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Complications of Splenectomy

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ABSTRACT

Surgical removal of the spleen, splenectomy, is a procedure that has significantly decreased in frequency as our understanding of the infectious complications of the asplenic state increased. The full spectrum and details of splenic function, however, have yet to be fully outlined. As a result, our comprehension of the long-term consequences of splenectomy remains incomplete. We review the evidence relating to the effects of splenectomy on infection, malignancy, thrombosis, and transplantation. Perhaps the best-defined and most widely understood complication of splenectomy is the asplenic patient's susceptibility to infection. In response to this concern, novel techniques have emerged to attempt to preserve splenic function in those patients for whom surgical therapy of the spleen is necessary. The efficacy of these techniques in preserving splenic function and staving off the complications associated with splenectomy is also reviewed in this article.
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The spleen is well known to be the largest lymphoid organ in the body. Unlike the lymph nodes, however, the spleen does not receive drainage from the lymphatic system but is rather connected to the systemic circulation. The spleen's functions are many, but they are generally in 1 of 4 categories: filtration, immunologic, reservoir, and hematopoietic functions. In terms of immunologic function, the spleen is only one of many organs, such as lymph nodes and liver, that provide immune protection to the body. Many of the spleen's immunologic functions, therefore, are in common with these other immunologic organs. On the other hand, several immunologic roles are uniquely exercised by the spleen. For example, the spleen is more efficient at removing non-opsonized bacteria, mostly encapsulated organisms, than is the liver.[1] It is the main site of immunoglobulin-M antibody synthesis. Serum immunoglobulin-M levels have been shown to decrease significantly after splenectomy.[2] The spleen is also the main site of the opsonins tuftsin and properdin synthesis.[3] Serum tuftsin levels have been shown to decrease after splenectomy,[4] and tuftsin deficiency may precede overt hyposplenism in conditions leading to functional asplenia.[5] It is this specificity in splenic function, along with the lack of ability of other organs to compensate, that renders the asplenic state ripe with immunologic sequelae.

Splenectomy is frequently preformed for a multitude of reasons, including trauma and various pathologic processes. Blunt abdominal trauma remains the most common indication for splenectomy, but patients with a variety of hematologic disorders also benefit from this procedure. In addition, splenectomy also is performed in cases of iatrogenic injury and involvement by adjacent pathologic processes, for diagnostic purposes, and for relief of hypersplenism or splenomegaly. Although some of the infectious complications are well known, efforts have mounted in clarifying other consequences of asplenia. Such consequences may include effects on malignancy, transplantation, and thrombosis. Awareness of the infectious sequelae of splenectomy has increased the emphasis on nonoperative management of splenic injuries. In addition, a multitude of techniques to preserve splenic function, especially in children, have surfaced in cases in which splenic trauma/pathology cannot be safely observed. Examples of such techniques include splenic repair, partial splenectomy, partial splenic angioembolization, and splenic autotransplantation. The exact efficacy of such efforts in staving off the complications associated with total splenectomy has generated controversy. In this review, we examine the consequences of splenectomy as they relate to 4 key areas: infection, cancer, thrombosis, and transplantation. We also examine the evidence concerning the role of spleen-preserving procedures in mitigating those complications.

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INFECTION

Asplenia has been known to predispose one to infection.[6] A particularly significant and specific infectious complication of splenectomy is overwhelming postsplenectomy infection.[7] This is caused by encapsulated organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Hemophilus influenzae* type B. This condition, which occurs at an annual frequency rate of 0.5% in patients postsplenectomy,[8] is associated with a 50% mortality rate.[7] The risk of overwhelming postsplenectomy infection increases with younger age at the time of splenectomy and reduced time interval from splenectomy.[8] Although the risk is highest in the first 2 years after splenectomy, patients are thought to harbor a lifelong, albeit undefined, risk of developing the condition. Several methods have been shown to be effective in preventing overwhelming postsplenectomy infection in patients postsplenectomy. Such methods include patient education, prophylactic antibiotics, and vaccination against encapsulated bacteria. Multiple reviews, however, have documented that the implementation of such methods has been widely variable and generally suboptimal.[9] Also, the optimal duration of antibiotic prophylaxis in patients postsplenectomy has yet to be determined. Thus, overwhelming postsplenectomy infection remains a menacing problem in the asplenic patient.

