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An assessment of the effectiveness of splenectomy in the treatment of immune thrombocytopenia in adults

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ABSTRACT

Introduction: Immune thrombocytopenia (IT) is an acquired immune-mediated disease characterized by a decrease in platelet count due to antiplatelet autoantibody-mediated increased platelet destruction. Platelets which are "labelled" by autoantibodies are recognized and destroyed first of all in the spleen, and, therefore, splenectomy is one of the treatment options, particularly in cases refractory to conservative treatment.

The objective of this study was to determine long-term outcomes of splenectomy in the treatment of IT in adult patients.

Materials and methods: Eleven patients, 7 men and 4 women with a mean age of 43 years and IT lasting 30 months on average underwent splenectomy. Indication to surgery was failed conservative steroid therapy in all patients. Outcomes of surgery were assessed in 9 patients on average 5 years following the surgery.

Results: In all patients, good response to the treatment was obtained (remission). None of the patients continued therapy against the disease and all had platelet count at the follow-up higher than 100 G/L. No serious complications were observed.

Conclusion: Splenectomy is an effective and relatively safe, second-line treatment of IT, in cases in which conservative therapy fails.

Keywords: immune thrombocytopenia; splenectomy; remission; long-term treatment outcomes.

INTRODUCTION

Immune thrombocytopenia (IT), also called "immune thrombocytopenic purpura", is an acquired immune-mediated disease characterized by a decrease in platelet count due to antiplatelet autoantibody-mediated increased platelet destruction and, in some cases, associated impaired platelet production. The direct cause of the disease remains unknown; however, a viral infection is a suspected factor inducing pathological immune response against patients' own platelets. The condition affects predominantly adolescents and young adults, and females more frequently than males [1, 2, 3]. Platelets which are "labelled" by autoantibodies are recognized and destroyed in the spleen and, to a lesser degree, in the liver. Splenectomy is thus one of the treatment options for this disease.

Immune thrombocytopenia manifests clinically with petechiae or purpura on the skin which, in the first days after the onset, may be misdiagnosed as an allergic rash. Other signs include non-occasional hematomas, persistent bleeding from wounds, mucosal bleeding, frequent or heavy epistaxis. When platelet count is very low, more serious bleedings can occur in the gastrointestinal and urinary tracts or into the central nervous system. The disease is usually diagnosed at the platelets count lower than 20–30 G/L (thousands/mm^3), but levels <10 G/L are not uncommon. One should remember that although normal platelets count is 150–450 G/L, the patients with IT frequently remain asymptomatic at the platelet count ranging 20–30 G/L. It is because their platelets are bigger, stronger and work very efficiently for maintaining haemostasis. For the same reason, surgeries on patients with very low platelet count are relatively safe, and pre- or intraoperative replacement of preserved platelet concentrate is rarely necessary [4]. The diagnosis of the condition is confirmed by histological examination of biopsy of the bone marrow, which shows a great number of megakaryocytes, the precursor cells for platelets.

The management of IT has evolved over the course of the past 25 years as new treatments have emerged. In general, the mainstays of medical therapy are corticosteroids and intravenous immunoglobulins. However, long-term remission rates are only 20–25% in adults, and therefore splenectomy is a viable choice that remains a main second-line treatment in refractory cases [1, 2]. Another and relatively novel treatment options include the monoclonal CD20 antibody (rituximab) and the thrombopoietin receptor agonists (eltrombopag and romiplostim), used following the diagnosis of impaired thrombopoiesis and megakaryocyte apoptosis in IT patients. All these drugs have been approved for children with persistent or chronic IT who have had an insufficient response to steroids, immunoglobulins or splenectomy [1].

The objective of this study was to assess the long-term outcomes of splenectomy in the treatment of IT.

MATERIALS AND METHODS

The study group included 11 patients, 7 men and 4 women aged 43 years old on average (range 27–69) with IT who had a splenectomy at Department of General and Hand Surgery of the Pomer-

