Prospective Study of the Incidence and Risk Factors of Postsplenectomy Thrombosis of the Portal, Mesenteric, and Splenic Veins

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Hypothesis: Splenectomy is recognized as a cause of portal, mesenteric, and splenic vein thrombosis. The exact incidence of the complication and its predisposing factors are not known.

Design: Prospective observational cohort study. The median follow-up time of the patients was 22.6 months.

Setting: University surgical clinic in a teaching hospital.

Patients: A total of 147 consecutive patients who underwent splenectomy in a 4-year period were enrolled in the study.

Interventions: Preoperative and postoperative evaluation included ultrasonography with color Doppler flow imaging of the portal system, results of blood coagulation tests, fibrinogen levels, D-dimer levels, and complete blood counts. Operative sheets were recorded and reviewed. When portal system thrombosis (PST) was diagnosed, a complete control for acquired and congenital thrombophilia disorders was obtained.

Main Outcome Measures: Primary end points of the study were the assessment of the incidence of postsplenectomy PST and the identification of risk factors for its occurrence.

Results: Portal system thrombosis occurred in 7 (4.79%) of 146 patients who underwent splenectomy. The age, sex, type or length of the operation, and use of preoperative and postoperative thromboprophylaxis with low molecular weight heparin did not prove to be significant factors in the occurrence of PST. Platelet count of more than 650,000/µL and greater spleen weight (>650 g) was associated with the development of PST ($P=0.01$, $P=0.03$). Normal D-dimer levels on diagnosis of the complication showed a negative predictive value of 98%. Two of the affected patients were diagnosed with thrombophilia disorders. In a median follow-up period of 22.6 months, no other case of PST was recorded.

Conclusions: Postsplenectomy PST occurs in approximately 5% of patients. Possible risk factors are thrombocytosis, splenomegaly, and congenital thrombophilia disorders.

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THROMBOSIS OF THE EXTRA-HEPATIC PORTAL SYSTEM FOLLOWING SPLENECTOMY OCCURS IN A SMALL PORTION OF PATIENTS AND IS MOSTLY AN UNPREDICTABLE EVENT. THE PORTAL VEIN, Splenic vein, superior mesenteric vein, and inferior mesenteric vein form an interactive venous system; alterations of the regional hemodynamics lead to different clinical presentations. This is reflected in the severity of clinical expression of a local thrombosis that varies from the subclinical radiologically detected lesion to a lethal event.

The actual incidence of postsplenectomy extrahepatic portal system thrombosis (PST) is not clearly determined. Retrospective studies report an incidence of less than 2% but are not reliable because most cases are not identified unless they become clinically evident. Two prospective studies identified in the literature show a 6.6% to 10% occurrence rate in samples of 50 to 60 patients. Ultrasound and color Doppler flow imaging have been studied extensively as diagnostic methods for portal vein thrombosis. Nevertheless, their exact sensitivity and specificity rates have not been reported.

Hypercoagulability, splenomegaly, and thrombocytosis have been proposed as risk factors, but this has not been proved statistically. It is obvious that any factor influencing the Virchow triad could be identified as a possible risk factor and...
thus should be examined. The Virchow triad was our guide in establishing a research protocol while the current international consensus on prophylaxis from thrombosis and antithrombotic treatment dictated our treatment strategy.

The study was undertaken in an effort to determine the exact incidence of the complication and to identify controllable risk factors. We propose an algorithm for the detection of postsplenectomy thrombosis of the portal system and a suggestion for management.

STUDY DESIGN

A prospective cohort study of all patients who underwent splenectomy from February 1999 until December 2003 was undertaken in a single university surgical department. Data were collected and stored in a standard electronic database. All patients gave written informed consent that they agreed to participate in the study and to fulfill the requirements of the follow-up period.

All patients who underwent therapeutic splenectomy or splenectomy as a part of any other procedure were considered eligible for the study and were initially enrolled. In total, 147 patients were enrolled but 1 was excluded due to early postoperative death.

PREOPERATIVE EVALUATION

Preoperative evaluation included an interview and physical examination with emphasis on history of prior thrombotic episodes and the use of drugs that affect blood coagulation (antithrombotic agents, contraceptives). An abdominal ultrasound with color Doppler flow imaging was obtained on all patients on admission when a splenectomy was scheduled. Of the patients who underwent accidental or nontherapeutic splenectomy, all had preoperative abdominal ultrasound and/or computed tomography ordered for other reasons and their reports were reviewed in terms of portal system patency. Preoperative prothrombin time, international normalization ratio, partial thromboplastin time, fibrinogen and D-dimer levels, and a complete blood count were obtained. Levels of D-dimer were considered normal when they were less than 0.5 µg/mL.

