet counts continues throughout childhood and reaches normal levels by the age of 11 [11]. Thrombocytosis in children is caused by the immaturity of their innate and/or adaptive immunity or more frequently by infections [12]. We found no statistically significant difference in the age of children with RT because splenectomized children in our cohort were on average older (9.2 years) and because of the cause of thrombocytosis itself.

RT in childhood is usually associated with bacterial or viral infections; less frequent causes include anemias (hemolytic or iron-deficiency), autoimmune diseases, cancers and drugs [11]. Since the spleen in healthy persons is a reservoir for approximately 1/3 of total body platelets, splenectomy is a well-recognized cause of RT [3, 5, 13, 14]. Our study revealed a very high (94%) prevalence of RT among the pediatric population undergoing splenectomy. Although this prevalence appears to be high, it is in line with the previous studies that have been reported in pediatric population [1, 3, 4, 13, 14]. In addition, splenectomy was found to be one of the main causes of extreme RT [15]. In our study, the extreme thrombocytosis accounted for 20% of all reported cases of postsplenectomy RT.

Another important finding from our study is a higher incidence of RT including extreme RT in male patients, with the male/female ratio 2.5:1, which is in agreement with the previous studies [16–18]. The reasons for male predominance can be partially explained by the synergistic effects of sex hormones, especially androgens, on thrombopoiesis and androgen modulation of platelet count and function [19].

Extreme thrombocytosis may predispose several complications including neurological (vasomotor), thrombotic, and hemorrhagic [20]. However, in case of postsplenectomy RT, the platelets retain their normal structure and function, the bone marrow is normal, and the interaction of platelets with the vessel wall remains normal. Therefore, the association of thrombocytosis with complications such as thrombosis and hemorrhage appear to be related to quantitative rather than qualitative platelet abnormalities [1, 20]. This was also confirmed in our study given that the measured INR was normal in all cases including extreme RT. However, thrombotic complications have been occasionally reported in pediatric RT following splenectomy for other reasons [21, 22].

Some observations suggest that leukocytosis may also increase the risk of thrombosis in patients with myeloproliferative disorders [23], but no such association was found in patients without myeloproliferative disorders. Among our patients, there were no cases of clinically suggestive thrombosis including cases of portal splenic vein thrombosis (PSVT).

Previous studies have suggested that fatal thrombotic complications in adult patients with postsplenectomy thrombocytosis can be prevented by prophylactic anticoagulants or antiplatelet drugs [24]. In contrast, studies that are more recent have shown a much lower rate of thrombotic events in postsplenectomy adult patients, which did not differ significantly compared to other postoperative groups [25]. The exceptions are patients with myeloproliferative neoplasms in whom platelets are often morphologically and functionally abnormal with the consequent increased risk of thrombosis and bleeding [26].

The treatment of asymptomatic infants and children with extreme RT is still controversial. However, 80% of children with extreme RT in our study did not receive any antiplatelet or anticoagulant therapy and had no any adverse event. These findings further support previous studies that revealed a low risk of complications among this population [1, 27–29].

Our study has several limitations including its retrospective nature, single center experience and small sample size. A longer follow-up period would provide valuable information on potentially late thrombotic events among the postsplenectomy children with persistent RT. In addition, a postoperative ultrasound scans were not part of the routine checkups for occult splenic and portal vein thrombosis, which may affect these patients [22]. Despite all the limitations, we confirm that RT is a very common event following splenectomy, but in this study it was not associated with clinically evident thrombotic or hemorrhagic complications in children undergoing splenectomy for trauma, structural lesions or non-neoplastic hematological disorders.

