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The diagnostic value of splenectomy in patients without a definitive preoperative diagnosis

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ABSTRACT

Background: The purpose of this study was to describe the diagnostic value and therapeutic benefit of diagnostic splenectomy.
Methods: Retrospective review was performed of patients undergoing splenectomy with an unknown diagnosis (UD), a hematologic malignancy (HM) or idiopathic thrombocytopenic purpura. Surgical indications and postoperative outcomes were evaluated.
Results: 113 splenectomy patients were identified. Of the UD patients undergoing splenectomy, 46% (n = 16) received a definitive diagnosis postoperatively. A change in diagnosis occurred in 12% (n = 4) of HM patients. Complete symptom relief was observed more often in UD patients who received a definitive diagnosis after splenectomy 69% (n = 11), compared to the 47% (n = 9) who did not receive definitive diagnosis postoperatively.
Conclusions: The diagnostic ability of splenectomy was 46% when the diagnosis was unknown preoperatively. Additionally, a majority of patients experienced relief of symptoms postoperatively. Splenectomy may be a useful diagnostic and therapeutic tool in select UD and HM patients.

Introduction

Splenectomy is a well-established treatment for certain benign diseases not responsive to medical therapy, most commonly idiopathic thrombotic purpura (ITP).[1] In patients with hematologic malignancies (HM), splenectomy may palliate symptoms, assist in staging, and in certain cases improve survival.[2,3] For both benign and malignant indications, the procedure is safe, with low morbidity and mortality.[4,5]

Splenomegaly and cytopenias are not necessarily immediate indications for splenectomy. However, these findings may be a result of an underlying, undiagnosed hematologic malignancy. Previous reports have shown the incidence of lymphoma in patients with idiopathic splenomegaly ranging from 37% to 57%, which is a more common finding if the patient is also symptomatic.[6–8] A definitive diagnosis of lymphoma or other HM generally results after extensive work-up including imaging, peripheral blood smears, and biopsies of bone marrow and enlarged lymph nodes. However, findings can be equivocal and a subset of patients may require splenectomy for a confirmatory diagnosis.[8] Although splenectomies are considered safe procedures, the efficacy of splenectomy when used as a diagnostic test is not well-established. Similarly, data demonstrating a clinical benefit of splenectomy either for cure or treatment in HM, particularly when compared to its known benefit in ITP, are limited. Therefore, surgeons may take pause prior to proceeding with such a surgery if the diagnostic or clinical benefits are not known to outweigh the risks.

The purpose of this study was to evaluate outcomes from splenectomies performed in a tertiary cancer center. Our primary aim was to establish the diagnostic value of splenectomy for patients without a definitive preoperative diagnosis. Secondary aims were to report the therapeutic benefit of splenectomy including the rate of changes in clinical management and the rate of improvement in symptoms and cytopenias after splenectomy, and to review surgical outcomes in patients undergoing splenectomy for benign disorders (ITP) and hematologic malignancies.

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Material and methods

A retrospective review of patients undergoing splenectomy at Mayo Clinic Arizona was performed. Consecutive patients, over 18 years of age, who received open or laparoscopic splenectomy for ITP, hematologic malignancy (HM) or unknown diagnosis (UD) from 2006 to 2016 were included. Non-diagnostic, non-hematologic or incidental splenectomies were excluded. The study protocol was approved by the Institutional Review Board of Mayo Clinic. Patient demographics and surgery outcomes were collected for each splenectomy case.

Indications for splenectomy in the UD group were categorized as cytopenia, splenomegaly, splenic mass, and the presence of B-symptoms, with otherwise non-diagnostic work-up. Similar categories of surgical indication were used for the HM group; however, these patients had an initial diagnosis of a hematologic malignancy and the splenectomy was either performed with therapeutic intent or if the initial diagnosis was under question. Cytopenia was defined as any blood component below the normal laboratory value. Splenomegaly was defined as the presence of symptoms such as abdominal discomfort, pain or early satiety and/or imaging demonstrating craniocaudal spleen length over 10 cm or extension of the spleen below the lower third pole of the kidney. The presence of any of the following B-symptoms was noted: fevers, sweats, unintentional weight loss. Elevated blood counts included any value over the normal limit. In each case, splenectomy was considered after exhaustive work-up was otherwise non-diagnostic.

