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Retrospective study of the incidence of portal vein thrombosis after splenectomy in hematological disorders: Risk factors and clinical presentation

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ABSTRACT

Objective: Portal vein thrombosis (PVT) has been described as a rare complication after splenectomy. PVT associated risk factors after splenectomy in hematological disorders are poorly recognized. The aim of this study was to assess the prevalence and risk factors of PVT incidence in splenectomized patients.

Methods: One hundred twelve splenectomized patients with various hematologic diseases between 2008 and 2018 were enrolled in this study. Diagnosis was confirmed by Doppler ultrasonography (DUSG) and risk factors for PVT were sought based on the comparison of clinical and laboratory features between patients without and with PVT.

Result: PVT was diagnosed in 4 (3.57%) patients in spite of receiving antiplatelet therapy. Patients with PVT were β-thalassemia major (n = 2) and β-thalassemia intermedia (n = 2). β-thalassemia patients had a 3.5 times higher odds for PVT (95% CI: 2.41–5.33). No significant differences between patients with and without PVT in terms of age, gender and laboratory features were found.

Conclusion: According to our data, β-thalassemia, especially intermediate form, may be a risk factor for PVT and it can occur in spite of receiving antiplatelet therapy. Given that β-thalassemia patients are at risk, early PVT detection may be useful for reduction of fatal PVT complication in splenectomized patients.

1. Introduction

Portal vein thrombosis (PVT) is a rare, but a serious life-threatening complication after splenectomy in hematological disorder [1]. The first case of PVT after splenectomy reported by Beeckman Delatoure in 1895 [2]. The various studies reported the overall incidence of this complication 12.3% with range of 4.8–51.5% after all splenectomized cases [3–6]. The incidence of PVT may be associated with symptoms such as abdominal pain, nausea, diarrhea, anorexia, and fever or may be developed without any symptoms [7]. However, high sensitivity and specificity radiographic imaging such as Doppler ultrasonography (DUSG) is the investigation of choice for PVT diagnosis and follow-up [8]. A number of risk factors including the underlying disease, especially myeloproliferative disorders, hemolytic anemia, and clinical and laboratory findings such as age, obesity, and previous thrombosis may lead to the development of PVT after splenectomy [8–11]. It is also has been shown that strokes, heart attacks, and atherosclerosis are delayed but relatively less common vascular events after splenectomy in hereditary spherocytosis [12–15]. Nowadays, antiplatelet and antithrombotic therapy including acetylsalicylic acid that usually followed by low-dose warfarin prophylaxis, is the best way to prevent PVT [7].

Although development has been made in understanding the nature of post-splenectomy PVT, however, there is no certain evidence about the role of physiopathological factors in the incidence of this complication. The aim of this study was to assess the incidence of PVT after splenectomy in patients with hematological disorders and clarify possible risk factors for predisposing to postoperative PVT.

2. Patient's selection and methods

A computerized record search was conducted to identify all patients with hematological diseases who underwent splenectomy between 2008 and 2018. Among these; any patients with hypertension and weight over the beyond of normal range, history of smoking, taking anti-pregnancy drugs and liver disease were excluded from the study. Afterward, informed consent was obtained from all patients who selected to this study and the following personal data for each patient

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included age, sex, underlying hematologic disease, complete blood count values at follow-up were extracted. Routine DUSG was performed to confirm the presence of PVT in patients. Postoperative clinical characteristics were compared between patients with or without PVT to determine risk factors for incidence of PVT after splenectomy. This study was approved by ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR. AJUMS. REC. 1396. 716).

3. Statistical analysis

All statistical analyses were performed using SPSS version 22, and quantitative data were expressed as mean ± SD. Patient characteristics were compared with Fisher's exact test and Mann–Whitney *U* test. The PVT risks were also expressed in terms of odds ratios with computation of 95% confidence intervals. A P value of < 0.05 was considered significant.

4. Results

One hundred twelve splenectomized patients over a 10-year period from 2008 to 2018 enrolled in this study. All of the splenectomized patients were operated by open surgery. The indications for splenectomy are shown in Table 1. Based on recorded data, postoperative thrombotic prevention was performed with combination of enoxaparin 1 mg/kg IV infusion and warfarin (0.2 mg/kg) per day used for a mean duration of 8 days immediately after treatment in ninety (80.3%) of splenectomized patients [16].This treatment was followed by acetylsalicylic acid orally (80 mg/kg daily) for with a mean duration of 6 months to 8 years. Twenty two (19.6%) patients who underwent splenectomy don't receive antithrombotic agent. There was no surgery, abdominal trauma, mortality, heart diseases, deficiencies in natural inhibitors of coagulation factors (protein C and S, antithrombin II), and bacterial infections in patient's history. β-thalassemia major ($n = 91$) and β-thalassemia intermedia ($n = 13$) were the most common diseases. The mean value of postoperative clinical characteristics of patients with and without PVT is shown in Table 2.

