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The spleen: Neglected but essential - Section 1

The spleen in immune thrombocytopenia

Julia T. Geyer,[1] James B. Bussel[2]

[1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY; [2]Department of Pediatrics, Division of Hematology/Oncology, Weill Cornell Medicine, New York, NY, USA

Take Home Messages

- Splenectomy is the only unequivocal curative treatment of Immune Thrombocytopenic Purpura.
- The unique anatomic configuration of blood flow and macrophages in the spleen allows the spleen to be the primary organ of immune response to blood borne antigens.
- Prediction of response to splenectomy by splenic sequestration studies is neither unequivocally established nor routinely available.

In Immune Thrombocytopenic Purpura (ITP), the spleen is as critical as the bone marrow[1] to understand the pathogenesis and clinical course of the disease. Many years ago, studies demonstrated that the spleen is the major place for platelet destruction and a very important site where antiplatelet antibodies are made.[2] Since then, advancements have been limited in understanding the role of the spleen in ITP. This review will consider serologic and anatomic considerations of the spleen and analyze response to splenectomy. Exposition of the anatomical features of the spleen will consider both the anatomy of blood flow through the spleen as well as its relationship to the creation and perpetuation of antiplatelet antibodies synthesized by the spleen[3]. Under serology, we will consider platelet antibodies and complement. Finally, we will analyze the benefits and risks of splenectomy in ITP including adverse events related to this option (described in Table 1).

Primary ITP is an autoimmune disorder in which platelet destruction is a consequence of both B- and T-cell dysregulation.[4,5] The spleen is a major site of platelet destruction and production of autoantibodies in ITP.[2] Autoantibodies not only accelerate platelet destruction but also impair platelet production by megakaryocytes in bone marrow.[1] Autoreactive antibodies bind to platelets, which are then sequestered by splenic macrophages primarily *via* Fc receptors. Antibody production in ITP is driven by CD4-positive helper T-cells reacting to platelet surface glycoproteins available via phagocytosis in the spleen; CD40:CD40L co-stimulation is likely important.[6] The $CD4^+$ cells correspond to T follicular helper cells which are expanded within ITP spleens.[7] IgG and/or IgM reactive to platelet glycoprotein complexes on platelets are found on platelets or in the plasma of many ITP patients.

It was originally thought that splenectomy was effective in ITP only by removing the site of platelet destruction. Splenectomy however is also responsible for "overwhelming post-splenectomy sepsis".[8] One study analyzed the distribution and phenotypic characteristics of B-cell subsets in non-splenectomized and splenectomized patients with ITP and demonstrated decreased frequencies of memory B cells in splenectomized individuals with a decline of $CD27^+IgD^+$ and $CD27^+IgD^-$ and $CD27^-/IgD^-$ cells.[9] Another study reported that the frequencies of circulating

Table 1. Adverse effects of splenectomy and remedies.

Overwhelming post splenectomy sepsis:[8] Minimization of this involves:

a) Vaccination to pneumococci (primarily conjugated vaccines), *Haemophilus influenzae* b, and the two meningococcal vaccines to cover the A, C, Y, W135 main meningococcal serotypes; liberal use of oral antibiotics, and an inviolate rule of immediate urgent administration of parenteral antibiotics if there is fever or chills. It is uncertain when and whether revaccination is required.

b) Complications of splenectomy: infections, bleeding and thromboembolic events with debate as to whether anticoagulation should be standard.

c) Long term consequences:
   a. Studies suggest an increased rate of pneumonia, meningitis, and septicemia as well as deep venous thrombosis and pulmonary embolism.
   b. Patients with hereditary spherocytosis have a high rate of pulmonary hypertension 10 years following splenectomy.
   c. Splenectomized patients have an increased risk of buccal, esophagus, liver, colon, pancreas, lung, and prostate carcinoma; and hematologic malignancies: lymphoma, multiple myeloma, acute and chronic myeloid leukemia.[15]