The primary endpoint was to determine the diagnostic ability of the splenectomy by recording a change in pre- and post-operative diagnoses as documented in the final pathology report. Secondary endpoints involved postoperative results. A change in medical management was defined as a change, initiation or discontinuation of medical therapy starting in the postoperative period and sustained for up to six months after surgery. Improvements of cytopenias were reported if the lab results returned to normal range or if the patients were no longer requiring transfusions to maintain adequate levels within six months after surgery. Surgical outcomes included: postoperative length of stay, use of surgical bed drains, pancreatic leaks, reoperation or percutaneous placement of drains, image proven venous thromboembolism by postoperative day 30, surgical site infection requiring intervention by postoperative day 30, pneumonia by postoperative day 30, overwhelming post-splenectomy infection (OPSI) at any time postoperatively, 30-day mortality, 30-day readmission, and overall mortality rates.

Statistical analysis

Categorical variables were compared using chi-square analyses and continuous variables using analysis of variance tests and Kruskal-Wallis tests as appropriate. Significance levels were set at $p < 0.05$ with confidence intervals of 95%. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) software.

Results

Patient and operative characteristics

A total of 113 patients were identified. There were 35 (40%) with UD, 33 (29%) with HM, and 45 (40%) patients with ITP. Baseline characteristics are shown in Table 1. BMI was significantly higher in ITP patients than HM and UD patients ($p = 0.002$). HM patients had the highest Charlson Comorbidity Index scores ($p = 0.0001$).

The majority of patients (74%) underwent laparoscopic splenectomy and a 4% conversion to open splenectomy rate was similar among all groups. HM patients were most likely to undergo upfront open splenectomy (36%), followed by UD (11%) and ITP groups (0%; $p < 0.001$). Spleens were significantly larger in weight and length for HM.

Operative indications

Of the UD patients, the most common surgical indication was a combination of cytopenias and symptoms (60%). Of this group, 9 patients presented with both cytopenia and splenomegaly and 7 others presented with cytopenia, splenomegaly, and B-symptoms. Cytopenias alone were observed in 23%, isolated splenomegaly in 9%, and B-symptoms alone in 3%. All patients had at least one symptom preoperatively (Table 2). The HM group had similar trends with multiple symptoms as the most frequent indication (55%). Cytopenias were more common in this group (30%), followed by isolated splenomegaly (12%) and B-symptoms alone (3%). As in the UD group, all HM patients exhibited at least one symptom preoperatively (Table 2). Patients with ITP underwent splenectomy according to the standard algorithm of therapy.

Diagnostic ability

Of the 35 patients undergoing splenectomy for UD, 46% (n = 16) of patients received a definitive diagnosis after postoperative

Table 1
Demographics and surgical outcomes in splenectomy patients.

	UD (n = 35)	HM (n = 33)	ITP (n = 45)	Total (n = 113)	p-value
Demographics					
Age in years, median	58	62	61	61	0.16
Female (percent)	43	46	42	43	0.96
Body Mass Index in kg/m2, median	25	25	29	26	0.0002
Charlson Comorbidity Index, median	2	4	3	3	0.0001
Surgery Type					<0.001
Laparoscopic	24 (69%)	17 (52%)	43 (96%)	84 (74%)	
Open	4 (11%)	12 (36%)	0 (0%)	16 (14%)	
Laparoscopic Hand-Assisted	7 (20%)	4 (12%)	2 (4%)	13 (12%)	
Conversion Rate	2 (6%)	1 (3%)	1 (2%)	4 (4%)	0.69
Operative Time in minutes, mean (SD)	150 (58)	132 (37)	123 (48)	134 (50)	0.04
Estimated Blood Loss in mL, mean (SD)	280 (355)	330 (534)	165 (327)	249 (408)	0.08
Spleen Weight in grams, mean (SD)	883 (701)	1645 (1129)	224 (115)	843 (929)	<0.001
Spleen Length in cm, mean (SD)	18 (6)	22 (7)	12 (2)	17 (7)	<0.001

UD = unknown diagnosis group, HM = hematologic malignancy group, ITP = idiopathic thrombocytopenia group.