Data from operative records were collected and recorded, including method of anesthesia, length of the operation, required replacement volumes, and mean arterial pressures. Operative technique with emphasis on the site and time of ligation of the splenic vessels and integrity of the removed spleen was recorded. All specimens were weighed on arrival at the pathology department.

POSTOPERATIVE EVALUATION

Postoperative evaluation included platelet count on every other postoperative day, international normalization ratio, prothrombin time, partial thromboplastin time, and fibrinogen and D-dimer levels on postoperative days 5 and 7 and on discharge. Abdominal ultrasound and color Doppler flow imaging were performed on postoperative days 7 and 30 by the same radiologist (S.N.). The portal vein was classified as thrombosed if echogenic material was identified within the lumen of the vein and/or there was absent or reduced flow. Pictures of all examinations were obtained and classified. On ultrasound, the width of the portal vein and the length of the splenic vein stump were measured in millimeters. When thrombosis of the portal system was identified, an independent radiologist repeated the examination to confirm the finding and abdominal computed tomographic scans with intravenous contrast were ordered. When thrombosis was evident, a complete control for acquired and congenital thrombophilia disorders was obtained. Thrombophilia control included testing of factors XII, VIII, IX, and X; activated protein C resistance; deficiency in proteins S and C; antithrombin III deficiency; plasminogen deficiency; factor V Leiden mutation; prothrombin 20210 mutation; hyperhomocysteinemia; lupus anticoagulant; and anticardiolipin antibodies IgG through IgM. All tests were performed at the department of transfusion and hemophilia of our institute.

PROPHYLAXIS AND MANAGEMENT OF THROMBOTIC COMPLICATIONS

According to the fifth THRIFT consensus, low molecular weight heparin (LMWH) was prescribed preoperatively and postoperatively for a minimum of 7 days when mild or severe risk of deep vein thrombosis was evident. In case of severe postsplenectomy thrombocytosis (platelet count >1000 x 10^9/L), aspirin (100 mg orally daily), or dipyridamole (75 mg orally daily) was administered after postoperative day 7. When their administration was contradicted, LMWH was continued for 30 days or until discharge.

When thrombosis of the portal system was diagnosed, therapy was administered according to the clinical evaluation and the ultrasound findings. In cases of subclinical presentation or partial thrombosis with patent vessels, the patient was treated with long-term administration of therapeutic doses of LMWH. If the patient was symptomatic or a complete PST was identified, continuous heparin infusion was administered until the desired partial thromboplastin time was reached. Following treatment with heparin, patients began receiving coumadin orally for a minimum of 6 months.

FOLLOW-UP

Face-to-face or phone interviews were conducted with all patients in the sixth postoperative month. Platelet counts and abdominal ultrasonography were obtained at the same time. Patients with PST submitted to a regular follow-up every 2 months until the completion of the study. It included abdominal ultrasound, complete blood count, and upper gastrointestinal endoscopy for evidence of esophageal varices.

END POINTS OF THE STUDY

The primary end point of the study was to assess the incidence of postsplenectomy PST and to identify risk factors for the development of the complication. In the course of the study, aspects of clinical manifestation of the complication and of its natural history were recorded and are discussed.

STATISTICAL ANALYSIS

We used a \( \chi^2 \) test and Fisher exact test for categorical comparisons of data. Differences in the means of continuous measurements were tested with the Mann-Whitney \( U \) test. Dichotomous variables were created out of continuous variables by using clinically important cutoff points. Univariate analysis and stepwise logistic regression analysis was used to determine the relative contribution of various factors to the risk of occurrence of the event. \( P \) values of less than .05 were considered significant; standard and confidence intervals were determined at the 95% level. Negative predictive values, likelihood ratios, and posterior probabilities were calculated by using the binomial distribution. Relative risks and
odds ratios were also calculated. Data were analyzed with the use of the SPSS 10.0 statistical package (SPSS Inc, Chicago, Ill).

RESULTS

Data for 146 patients who underwent splenectomy were analyzed (Table 1). Postoperative mortality was 0 for elective or emergency splenectomies, rising to 7.81 when splenectomy was part of a major intra-abdominal procedure. Postoperative morbidity was 29.26% and 43.75%, respectively. Two patients underwent surgery a second time, one for postoperative bleeding and one for foreign body removal. Clinically evident deep vein thrombosis was diagnosed in 1 patient. Eight patients were diagnosed postoperatively with upper abdomen fluid collection.