GPIIb/IIIa-reactive T- and B-cells were significantly decreased after splenectomy in complete responders but unchanged in non-responders, suggesting that GPIIb/IIIa-reactive T- and B-cell interactions that induce anti-platelet antibody production in patients with ITP occur primarily in the spleen.[4] Responders to splenectomy had predominantly normal distribution of VB TCR clonality whereas non-responders had increased oligo- and monoclonality.[10] This suggests that splenectomy can "cure" primarily antibody-mediated ITP but not cases with autoreactive T cells. The ITP spleen is usually mildly enlarged (weight <200g). The morphology in untreated ITP shows evidence of active antibody production with well-developed germinal centers. The red pulp shows histologic evidence of antibody-coated platelets within cordal macrophages. The number of splenic macrophages is increased and they have abundant foamy cytoplasm (Figure 1). Splenic macrophages are central to the maintenance of anti-platelet autoantibody production in ITP patients.[3] By virtue of the tortuous blood vessels in the spleen, the flow is slow, facilitating phagocytosis by adjoining macrophages. In turn, the phagocytosis leads to antibody production, normal and autoreactive.[3]

The clinical role of splenectomy in ITP starts in 1916 when a medical student named Kaznelson in Czechoslovakia "convinced" a surgeon to remove the spleen in a woman with ITP.[5] Apocryphal parts of this story may be:

1) why did Kaznelson think the spleen should be removed at all;
2) why a surgeon, a little more than 100 years ago, would actually listen to a medical student, and
3) why a surgeon would have to be "talked into" operating.

This splenectomy initiated the role of splenectomy in "idiopathic" thrombocytopenia. Subsequently splenectomy became a central feature of management of ITP and, through at least 1981, was one of only two frequently-used treatments of ITP. No medical therapies in use now, even prednisone, were available until at least the 1950's.