Table 2
Indications for surgery for unknown diagnosis and hematologic malignancy.

	UD	HM
Cytopenia alone	8 (23%)	10 (30%)
Splenomegaly alone	3 (9%)	4 (12%)
B-symptoms alone	1 (3%)	1 (3%)
Splenic mass alone	2 (5%)	0 (0%)
Multiple	21 (60%)	18 (55%)
Cytopenia + Splenomegaly	9	8
Cytopenia + Splenic mass	1	0
Cytopenia + B-symptoms	1	0
Splenomegaly + B-symptoms	1	4
Splenic mass + B-symptoms	1	0
Cytopenia + Splenic mass + B-symptoms	1	0
Cytopenia + Splenomegaly + B-symptoms	7	6

UD = unknown diagnosis group, HM = hematologic malignancy group.

Table 3
Diagnoses obtained after splenectomy in patients with unknown diagnosis preoperatively.

Definitive Diagnosis	46% (n = 16)
Non-Hodgkin Lymphoma	
Diffuse Large B-cell Lymphoma	31% (n = 5)
Marginal Zone Lymphoma	25% (n = 4)
Mantle Cell Lymphoma	6% (n = 1)
Lymphoplasmacytic Lymphoma	6% (n = 1)
Total	69% (n = 11)
Other	
Hodgkin's Lymphoma	6% (n = 1)
T-cell Lymphoma	6% (n = 1)
Benign angioma	6% (n = 1)
Benign sclerosing angiomatoid nodule transformation	6% (n = 1)
NK cell lymphoproliferative disorder	6% (n = 1)
Total	31% (n = 5)
Normal tissue, congestion, extramedullary hematopoiesis	54% (n = 19)

hematopathology evaluation. Non-Hodgkin lymphoma (69%, n = 11) was most commonly identified, with diffuse large B-cell lymphoma and marginal zone lymphoma being the most frequently observed subtypes (Table 3).

Among the UD group, no obvious significant factors were found to be characteristic of the 46% of patients who received a diagnosis post-splenectomy. The preoperative workup, including blood work, biopsy and imaging were similar between those receiving a diagnosis and those whose splenectomy was ultimately non-diagnostic despite thorough pathologic review (Table 4). Analysis of preoperative factors which may predict a diagnosis other than benign after diagnostic splenectomy was statistically underpowered and therefore no p-values are reported.

In 12% (n = 4) of patients undergoing splenectomy for HM, there was discordance between the initial diagnosis and final pathology. Two patients diagnosed with myelofibrosis demonstrated myeloid tumor. One patient with myelofibrosis was also found to have diffuse large B-cell lymphoma. Another patient diagnosed with chronic lymphocytic leukemia (CLL) prior to splenectomy was found to have evidence of CLL in splenic lymph nodes in addition to a newly diagnosed diffuse large B-cell lymphoma in the spleen. Specimens from six patients receiving preoperative chemotherapy followed by splenectomy demonstrated either complete pathological response or no evidence of splenic involvement. Preoperative diagnosis in these six patients included Hodgkin's lymphoma, marginal zone lymphoma, Castleman's disease of the spleen, diffuse large B-cell lymphoma, hairy cell leukemia, and CLL.