anian Medical University in Szczecin in the years 2005–2007. The average duration of the disease before the surgery was 30 months (range: 2 months–8 years). In 9 patients the symptom was petechiae on the trunk and extremities, in 1 mucosal bleeding, and 1 had the disease diagnosed accidentally, during hospitalization due to a minor head trauma. The mean platelet count at the diagnosis was 26 G/L (range 1–64 G/L). Before the surgery all patients had been treated conservatively with intravenous or oral corticosteroids; 4 of them longer than 1 year. All patients were referred to the hospital by haematologists and in all cases the direct cause of undergoing surgery was a poor response to steroid therapy or the shortening of the remission periods following the therapy. Prior to the surgery, most patients had scintigraphy tests for assessment of an uptake ratio of ^{99m}Tc labelled platelets between the spleen and the liver, showing the predominance of the spleen uptake. Ultrasound examination of the abdomen was performed to assess size of the spleen (no enlargement was seen). All patients were vaccinated in advance against meningococcal, pneumococcal and HBV infections. Nine of the 11 patients were prepared before the surgery by intravenous or oral steroid therapy for increasing platelets count to min. 100 G/L. In 2 patients, this therapy failed and they were operated on with a lower platelet count (see next section). The patients were operated on by laparotomy and underwent standard splenectomy. The patients were followed up for 5 years on average (range 3–7) by conducting phone interviews. Nine of 11 patients were available for interviews and the long-term outcomes in this group are the subject of our analysis in this paper.

RESULTS

Intraoperative findings

In all patients the surgery was uneventful. No serious bleeding was observed and no blood replacement was necessary. Two patients who had been operated on with platelet count of 36 G/L and 38 G/L, respectively, received intraoperative transfusion of 3 units of preserved platelets, immediately after the resection of the spleen. In these patients, careful preparation of the spleen was performed with meticulous haemostasis, and thus intraoperative bleeding was normal. All resected spleens had an average size of 11 cm in the long axis (range 10–15) and their histological examination revealed no pathologies.

Post-operative course

In all but 1 patient, the post-operative course was uneventful. Operative wounds healed by primary intention and no complications occurred. One patient had persistent dull pain in the upper abdomen lasting several days after the operation. Ultrasonography revealed the portal vein partial thrombosis which was confirmed by elevated D-dimers. A rapid increase in platelet count to 800 G/L was observed in this patient for the first 3 weeks following surgery. The patient received antithrombotic therapy with fractioned heparin in a curative dosage and the symptoms slowly resolved. Ultrasonography performed 4 months after that showed the recanalization of the portal vein. The platelets count decreased to 400 G/L. Table 1 illustrates the demographics of the patients, duration of the disease, baseline and post-operative platelet counts in the first 3 post-operative days. In all but 2 patients a rapid and robust response to the treatment was observed in terms of an increase in platelet counts. In 2 patients (No. 3 and no. 10 in Table 1), poor or no response was observed; however, their platelet counts slowly increased in the next few weeks.

Long-term outcomes

Nine patients were identified a few years following the surgery, 5 years on average (range 3–7 years). A phone interview was conducted and the questions concerned their actual health status: full recovery (or not) from the disease; the necessity of medication due to persistent thrombocytopenia; potential complications caused by lack of the spleen, e.g. more frequent infections and poorer general health. All 9 available patients

TABLE 1. Demographics of the patients, duration of the disease, baseline and post-operative platelets counts in the first 3 days following splenectomy

No.	Age	Gender	Duration (months)	Baseline platelet count (G/L)	Post-operative platelet count (G/L)		
					1st day	2nd day	3rd day
1.	31	F	48	81	184	214	225
2.	25	M	72	36	156	167	189
3.	28	M	3	55	41	67	70
4.	56	F	96	38	112	134	187
5.	58	M	8	241	287	352	378
6.	25	M	12	105	140	178	212
7.	47	M	6	65	104	127	128
8.	69	F	6	250	179	324	415
9.	45	M	12	181	165	194	226
10.	66	F	72	95	97	83	92
11.	27	M	2	170	163	214	323

recovered from thrombocytopenia and no one continued medication to increase the platelet count. Nevertheless, 2 patients whose post-operative response was mild had platelet counts stabilized at a level slightly above 100 G/L. The remaining patients had normal platelet counts. Two patients reported slightly decreased immunity: they noticed more frequent viral infections of the respiratory tract but with no serious complications. All patients continued prescribed vaccination against meningococcal, pneumococcal and flu infections. They led normal life and effective therapy of IT allowed them return to normal life.

DISCUSSION

Immune thrombocytopenia was first described in the 18th century by Paul Gottleib Werlhof, even prior to the identification of platelets as a component of blood. Splenectomy was first time performed in 1916 in the treatment of this disease, with full success [1]. Laparoscopic splenectomy was carried out first time in 1991. In spite of the introduction of novel therapies for IT, splenectomy remains the main second-line treatment in cases of poor response or non-response to standard medication [1, 2]. The results of the present study showed a very good response in all patients and confirmed the effectiveness of surgery in correctly selected cases of IT.