Complete PST was diagnosed postoperatively in 6 patients and partial thrombosis in 1 patient (7 patients total or 4.79%) (Figure 1 and Figure 2). Six cases were identified on postoperative day 7; the remaining 1 was diagnosed before postoperative day 30. The radiological features, clinical presentations of the complication, and patients’ characteristics are given in Table 2.

On the preoperative tests, 1 patient had splenic vein thrombosis and left portal hypertension as a result of chronic pancreatitis with pseudocyst formation. This patient developed complete portal vein thrombosis postoperatively. Six female patients received oral contraceptives in the last preoperative month, but none developed thrombosis. Another 6 patients received permanent antithrombotic medication for atrial fibrillation or prosthetic valve. They also did not develop thrombosis.

Age, sex, type or length of the operation, type of anesthesia, intraoperative transfusions, and volume of replacement fluids did not prove of any significance related to the occurrence of PST. Lengthy intraoperative drops of mean arterial pressure (>60 min with pressure <70 mm Hg) were initially associated with postoperative PST in the univariate analysis (relative risk, 5.79; odds ratio, 12.96; \( P = .01 \); CI, 0.04-0.33). The only predictor of the extent of increase in platelet count was the preoperative count (\( P < .001 \)). Mean ± SD spleen weight was 507.82 ± 489.11 g. It was proved to be associated with the development of PST only in the univariate analysis (relative risk, 4.45; odds ratio, 5.01; \( P = .03 \); CI, 0.01-0.20). The length of the splenic stump was measured in 44 patients when the junction with the inferior mesenteric vein was clearly recognized; the measurements were judged of minimal accuracy and were therefore excluded from further analysis.

Abdominal ultrasound was judged to be of diagnostic value for 134 patients on postoperative day 7. Inability to assess the portal vein due to projection of bowel gas led to repeated examination on postoperative day 10 of 6 patients. In 3 cases, the ultrasound was performed between postoperative days 11 and 14. Color Doppler flow imaging showed complete loss of flow of the portal vein and early development of collateral circulation in 4 of 7 patients with PST. On computed tomographic scan, portal vein thrombosis was directly identified on all 7 patients (Figure 3).

Table 1. General Characteristics of the Patients Who Underwent Splenectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>84/62</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>46.6 ± 21.15</td>
</tr>
<tr>
<td>Indication, No.</td>
<td></td>
</tr>
<tr>
<td>GI cancer</td>
<td>62</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>62</td>
</tr>
<tr>
<td>Myeloproliferative disorder</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
</tr>
<tr>
<td>PST</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; PST, portal system thrombosis.
By using ultrasound diagnosis as a standard reference, the D-dimer assay showed a sensitivity and specificity of 85.7% (CI, 0.49-0.97) and 74.1% (CI, 0.66-0.81), respectively, and a likelihood ratio of a negative result of 0.19 (CI, 0.03-1.19), representing a negative predictive value of 99%. Tests for congenital and acquired thrombophilia disorders of the patients who developed PST revealed 1 patient with protein S deficiency and 1 with factor V Leiden mutation.

Follow-up with ultrasound was possible in 96 patients during the sixth postoperative month. No additional PST cases were discovered. Two patients developed extensive splenic vein thrombosis (involving the inferior vena cava) due to end-stage carcinomatosis. At the end of the study and for a median follow-up period of 22.6 months, no additional PST case was recorded for 68 patients. Follow-up data for the patients who developed the complication are given in Table 1. The 7 patients required a total of 21 readmissions for various problems associated with PST.

**COMMENT**

Portal vein thrombosis has been recognized as a potential complication following splenectomy since 1895, and has been reported in various populations. The incidence of PST in this study was 10.6%, which is consistent with previous reports. The positive predictive value of ultrasound for detecting PST was 99%, indicating a high likelihood of the diagnosis if the test is positive. However, the negative predictive value was only 97%, suggesting that ultrasound may miss some cases of PST. Further studies are needed to determine the optimal management strategies for PST and to improve the accuracy of diagnostic tests.
it is still considered an eligible entity for a case report.6-9 A prospective study in the literature referred to 60 hematologic patients and showed a frequency of 6.6% for postsplenectomy portal vein thrombosis.2 Splenomegaly, thrombocytosis, and the diagnosis of myeloproliferative disorder were assumed to be risk factors because they were present in all the reported cases. Retrospective studies have shown a prevalence of the complication from 0.87% to 7%.3,10,11 The fact that PST may be asymptomatic renders retrospective studies unreliable when postoperative ultrasound is not routine.