In addition to encapsulated organisms, the asplenic patient is at an increased risk for the development of other types of infections. Gram-negative organisms, *Capnocytophaga canimorsus,* and intraerythrocytic parasites, such as *Babesia microti* and *Plasmodia falciparum,* have all been implicated as presenting a higher risk than average in splenectomized patients.[10] The risk of infectious complications is the most widely understood among the features defining the unique postsplenectomy state.

CLINICAL SIGNIFICANCE

- The major impact of splenectomy/asplenia relates to issues in 1 of 4 categories: infection, malignancy, thrombosis, and transplantation.
- Infectious and thrombotic complications of the postsplenectomy state are well documented and deserve special perioperative management and discussion with the patient.
- The ideal perioperative management of infectious and thrombotic complications of splenectomy needs further clarification with ongoing and future studies.
- Evidence regarding the effects of splenectomy on malignancy and transplantation remains inconclusive and not well studied.

MALIGNANCY

The question of whether asplenia predisposes one to increased cancer growth or recurrence has been the subject of considerable investigation. Numerous experimental studies in animals have examined the role of splenectomy on tumor growth and progression. Generally these studies have provided support for some role of splenectomy in carcinogenesis. Many of these studies have affirmed a time-sensitive effect of splenectomy on tumor growth but have yielded conflicting results on the exact nature of this effect. Some have demonstrated accelerated tumor growth when splenectomy is performed late after tumor transplantation and retarded growth when it is performed before or early after tumor transplantation.[11] One study found that splenectomy performed early after the development of melanoma in mice reduced tumor growth and increased mouse survival, but when performed long before melanoma development it had no effect.[12] Another study found that a small amount of tumor cells relative to spleen cells stimulated tumor growth, whereas a large amount of tumor cells relative to spleen cells inhibited tumor growth.[13] Other studies performed on rats with mammary tumors revealed that splenectomy inhibits malignant degeneration of benign tumors but does not retard established carcinogenesis.[14] Firm conclusions based on these animal studies remain elusive given the different methodologies, animal subjects, and tumors studied. In addition, the extrapolation of these findings to human subjects remains problematic.

Few clinical studies on humans have examined the effect of splenectomy on carcinogenesis. A study from Denmark followed a cohort of 6315 patients who had undergone splenectomy for a variety of reasons.[15] With a mean follow-up of 6.8 years, no increase in cancer risk was detected among the patients who had a splenectomy performed for trauma. Among patients who had a splenectomy performed for nontraumatic causes, however, a 2-fold increase in cancer risk was noted. This striking result should be interpreted with caution because it may be confounded by the carcinogenicity of the underlying condition, prior chemotherapy or radiotherapy, and patient factors such as age and smoking. A Swedish study that followed 2280 patients for an average of 11.8 years revealed no increased risk of cancer among patients splenectomized for trauma.[16] This study did show a nonsignificant increase in cancer risk for patients who had an incidental splenectomy performed for nonmalignant conditions. As in the case of postsplenectomy infection, the risk of cancer was found to be higher in younger patients. An older study of 740 American veterans who underwent splenectomy after trauma also showed no increased risk of cancer.[17] On the other hand, splenectomy performed as part of a staging procedure for Hodgkin's disease was linked to a higher risk of breast cancer and leukemia.[18] One can conclude from the evidence thus far that splenectomy for trauma does not seem to increase the risk of cancer, whereas splenectomy for other reasons may or may not increase that

risk. The relationship between splenectomy and carcinogenesis needs to be further examined by better-designed, larger-sample trials.