The total remission rate after splenectomy reported in the literature is estimated at 70–90% [1, 2, 3]. Despite this high response rate, some patients do not benefit from surgery. It is therefore important to try to identify risk factors for an unsatisfactory clinical response. These investigations were conducted in 2 studies. Avila et al. reported long-term outcomes of splenectomy in 239 children, 135 females (57%) and 104 males (43%), at a mean age of 12 years (range 8–15 years) suffered from IT. The median age at the time of IT diagnosis was 9 years (range 5–13 years). Sixty-two of the 239 patients (26%) had their splenectomy performed <1 year after diagnosis, thus before reaching chronic IT status [2].

The median follow-up period was 25 months (range 8–53) and assessments included a response to the treatment and adverse events during and after the operation. Minimal adverse events occurred in the peri-operative window in 36 patients: 12 patients (5%) had intraabdominal bleeding and 24 (10%) had a fever. No case of death or sepsis was noted. Of the 168 patients followed for ≥6 months, 18 (11%) had secondary hospital admissions due to a fever and 5 (3%) for sepsis. A response was notable for 222 (93%) of patients achieving complete remission. No response was seen in only 4 children (2%). Predictors to achieve complete remission included older age of the patient at the time of diagnosis, older age of the patient at the time of splenectomy, higher platelet counts in the 1st month following splenectomy and a negative correlation with prior second-line therapies [2].

Kwiatkowska et al. reported outcomes of splenectomy in 165 adults, 113 females (68%) and 52 males (32%), at a mean age of 35 years (range 25–52 years) suffered IT. The median time from IT diagnosis to operation was 2 years (range 0,5–5 years). Median time of preoperative conservative treatment was 9 months (range 5–30). All patients received a laparoscopic splenectomy. Complications occurred in 13 patients (8%). One patient died after surgery due to a pulmonary embolism. Other non-fatal complications included intra-abdominal bleeding, requiring blood replacement in 5 cases (3%), pneumonia in 2 cases (1.2%) and acute pancreatitis in 2 cases (1.2%). There were single cases of gastric perforation, sub-phrenic abscess, sub-phrenic fluid collection and postoperative fever. Median follow-up was 9.5 years (range 5–15) post-operatively. Remission (good response) was defined as a platelet count of >100 G/L in follow-up, no symptoms of IT and no bleedings at the time of follow-up. Out of the 165 patients, 113 (69%) responded well and 52 (31%) did not respond to the treatment (according to assumed criteria). The authors performed an analysis of factors that predict the good response and non-response following the surgery. They found that the independent prognostic factors for IT remission after laparoscopic splenectomy were: age <41 years; BMI <24.3 kg/m^2; and preoperative platelet count at 97–103 G/L. Interestingly, the duration of the disease prior to surgery and the time of conservative treatment did not influence remission [3]. These findings are not consistent with those reported by Avila et al., but one should remember that the patients included in these studies were different with regard to age (paediatric vs. adults) [2].

Several reports are available in the literature presenting results of surgery (splenectomy) for IT. Tastaldi et al. reported 68% of remissions at a median of 5-year follow-up following laparoscopic splenectomy [5]. Rijcken et al. reported stable remission in 44 of 72 patients (61%) [6]. Differences in haematological outcomes might come from different criteria of "complete remission" used in different studies. Some authors define complete response as a platelet count of >100 G/L in the follow-up, but others consider platelet count of >50 G/L a good response [3, 7, 8].

Splenectomy is, however, an irreversible procedure that can be associated with morbidity. Finianos et al. analyzed the trends of splenectomy in adults with IT in the USA. They employed the American National Inpatient Sample to identify hospitalizations for adult patients with diagnosed IT 2007–2017. A total of 36,141 hospitalizations for IT were included in the study. The splenectomy rate declined over 11 years, from 16% in 2007 to 8% in 2017 (negative trend, $p < 0.01$). In-hospital mortality after splenectomy also decreased significantly. Despite a stable hospitalization rate due to IT over the past decade, and despite listing splenectomy as a second-line option for management of this disease in major guidelines, splenectomy rates consistently declined over time [9]. This study shows that operative treatment of IT by splenectomy has diminished in popularity, probably due to the introduction of new conservative therapies, particularly for children. There is however no data that would help confirm such trends in Poland.

This study has a number of limitations. It is based on a relatively small number of patients, which is associated with a relative rarity of this disease in adults; collecting a greater group

would need much more time. I decided to publish my results because Polish literature is lacking papers investigating this problem, particularly among adults. The 2nd limitation is associated with the used technique of splenectomy by laparotomy, even though a laparoscopic splenectomy is considered a gold standard. However, in the years when this study was conducted I did not have adequate skills to resect the spleen using laparoscopy. Nevertheless, for the evaluation of the long-term effectiveness of this treatment for IT, the operative technique is not significant. The strong point of this study is a detailed pre-operative assessment of patients and a relatively long-term follow-up.

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