The extrapancreatic portal vein with the superior mesenteric vein, the inferior mesenteric vein, and the splenic vein form a communicating venous system without valves. A thrombotic incidence in any of these vessels will alter the flow patterns of the rest. In addition, the clot may expand and occupy the entire vessel network. Therefore, the study of postsplenectomy regional thrombosis cannot be limited to the portal vein because there have been reported cases of all possible combinations of sites of thrombosis.12-14 Our study concurs with this.

The studied cases include a combination caseload of indications for splenectomy representative of a general surgery department. Myeloproliferative disorders are known to predispose to spontaneous and postsplenectomy splanchic vein thrombosis.13,15 The impact of myeloproliferative disorder on the development of the complication could not be assessed in the present study because only 2 such cases were included. Nevertheless, it should be stressed that only polycythemia vera, myelofibrosis, chronic myelogenous leukemia, and primary thrombocytosis are considered genuine myeloproliferative disorders. In our study, equivocal diagnoses were not considered as such. The general predisposition of patients with cancer to thrombotic events was also not reflected in our results. This may be attributed to the fact that we included in the analysis a variety of types and stages of malignancy. The studied population restricted further categorization. Preoperative existence of thrombus in any of the related vessels should be considered a major risk factor.16 The surgeon cannot actually protect the patient by removing the clot, especially if it extends proximally to the inferior mesenteric vein–splenic vein junction.

Abdominal ultrasonography was used as the standard diagnostic procedure because it appears to have a reliable sensitivity and specificity rate in the diagnosis of portal vein lesions and it is easy to perform, inexpensive, and repeatable.17-20 Technical difficulties resulting from postoperative bowel distention are common but not restrictive for the use of ultrasound. The examination can simply be postponed until the local conditions are appropriate. Flow study with the use of Doppler techniques provides valuable information because the clinical presentation of the syndrome is mostly determined by the existence of flow and the adequacy of collateral circulation. Abdominal computed tomographic scans, portography, and magnetic resonance portography have been proved of equal if not higher accuracy but are more expensive and not always readily available.21-24 In addition, they cannot provide objective hemodynamic data regarding flow direction and flow pattern. In the search of a test that can be used routinely for the screening of splenectomized patients, ultrasound proves to be invaluable.

The best postoperative day to perform the ultrasound is not known. Most of the cases of PST reported in the literature are diagnosed before postoperative day 15 and all symptomatic cases before postoperative day 7.1,11 Few cases of late presentation (13-46 months postoperatively)25,26 could be attributed to the underlying disease (myeloproliferative disorder) that can lead to spontaneous portal vein thrombosis and probably get disconnected from splenectomy. In our study, 6 of 7 cases were identified around postoperative day 7 and none after the first month. The latest diagnosis (14th day) referred to a man who underwent surgery for pancreatic cancer who had a nondiagnostic ultrasound on the seventh day. Therefore, it seems reasonable to advocate for routine ultrasound examination of splenectomized patients during the first postoperative week.

The clinical presentation of the identified cases depended largely on the flow pattern of the portal vein and the superior mesenteric vein.27 In fact, it was the superior mesenteric vein’s occlusion that caused early and worrying symptoms like ileus. Low fever was a constant finding not necessarily accompanied with leukocytosis. It was not connected to other septic events and its nature is unclear. Ascites was predominately present when the entire portal vein and its major branches were clotted and the collateral network immature. Pain was mostly connected with bowel distention.

Patients who underwent major abdominal operations did not prove to be at additional risk for PST. The length of the operation or the surgical manipulation of the relevant vessels did not predispose to postoperative PST. What may be important is the intraoperative achievement of adequate splanchic blood flow. We assumed that lengthy intraoperative drops of mean arterial pressure would lead to diminished portal flow. That could create the necessary conditions for the portal vein to clot. The assumption was confirmed in the univariate analysis.

It was believed that early ligation of the splenic artery to reduce spleen weight and contain intraoperative hemorrhage may induce PST. That was not proved in our study. The regional hemodynamics will alter despite such maneuvers; the result will be permanent and a few more minutes of full flow to the portal system are of no importance.