Author Contributions

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References

1. Schafer AI. Thrombocytosis. *N Engl J Med.* 2004; 350(12):1211–9. <https://doi.org/10.1056/NEJMra035363> PMID: 15028825
2. Schafer AI. Thrombocytosis and thrombocythemia. *Blood Rev.* 2001; 15(4):159–66. <https://doi.org/10.1054/blre.2001.0162> PMID: 11792116
3. Boxer MA, Braun J, Ellman L. Thromboembolic risk of postsplenectomy thrombocytosis. *Arch Surg.* 1978; 113(7):808–9. <https://doi.org/10.1001/archsurg.1978.01370190030004> PMID: 678089

4. Oida T, Kano H, Mimatsu K, Kawasaki A, Kuboi Y, Fukino N, et al. Thrombocytosis following splenectomy: with or without additional organ resection. *Hepatogastroenterology*. 2012; 59(116):1033–5. <https://doi.org/10.5754/hge10032> PMID: 22580653
5. Khan PN, Nair RJ, Olivares J, Tingle LE, Li Z. Postsplenectomy reactive thrombocytosis. *Proc (Bayl Univ Med Cent)*. 2009; 22(1):9–12.
6. Troendle SB, Adix L, Crary SE, Buchanan GR. Laboratory markers of thrombosis risk in children with hereditary spherocytosis. *Pediatr Blood Cancer*. 2007; 49(6):781–5. <https://doi.org/10.1002/pbc.21319> PMID: 17854065
7. Das A, Bansal D, Ahluwalia J, Das R, Rohit MK, Attri SV, et al. Risk factors for thromboembolism and pulmonary artery hypertension following splenectomy in children with hereditary spherocytosis. *Pediatr Blood Cancer*. 2014; 61(1):29–33. <https://doi.org/10.1002/pbc.24766> PMID: 24038836
8. Kashuk JL, Moore EE, Johnson JL, Biffi WL, Burlew CC, Barnett C, et al. Progressive postinjury thrombocytosis is associated with thromboembolic complications. *Surgery*. 2010; 148(4):667–74; discussion 74–5. <https://doi.org/10.1016/j.surg.2010.07.013> PMID: 20719351
9. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*. 2018; 8(2):15. <https://doi.org/10.1038/s41408-018-0054-y> PMID: 29426921
10. Matsubara K, Fukaya T, Nigami H, Harigaya H, Hirata T, Nozaki H, et al. Age-dependent changes in the incidence and etiology of childhood thrombocytosis. *Acta Haematol*. 2004; 111(3):132–7. <https://doi.org/10.1159/000076520> PMID: 15034233
11. Dame C, Sutor AH. Primary and secondary thrombocytosis in childhood. *Br J Haematol*. 2005; 129(2):165–77. <https://doi.org/10.1111/j.1365-2141.2004.05329.x> PMID: 15813844
12. Kucine N, Chastain KM, Mahler MB, Bussel JB. Primary thrombocytosis in children. *Haematologica*. 2014; 99(4):620–8. <https://doi.org/10.3324/haematol.2013.092684> PMID: 24688110
13. Rottenstreich A, Kleinstern G, Spectre G, Da'as N, Ziv E, Kalish Y. Thromboembolic Events Following Splenectomy: Risk Factors, Prevention, Management and Outcomes. *World J Surg*. 2018; 42(3):675–81. <https://doi.org/10.1007/s00268-017-4185-2> PMID: 28808782
14. Zvizdic Z KK, Jonuzi A. Clinical evaluation of postsplenectomy reactive thrombocytosis in childhood. *Med Journal*. 2011; 17(1):66–9.
15. Park YM PJ, Jo Y, Kim SH, Shin KC, Won IS, et al. Prolonged extreme thrombocytosis in a postsplenectomy patient with hereditary spherocytosis. *Korean J Hematol*. 2009; 44:298–303.
16. Denton A, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. *Arch Dis Child*. 2007; 92(6):515–6. <https://doi.org/10.1136/adc.2006.111484> PMID: 17515621
17. Yohannan MD, Higgy KE, al-Mashhadani SA, Santhosh-Kumar CR. Thrombocytosis. Etiologic analysis of 663 patients. *Clin Pediatr (Phila)*. 1994; 33(6):340–3.
18. Chen HL, Chiou SS, Sheen JM, Jang RC, Lu CC, Chang TT. Thrombocytosis in children at one medical center of southern Taiwan. *Acta Paediatr Taiwan*. 1999; 40(5):309–13. PMID: 10910539
19. Li AJ, Karlan BY. Androgen mediation of thrombocytosis in epithelial ovarian cancer biology. *Clin Cancer Res*. 2005; 11(22):8015–8. <https://doi.org/10.1158/1078-0432.CCR-05-1058> PMID: 16299230
20. Johnson M, Gernsheimer T, Johansen K. Essential thrombocytosis: underemphasized cause of large-vessel thrombosis. *J Vasc Surg*. 1995; 22(4):443–7; discussion 8–9. [https://doi.org/10.1016/s0741-5214\(95\)70013-7](https://doi.org/10.1016/s0741-5214(95)70013-7) PMID: 7563405
21. Oomen MW, Bakx R, van Minden M, van Rijn RR, Peters M, Heij HA. Implementation of laparoscopic splenectomy in children and the incidence of portal vein thrombosis diagnosed by ultrasonography. *J Pediatr Surg*. 2013; 48(11):2276–80. <https://doi.org/10.1016/j.jpedsurg.2013.03.078> PMID: 24210199
22. Stringer MD, Lucas N. Thrombocytosis and portal vein thrombosis after splenectomy for paediatric haemolytic disorders: How should they be managed? *J Paediatr Child Health*. 2018; 54(11):1184–8. <https://doi.org/10.1111/jpc.14227> PMID: 30246317
23. Kushnir M, Cohen HW, Billett HH. Persistent neutrophilia is a marker for an increased risk of venous thrombosis. *J Thromb Thrombolysis*. 2016; 42(4):545–51. <https://doi.org/10.1007/s11239-016-1398-4> PMID: 27383828
24. Schafer AI. Bleeding and thrombosis in the myeloproliferative disorders. *Blood*. 1984; 64(1):1–12. PMID: 6375757
25. Lee DH, Barmparas G, Fierro N, Sun BJ, Ashrafian S, Li T, et al. Splenectomy is associated with a higher risk for venous thromboembolism: A prospective cohort study. *Int J Surg*. 2015; 24(Pt A):27–32. <https://doi.org/10.1016/j.ijsu.2015.10.011> PMID: 26493210