4.1. Incidence of portal venous thrombosis after splenectomy

Four patients, two males (3.7) and two females (3.4) (males/females odds ratio 1.07) were diagnosed to have PVT (Fig. 1). The incidence of PVT was two of patient's with β-thalassemia major (1.78%) and two of patients with β-thalassemia intermedia (1.78%). No patients with sickle cell anemia and hereditary spherocytosis' had PVT (Table 1). Patients who had β-thalassemia have a 3.5 times higher odds for PVT (95% CI: 2.41–5.33) than other hematological disorders. Of the four patients who developed PVT, three had abdominal pain and fever; however, one patient did not show any clinical symptom.

4.2. Risk factors for portal venous thrombosis

There were no significant differences between patients who developed and without PVT in terms of age, gender and laboratory and physiological parameters including weight and blood pressure as shown in Table 2. The mean age of patients with PVT was 21.50 ± 8.39 years (range, 9–27) and the mean age of patients without PVT was 26.91 ± 9.11 years (range, 5–53). Patients with PVT had higher levels of platelet and white blood cell (WBC) counts; however, no difference significant was found (Table 2). On the other hand, the univariable analysis showed that for per unit (10^3/μl) increase platelet counts related to a 1.02 times increased odds for PVT (95% CI: 0.99–1.21). Also, for per unit (10^3/μl) increase WBC counts related to a 1.01 times increased odds for PVT (95% CI: 0.98–1.13). In contrast, hemoglobin (Hb) level was lower in patients with PVT than patients without it. Although the difference was not statistically significant ($P = 0.115$), the univariable analysis showed that for per unit (1 g/dl) decrease of Hb counts associated with a 1.59 times increased odds for PVT (95% CI: 0.54–1.73). Also, we found that patients with PVT had a non-significant higher level of ferritin compared to those who without PVT ($P = 0.710$). On the other words, for five hundred ng/mm increase ferritin level related to a 1.10 times increased odds for PVT (95% CI: 0.14–2.41). The mean duration between initial diagnosis and date of splenectomy was 15.6 ± 9.44 years in patients with PVT. Also, univariable analysis showed that the one year increase in duration after splenectomy can be related to a 1.04 times increased odds for PVT (95% CI: 0.96–1.13). Regarding our data of treatment modalities of splenectomized patients, we found that there were twenty two (19.6%) patients who were not undergo any antiplatelet therapy. However, ninety patients received antiplatelet prophylaxis consisting of acetylsalicylic acid (80.3%). Interestingly, we observed PVT in (4.44%; 4/90 cases) patients who receiving antiplatelet therapy, while patients who did not receive antiplatelet agents didn't show post-splenectomy PVT. Blood pressure and weight in patients without PVT were higher than in those with PVT, but the difference was not statistically significant (Table 2).

Table 1
Hematological disorders of patients.

Hematological disorders	Number of patients, n (%)	
	PVT	No of PVT
β-thalassemia major	2 (1.78)	89 (79.46)
β-thalassemia intermedia	2 (1.78)	11 (9.82)
Sickle cell anemia	–	7 (6.25)
Hereditary spherocytosis	–	1 (0.89)
Total	4	108

Abbreviation: PVT: port vein thrombosis; n: number.