Therapeutic benefit and surgical outcomes

Of all patients analyzed, 56% underwent a change in their medical management immediately after splenectomy. The majority of UD (56%) and ITP (68%) patients and a minority of HM (43%) patients were either able to discontinue medical therapy or received a more targeted therapy based on hematopathologic reporting (p = 0.14). Treatment alterations made more than six months after splenectomy were not considered to be a direct result of the information received from surgery.

Table 4
Characteristics of Unknown Diagnosis Group: Diagnostic vs. Non-Diagnostic.

Preoperative Work-up	Diagnostic n = 16	Non-Diagnostic n = 19	Total n = 35
Cytopenia	11 (69%)	16 (84%)	27 (77%)
Splenomegaly	8 (50%)	12 (63%)	20 (57%)
B-symptoms	8 (50%)	4 (21%)	12 (34%)
Bone Marrow Biopsy			
No	4 (25%)	1 (5%)	5 (14%)
Yes, non-diagnostic	12 (75%)	18 (95%)	30 (86%)
Lymph Node Biopsy			
No	14 (88%)	15 (79%)	29 (83%)
Yes, non-diagnostic	2 (12%)	4 (21%)	6 (17%)
Peripheral Smear			
No	9 (56%)	8 (42%)	17 (49%)
Yes, non-diagnostic	7 (44%)	11 (58%)	18 (51%)
Imaging			
Splenic uptake on PET	5 (31%)	3 (15%)	8 (23%)
Splenomegaly on CT or MRI	11 (69%)	13 (68%)	24 (68%)
Negative PET	0 (0%)	2 (11%)	2 (6%)
Negative CT	0 (0%)	1 (5%)	1 (3%)

For the UD patients who had a change in management post-operatively, the most common change was initiation of chemotherapy in 9 of 19 (47%), followed by cessation of immunosuppression in 6 of 19 (32%), de-escalation of therapy in 2 of 19 (11%), initiation of phlebotomy in 1 (5%) and empiric immunosuppression for hemophagocytic lymphohistiocytosis in 1 (5%). The most common change in management for HM patients was cessation of medication in 7 of 13 (54%), followed by initiation of chemotherapy in 3 of 13 (23%), autologous stem cell transplantation in 2 of 13 (15%) and a change in chemotherapy in 1 of 13 (7%). In patients with ITP, 23 of 25 (92%) stopped all immunosuppression and/or IVIG treatment and 2 of 25 had changes in medications neither escalation nor de-escalation.

A majority (55%) of HM patients reported improvement of at least one symptom of cytopenia, B-symptoms or splenomegaly by six months post-splenectomy and 42% (n = 14) experienced relief of all symptoms in the same time period. The symptom most likely to resolve for HM patients undergoing splenectomy was B-symptoms. Of patients with B-symptoms preoperatively, 55% experienced relief by 6 months postoperatively. Of HM patients with preoperative cytopenias, 50% corrected postoperatively. 32% of HM patients experienced relief from splenomegaly or mass effect symptoms.

All UD patients had at least one symptom of cytopenia, splenomegaly or B-symptoms preoperatively. By six months post-operatively, 54% of patients had relief of all symptoms and 46% of patients reported at least one residual symptom. Overall, cytopenias persisted postoperatively in 37%, splenomegaly-related symptoms in 20%, B-symptoms in 6% and splenic mass related symptoms in 9% (Fig. 1).

Of UD patients who received a definitive diagnosis after splenectomy, 69% (n = 11) had relief of all symptoms, compared to 47% (n = 9) for patients who did not receive definitive diagnosis after surgery. Diagnostic splenectomy patients experienced more frequent reductions in individual symptoms than non-diagnostic (benign) patients: cytopenias 64% vs. 44%; splenomegaly 75% vs. 46%; and B-symptoms 88% vs.75% (Fig. 2).