So far, we have discussed the effects of splenectomy on carcinogenesis in general terms. The risk pertaining to specific cancer types has also been studied, but the results have been disparate. With regard to gastric cancer, for example, many studies have examined the effect of splenectomy on patient outcomes.[19-21] Although these studies found increased perioperative morbidity and mortality, effects on tumor recurrence and survival have not been clearly defined. Also, these studies assessed concomitant rather than previous splenectomy in terms of gastric cancer outcome. Thus, the confounding effects of a more locally advanced tumor, increased operative time, and increased blood loss may hinder the utility of such studies. With regard to pancreatic cancer, one study found a decreased disease-specific and overall survival in patients who underwent concomitant splenectomy during their cancer operation.[22] Again, the conclusions one can draw from this study should be guarded; the small number of patients who underwent concomitant splenectomy in this cohort were also more likely to require portal vein resection and a total rather than partial pancreatectomy, and have increased blood loss and transfusions. The performance of a splenectomy in this patient cohort may merely represent a marker of advanced tumor (with poorer patient outlook) rather than any independent effect. A study that examined the effect of previous or concomitant splenectomy in patients with colon cancer found it to be associated with a significant decrease in 5-year survival, but only in patients with stage C cancer.[23] Studies have also examined the effect of incidental splenectomy in esophageal cancer cases. They demonstrated that it results in increased blood loss, but an effect on long-term survival has not been determined.[24]

Not all evidence points to a role of splenectomy in carcinogenesis. For example, the presence of hyposplenism in celiac disease, reported in 16% to 77% of patients, does not increase the risk of gut lymphoma,[25] a well-known complication of celiac disease. In short, the role of splenectomy in carcinogenesis in humans remains largely undefined despite numerous investigations. Moreover, the mechanisms by which the spleen, or lack thereof, may influence tumor development or growth are yet to be elucidated.

TRANSPLANTATION

The effect that splenectomy may, or may not, have on transplant rejection or success has also been examined. Chosa et al[26] demonstrated that the spleen plays a significant role in inducing tolerance to allografts. Further animal studies have shown a delay in xenograft rejection when pretransplant splenectomy is performed.[27,28] Xu et al[29] found that pretransplant splenectomy combined with immunosuppression delayed humoral rejection of pig xenografts in neonatal goats. Studies in human subjects have been scarce and less convincing. A study of renal transplant recipients showed improved initial but not long-term graft survival and no difference in overall survival between splenectomized and nonsplenectomized patients.[30] A recent small case series reported a dramatic effect of urgent splenectomy on salvaging renal transplants that were undergoing acute rejection.[31] Hematopoietic stem cell transplantation is a therapy that is used to treat patients with various hematologic diseases, such as multiple myeloma and lymphoma. Patients with preexisting hypersplenism, often related to their underlying disease, experience diminished engraftment. These patients show improved engraftment when a splenectomy is performed before transplantation.[32] Similar to total splenectomy, partial splenectomy has also been found to improve the rate of hematopoietic stem cell transplantation success.[33] This study also provided indirect evidence for the efficacy of partial splenectomy in relieving hypersplenism.

Although some evidence, particularly from animal experiments, suggests that splenectomy may improve the success of transplantation, convincing evidence of significant benefit in humans is still lacking. The exception to this is cases of preexisting hypersplenism that is adversely affecting engraftment. The subject needs to be studied in greater length and detail before any conclusions can be made.