5. Discussion

The accurate incidence and risk factors of post-splenectomy PVT is not clearly determined. Since, presenting symptoms of PVT after splenectomy are often ambiguous; the incidence of this event may be unpredictable. The incidence of PVT in 112 our series patients was 3.57% which is slightly less than the overall incidence of post-splenectomy PVT that has been reported in previous studies [4–6,17,18]. From the result of univariable analysis in present study, male's patients higher odds for PVT, however no any significant difference between males and females was found to explain the males in our series predominantly tend to develop PVT. This finding in disagreed with previous studies have demonstrated that females are predominance to develop PVT [19–21]. So that, further studies are required to answer this question whether this association may be an effect of sexual hormones or not. In present study four patient who had major and intermediate β-thalassemia showed higher odds for developed PVT compared to other studies have identified myeloproliferative disorders and hemolytic anemia as common risk factors for post-splenectomy PVT [9,20,22]. In addition, we found a larger prevalence of PVT in patients with β-thalassemia intermedia (15.38%) than in patients with β-thalassemia major (2.19%). These results were accordance with previously epidemiological studies, which demonstrated that a thrombotic event in β-thalassemia intermedia is higher than β-thalassemia major [21,23–25]. The molecular mechanisms underlying of PVT in β-thalassemia intermedia is unclear, however, several factors including a procoagulant activity of hemolyzed circulating red blood cells (RBCs), increased platelet activation, and deficiency of antithrombotic factors such as antithrombin III, protein C and S has been reported as possible mechanism for PVT incidence in β-thalassemia intermedia, especially after splenectomy [21,26]. The other possible causes for this phenomenon, including this fact that patients with β-thalassemia intermedia continue to have in circulation mainly their own RBCs in contrast to patients

Table 2
Comparison of patient's characteristics and relative risk (odds ratio) of PVT.

Variable	No of PVT	PVT	Odds ratio (95% CI)	P-value
Sex n (%)				
Male	52 (96.2)	2 (3.7)		0.998
Female	56(96.5)	2 (3.4)	1.07	
Age (year)	26.91 ± 9.11	21.50 ± 8.39	0.93 (0.82–1.09)	0.245
Hemoglobin level (g/dl) (mean ± SD)	8.68 ± 1.54	7.13 ± 1.96	1.59 (0.54–1.73)	0.115
Duration after operation (year) (mean ± SD)	10.13 ± 9.46	15.6 ± 9.44	1.04 (0.96–1.13)	0.195
Platelet counts ($\times 10^3/\mu L$) (mean ± SD)	663.85 ± 218.93	705.50 ± 102.78	1.02 (0.99–1.21)	0.562
WBC counts ($\times 10^3/\mu L$) (mean ± SD)	29.78 ± 22.83	39.68 ± 28.54	1.01 (0.98–1.13)	0.515
Freitin (ng/mm) (mean ± SD)	2468.70 ± 2369.45	4424.75 ± 6041.44	1.10 (0.14–2.41)	0.710
Weight (Kg) (mean ± SD)	49.09 ± 12.08	43 ± 15.87	0.95 (0.88–1.04)	0.556
Blood pressure (mmHg)	10.75 ± 1.03	10.68 ± 0.6	0.93 (0.35–2.47)	0.689

Abbreviation: PVT: port vein thrombosis; n: number, WBC: white blood cell, CI: confidence interval.

with β-thalassemia major who are in chronic transfusions. In fact, abnormal erythropoiesis can elevated levels of circulating nucleated red blood cell (NRBC) and procoagulant microparticles as well as thrombotic event in patients with β-thalassemia intermedia [27–30]. We believe, regular transfusion could be able to minimize the circulating abnormal RBCs as well as thrombotic event via the suppressing endogenous erythropoiesis in β-thalassemia intermedia, particularly after splenectomy. In addition, hydroxyurea, alone or with blood transfusion frequently used for prevention of thrombotic events in β-thalassemia intermedia [16]. Although we do not know how long patients had been receiving hydroxyurea, in our β-thalassemia intermedia patient's, formation a drug resistance against hydroxyurea may be other possible causes for PVT development. Interestingly, these PVT patients underwent antiplatelet therapy. This finding in our series correlated with other previous studies that have been shown PVT can occurs in splenectomized patients despite receiving antithrombotic therapy [6,9,19,31]. Our hypothesis here is that this finding may be related to short duration and low dosage of prophylactic therapy or may suggest that prophylactic agents alone are insufficient to prevent the development of PVT. In contrast to Ikeda et al. study who found that the lack of thromboprphylaxis might have contributed to the significantly high incidence of post-splenectomy PVT [4], twenty two (19.6%) of splenectomised patients in our study didn't show PVT in spite of lack of receiving thromboprphylaxis which is the most considerable difference between our series and pervious literature. Mesa et al. implicated that thrombocytosis following splenectomy is a most important risk factor for predisposing of PVT [32]. In our series thrombocytosis was observed in all patients with and without PVT (Table 2). However, Oure data showed that mean platelet counts in patients who developed PVT was slightly higher than patients without PVT. In contrast this finding, the results of Ikeda et al. studies have been shown that PVT can occurs in patients with normal platelet counts [4,5]. It may be in this condition PVT related to platelets dysfunction rather than platelet counts. In our experience, the average ferritin level and WBC counts in patients with PVT were greater than in those without PVT, but the difference was not statistically significant. Similar with this result, Atichartakarn et al. study reported that abnormal WBC counts and serum ferritin levels are risk factors in β-thalassemia patients after splenectomy [33]. Given that, it is unclear whether WBC counts and ferritin level abnormality may be associated with the onset of post-splenectomy PVT, thus, further studies are warranted to clarify these issues.