Low molecular weight heparins have been proved of value in certain cases of antithrombotic prophylaxis. In our series, their use did not prove to lower the risk of postsplenectomy PST. A possible explanation could be that studies on perioperative use of LMWH mainly examine the effect on deep vein thrombosis.28,29 Postoperative splanchic vein thrombosis has not been studied extensively, and it is possible that significant unknown risk factors exist. In this study, the actual platelet count was the only risk factor definitely confirmed in multivariate analysis. A rise in the platelet count of more than 150 x 10^3/µL is directly associated with the development of PST. It is therefore advisable to administer antiplatelet agents (dipyridamole, aspirin) when severe thrombocytosis occurs postoperatively despite the surgeons’ reluctance in their early use. To identify the patients who will develop severe thrombocytosis postop-
eratively, one has to consider the preoperative platelet count because it proved to be the most reliable predictor of postsplenectomy thrombocytosis. In cases of non-therapeutic splenectomies, when there is no need to excise all accessory spleens, the spleens should be preserved because they control postoperative thrombocytosis.30

Greater spleen weight has been recognized as a potential risk factor for postsplenectomy PST.1 There are several explanations for this finding. There is a correlation between spleen weight and the diameter of the splenic vein. This means that in cases of severe splenomegaly, the remaining splenic vein stump will form a large cul-de-sac with a considerable traumatic surface at the site of the ligation. This may set off the formation of a clot that expands centripetally. However, our finding of partial portal vein thrombosis challenges this theory. On the other hand, greater spleen weight may be a risk factor simply because large spleens are found in myeloproliferative or other disorders that are connected to postsplenectomy thrombosis.31

There seems to be more than 1 risk factor of different importance in each patient for the development of the complication. The finding of congenital thrombophilia disorders in 2 of 7 patients may explain why some patients develop thrombotic episodes in the absence of known risk factors.31 That is particularly interesting in cases of thalassemia because it is known that the percentage of patients with protein S deficiency is larger among patients with thalassemia compared with the general population.32 A similar case of a patient with hereditary protein C deficiency has also been reported.33 The screening for thrombophilia of all patients under going splenectomy is not cost-effective, and some of the tests may cause significant delays in surgery. In the case of thrombosis, however, and especially for young patients, the tests should be performed so that a specialist may advise and treat the patient.34

Along with the ultrasound, it is advisable to test the patient's D-dimer levels. D-dimer tests are considered of adequate sensitivity and of high negative predictive value in diagnosing thrombotic events.35,36 The reported low specificity rate is expected because D-dimer levels are elevated in such different conditions as disseminated intravascular coagulation and sepsis.37 Elevated D-dimer levels are found in patients after major abdominal surgery and especially when its course is complicated by a septic event.37,38 In our series, elevated D-dimer levels were found in patients with septic collections, prolonged stays in intensive care, or deep vein thrombosis. Still, the negative predictive value of the test is significant. Negative test results will strengthen the diagnostic value of ultrasound, and the need for more specific studies will be minimal.

In case of postsplenectomy PST, the patient should be examined at regular intervals. Follow-up should include ultrasound and color Doppler flow imaging to determine the level of organization of the clot and the patency of the portal vein. More sophisticated studies such as portography could be considered for unclear cases or within the design of a protocol. Endoscopy for the diagnosis of esophageal varices should be done as early as 2 months postoperatively, and the patient should be treated as in any case of portal hypertension.

Treatment of the postsplenectomy PST is not standardized. In principle, PST is treated as any thrombotic episode with heparin followed by coumarin for a period of 4 to 6 months. The use of LMWH in therapeutic doses is not clearly justified.39 We used LMWH in the case of partial portal vein thrombosis, considering that the vessel was patent and the patient was asymptomatic. The clot dissolved in less than 2 months and normal portal flow was restored. Thrombolysis with the use of tissue plasminogen activator or even thrombectomy has been occasionally reported but is not the standard of care.6,30-43

The attending physician should expect multiple readmissions of patients with portal vein thrombosis because they follow the course of any patient with portal hypertension.

As reported in the literature, portal vein thrombosis can be lethal.33 However, we did not observe life-threatening complications in our series. We counted 5 deaths in 104 confirmed cases of postsplenectomy PST presented in the literature (4.8%). A fatal outcome seems more likely in cases of delayed diagnosis or subsequent treatment and when massive superior mesenteric vein thrombosis occurs. Five more reported cases from the literature required emergency surgery. The indication for the operations is not always clear, but in general, surgery should be delayed in the absence of profound intra-abdominal sepsis. It seems reasonable that early detection of the complication and thorough follow-up of the patient will prevent catastrophic events.

As a conclusion, we suggest routine ultrasound and D-dimer surveillance in cases of splenectomy.44 When severe thrombocytosis occurs, initial treatment with antiplatelet drugs may prove beneficial. Patients who develop portal system thrombosis should undergo regular follow-up because portal hypertension develops and the readmission rate is high.

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REFERENCES