THROMBOSIS

Portal vein thrombosis is a well-recognized complication of splenectomy. Increases in accuracy and frequency of imaging studies have led to an increase in the detection of portal vein thrombosis.[34-36] Prospective studies of open splenectomy have documented a 4.7% to 6.6% rate of postsplenectomy portal vein thrombosis.[37] Variability among studies with regard to the underlying disease, timing of follow-up, and imaging used for detection has made firm conclusions on the causes and incidence of this complication difficult. Furthermore, the clinical significance of postsplenectomy thrombosis (in terms of rate of progression to symptoms and serious sequelae) has not been defined. This is because many studies have only reported cases of portal vein thrombosis that were symptomatic. One series examining this issue found that 50% of cases of portal vein thrombosis were asymptomatic.[38]

Evidence supports the notion that the risk of postoperative portal vein thrombosis depends on the underlying condition for which the splenectomy is being performed. Patients with myeloproliferative disorders have been found to sustain higher rates of postsplenectomy portal vein thrombosis than others.[39] Another compounding factor is that many patients presumed to be undergoing a splenectomy for nonhematologic disease are ultimately found to have a systemic thrombotic disorder.[40,41] Indeed, one study found a 50% rate of other thrombotic disease (eg, deep vein thrombosis and stroke) among patients with portal vein thrombosis postsplenectomy.[42] No clear association between thrombocytosis, a frequent consequence of splenectomy, and portal vein thrombosis has been found.[41] Splenomegaly has

also been cited as a risk factor for postsplenectomy portal vein thrombosis.[40] The risk of postoperative portal vein thrombosis has been found to be higher with laparoscopic splenectomy compared with open splenectomy.[45]

Optimal treatment for portal vein thrombosis (in terms of type, duration, and dosage of anticoagulation) has not been established. In addition, optimal prophylaxis against portal vein thrombosis in patients undergoing splenectomy is not yet known. Current evidence suggests that postoperative low molecular weight heparin alone is insufficient for this purpose.[39-41] A combination of postoperative heparin, possibly warfarin, and antiplatelet agents may prove more efficacious but has not been validated.

SPLEEN-PRESERVING TECHNIQUES

Recent studies have shown partial splenectomy to be protective against severe postoperative infections compared with total splenectomy.[42] No studies have rigorously examined the effects of partial splenectomy on malignancy, thrombosis, or transplantation. Splenic angioembolization is another spleen-preserving technique that has gained widespread acceptance for specified circumstances. Although it seems logical to assume that this method, especially *partial* embolization, preserves splenic function, the long-term immunologic consequences have not been documented.

Splenic autotransplantation in patients in whom total splenectomy is necessary has also been advocated as a means to conserve splenic function. Some studies on immunologic function after total splenectomy and splenic autotransplantation in rats have pointed to a loss of immunologic function.[43-48] Other studies, however, have demonstrated retained immunologic function to some degree.[49,50] For example, Miko et al demonstrated improved erythrocyte deformability and T-cell, immunoglobulin-M, and lymphocyte counts with splenic autotransplantation in splenectomized mice.[50] Another study found that the residual immune splenic function was proportional to the amount of splenic tissue that was successfully autotransplanted.[51] The long-term immunologic outcome in humans is still under study; currently it is recommended that these patients be treated with standard splenectomy precautions, including vaccination, prophylactic antibiotics, and patient education. Studies agree that autotransplanted subjects do not exhibit the postoperative thrombocytosis or leukocytosis characteristic of splenectomized subjects.

Splenosis is a frequent occurrence after trauma and has been shown to lead to some retention of splenic function. Case reports of absence of Howell-Jolly and Heinz bodies and siderocytosis in cases of documented splenosis after splenectomy are present in the literature. Other case reports of splenosis have documented recurrence of immune thrombocytopenic purpura and Felty's syndrome years after splenectomy.[52-54] It is not known whether splenosis leads to adequate long-term immunologic splenic function or whether the degree and pattern of splenosis or mode (ie, after trauma vs surgery) affect subsequent splenic function.

CONCLUSIONS

The risks of postoperative infection and thrombosis after splenectomy are now widely accepted among medical professionals. In contrast, the effects of splenectomy on malignancy and transplantation have been less well characterized and require further study. The role of alternatives to total splenectomy (that aim to maintain splenic function), such as partial splenectomy and splenic autotransplantation, in postsplenectomy complications are not yet known. Our knowledge of the consequences of the asplenic state is still in its infancy and will be the subject of ongoing investigations for many years to come.

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