6. Conclusion

In conclusion, our data show that PVT is a rare post-splenectomy complication for hematologic diseases especially β-thalassemia intermedia. Since in our series post-splenectomy PVT was observed in patients who underwent antiplatelet therapy, and no clear prophylactic strategy guidelines exist to establish an appropriate approach for prevention of PVT, we believed that prophylactic therapy needs to use in effectiveness dose and optimal duration based on underlying disease in splenectomized patients. In addition, PVT may be recognized early by assessment of erythropoiesis and circulating blood cells after splenectomy in β-thalassemia intermedia patients. However, we are aware that our pilot study may have some limitations. First, our study is based on the limited number of patients who did not sufficient to place their data into high risk including patients with large spleen size and hemolytic anemia or low risk group such as splenectomized patients due to immune thrombocytopenic purpura (ITP) or trauma. Second, continuous follow-up of patients from the time of the splenectomy until the

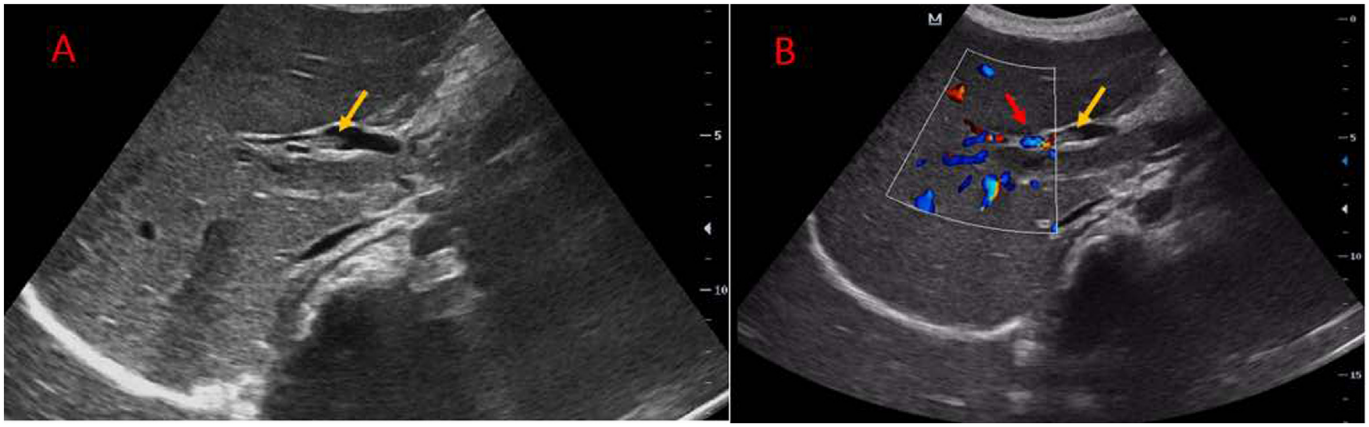

Fig. 1. Portal vein thrombosis: (A) Grayscale B-mode ultrasound image shows an echogenic thrombosis (indication by yellow arrow) with nearly total luminal occlusion in main portal vein. (B) Color-Doppler ultrasound shows complete occlusion of main poral vein with portal collateral veins (indicated by red arrow) in porta hepatis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

exact diagnosis of the PVT hasn't taken place. Therefore, more research with a higher number of patients is necessary for the detection of prevalence and risk factor which are associated with predisposition of post-splenectomy PVT.

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Authors' contributions

B.K. has conceived the manuscript and revised it. A.S., M.J., M.M.B and M.M. wrote the manuscript. B.K. provided clinical data and information. A.S. performed the technical tests.

Conflict of interest

The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS. REC.1396.716) as well as 1946 Helsinki declaration. Written informed consent was obtained from all patients.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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