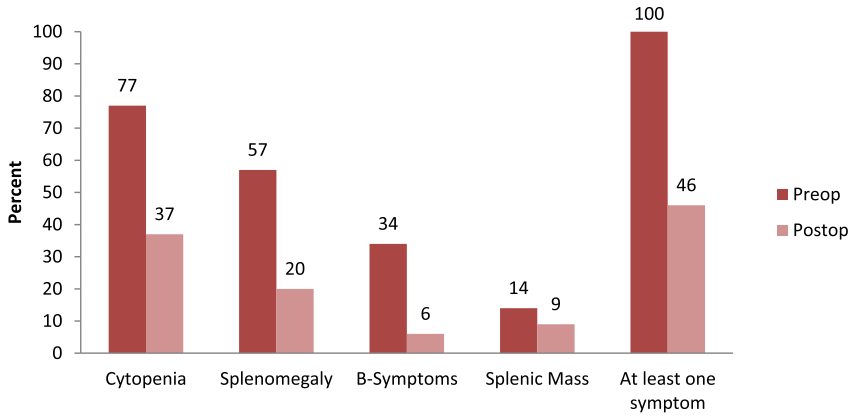

Fig. 1. Percent of patients with symptoms pre- and post-operatively following splenectomy for an unknown diagnosis. All symptoms decreased following splenectomy with a majority of patients experiencing relief of at least one symptom.

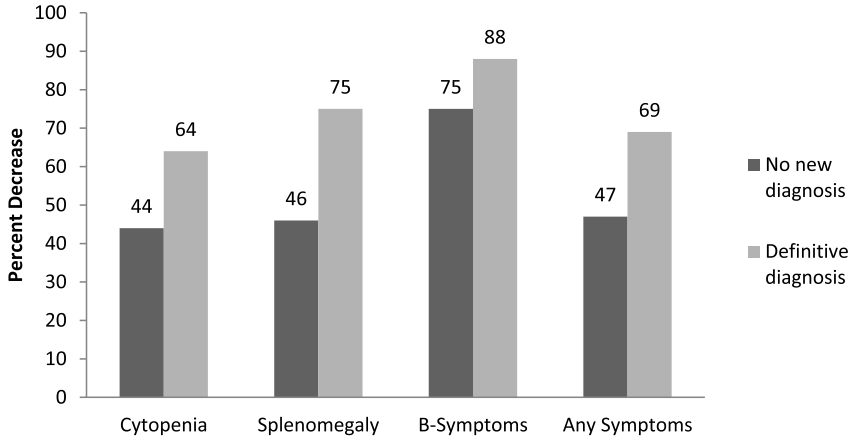

Fig. 2. Percent decrease in symptoms following splenectomy for patients with a definitive diagnosis and those with no new diagnosis. Patients who received a definitive diagnosis after surgery experienced more improvement in symptoms on average than those with no new diagnosis.

Post-operative complications and outcomes were similar among the groups, with the exception of a shorter length of stay in the ITP group. No significant differences were found among the groups for the placement of drains at first operation, pancreatic leak, reoperation, need for percutaneous drain placement, venous thromboembolism, surgical site infection, pneumonia, OPSI, and 30-day readmission (Table 5).

Median follow-up length was 24 months (range 3-58 months) for ITP, 38 months (range 6-60 months) for HM, and 26 months (range 8-54 months) for UD ($p = 0.81$). HM patients experienced significantly lower overall survival of 51% compared to 80% for both ITP and UD patients ($p = 0.008$). However, 30-day mortality was not different among the groups with rates of 6% for HM, 2% for ITP and 3% for UD ($p = 0.64$). 30-day readmission was also not significantly different among the groups (Table 5).

Table 5
Surgical outcomes following splenectomy.