26. Michiels JJ, Budde U, van der Planken M, van Vliet HH, Schroyens W, Berneman Z. Acquired von Willebrand syndromes: clinical features, aetiology, pathophysiology, classification and management. *Best Pract Res Clin Haematol*. 2001; 14(2):401–36. <https://doi.org/10.1053/beha.2001.0141> PMID: [11686107](https://pubmed.ncbi.nlm.nih.gov/11686107/)
27. Zulkafli Z, Janaveloo T, Wan Ab Rahman WS, Hassan MN, Abdullah WZ. Extreme Thrombocytosis in a Child: Laboratory Approaches and Diagnostic Challenges. *Oman Med J*. 2019; 34(4):336–40. <https://doi.org/10.5001/omj.2019.65> PMID: [31360323](https://pubmed.ncbi.nlm.nih.gov/31360323/)
28. de Lama Caro-Paton G, Garcia-Salido A, Iglesias-Bouzas MI, Guillen M, Canedo-Villaroya E, Martinez-Romera I, et al. [Extreme reactive thrombocytosis in a healthy 6 year-old child]. *An Pediatr (Barc)*. 2014; 81(5):318–21.
29. Oliveira JA, Moeda S, Contreiras M, Costa-Lima S, Ferrao A. Extreme reactive thrombocytosis in an infant: Much ado about nothing? *Pediatr Blood Cancer*. 2019; 66(1):e27467. <https://doi.org/10.1002/pbc.27467> PMID: [30251331](https://pubmed.ncbi.nlm.nih.gov/30251331/)