	UD	HM	ITP	Total	p-value
Length of Stay in days, mean (SD)	6 (5)	6 (4)	3 (2)	4 (4%)	**<0.001**
Postoperative blood transfusion	11 (32%)	13 (40%)	7 (16%)	31 (27%)	0.05
Ileus	9 (26%)	11 (33%)	6 (13%)	26 (23%)	0.11
Drain placed at first operation	4 (11%)	6 (18%)	3 (7%)	13 (12%)	0.29
Pancreatic leak	1 (3%)	2 (6%)	0 (0%)	3 (3%)	0.26
Reoperation or percutaneous drain placement	1 (3%)	4 (12%)	1 (2%)	6 (5%)	0.12
Venous thromboembolism	0 (0%)	2 (6%)	1 (2%)	3 (3%)	0.29
Surgical site infection	1 (3%)	0 (0%)	0 (0%)	1 (1%)	0.32
Pneumonia	0 (0%)	3 (9%)	4 (9%)	7 (6%)	0.19
OPSI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
30-day all-cause mortality	1 (3%)	2 (6%)	1 (2%)	4 (4%)	0.64
30-day readmission	8 (23%)	9 (27%)	4 (9%)	21 (19%)	0.09
All-cause mortality	7 (20%)	17 (49%)	9 (20%)	33 (29%)	**0.008**
Follow-up time in months, median (IQR)	26 (46)	38 (54)	24 (55)	26 (52)	0.81

UD = unknown diagnosis group, HM = hematologic malignancy group, ITP = idiopathic thrombocytopenia group.

Discussion

Splenectomy is a well-established treatment for a few benign and malignant diseases. However, for patients without a definitive diagnosis at the time of surgery, the role of the diagnostic splenectomy is less clear. At our institution, the diagnostic ability of splenectomy was 46% when the diagnosis was unknown preoperatively. This rate is similar to other studies in the literature examining idiopathic splenomegaly.[6–8] Our study differs from those previously reported in that we included patients undergoing splenectomy for cytopenias and B-symptoms as well as those with symptoms or signs of splenomegaly preoperatively. Non-Hodgkin's lymphoma was the most likely new diagnosis in UD patients and their medical management was tailored accordingly, thereby making splenectomy an effective diagnostic test. Even when a diagnosis was known prior to surgery, as in the HM group, a small percentage of these highly selected patients received additional or new diagnoses. Again, the information garnered from this procedure resulted in changes to or discontinuation of medical management in over 40% of the HM group.

Since splenectomy will provide a diagnosis in approximately half of UD patients, it is helpful to investigate if the procedure provides any additional benefit or harm. One noted benefit is reduction in symptoms. A majority of patients in both the UD and HM groups experienced a decrease in symptoms postoperatively. Additionally, over half of UD patients were symptom free within six months post-splenectomy. Despite a longer length of stay in the UD and HM groups, there were no differences in adverse outcomes inherent to the operation. These longer lengths of stay are likely due to the higher rate of open splenectomies compared to the frequently used laparoscopic approach for ITP splenectomies. This trend is similar in other studies comparing laparoscopic and open approaches.[5,9] HM patients had lower overall survival rates, which can be explained due to the malignant disease in this group. Among the three groups, there were no significant differences in complications and therefore, splenectomy performed for diagnostic purposes or other hematologic indications other than ITP is still a safe procedure.

This study is limited by its retrospective nature. It is also an analysis of a single institution and small sample sizes reduced the power to detect significant effects in some sub-groups. As a large tertiary referral center, a potential exists for selection bias as more complex or unusual cases can be referred to our hospital. Larger studies would make these findings more robust.

Conclusions

For patients presenting with hematologic signs or symptoms, full workup with imaging, biopsies and blood cytology is still recommended. In select cases with equivocal findings, proceeding with splenectomy may provide a diagnosis in approximately 50% of patients, may alleviate symptoms or cytopenias in a majority of patients, and is not associated with increased adverse outcomes.

Conflicts of interest

The authors of the submission “The diagnostic value of splenectomy in patients without a definitive preoperative diagnosis” (Patrick T. Hangge, William W. Sheaffer, Matthew Neville, Nabil Wasif, Richard J. Gray, Barbara A. Pockaj, and Chee-Chee H. Stucky) have no financial or personal relationships with people or organizations that could inappropriately influence this work.

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