More recently, the use of splenectomy has declined substantially

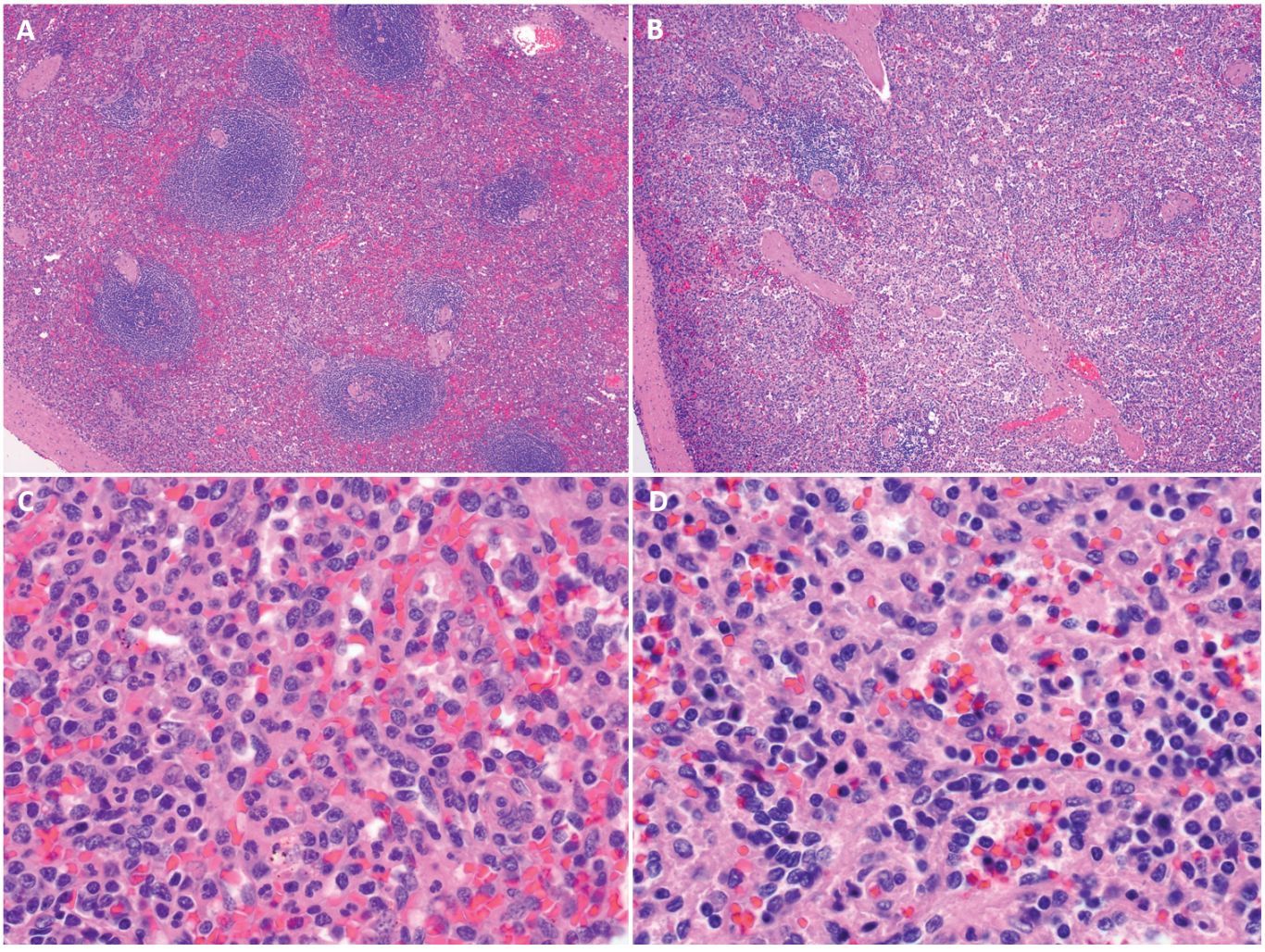

Figure 1. Histology of the spleen in ITP. A, C) Patient with no recent therapy for ITP. The white pulp is prominent with focal germinal centers and hyperplastic marginal zones (A, 4x magnification). The red pulp is cellular with presence of histiocytes, activated lymphocytes (immunoblasts) and neutrophils. Macrophages have evidence of intracytoplasmic phagocytosis (C, 40x magnification). This patient's ITP returned one year after splenectomy. B, D) Patient with refractory ITP on steroid and TPO agent therapy. The red pulp is markedly expanded and the white pulp is atrophic (B, 4x magnification). There is an increased number of cordal macrophages with evidence of phagocytosis of antibody coated platelets. Note the typical "dirty" appearance to the cords of Billroth with granular platelet debris both within macrophages and extracellularly (D, 40x magnification). This patient achieved durable remission following splenectomy.

over the last 20-30 years.[11] This is true in the United States and Europe, perhaps less so worldwide. Reasons for this decline are varied. The most obvious is the relatively large number of available treatments, in particular, thrombopoietic agents and rituximab. A second reason is that a fraction of adults with ITP will improve spontaneously, not as a rare phenomenon.[12] Hence the current (data-free) recommendation in adults is to wait for one year from onset of ITP to perform splenectomy. If a patient is doing adequately at that time with or without treatment but without important bleeding, decrement in quality of life, and side effects of treatment, then most patients would opt to continue even after 1 year. Third, the response to splenectomy is considered to be approximately 2/3 of all patients.[13] Given that there are now multiple options, patients are increasingly reluctant to undergo splenectomy when they know that one third of the time it will not work. Fourth there are newer findings on the long-term side effects of splenectomy that may outweigh the benefits, including the risk of infection, thromboembolism and predisposition to both solid tumors and hematopoietic malignancies.[14,15] Finally, with large patient groups in contact via the internet, splenectomy is frequently discouraged because patients who have undergone it and not had success are much more likely to remain involved than are patients in long-term remission.

A key is response to splenectomy overall. The data, summarized in 2004 by Kojouri,[13] is a 65% long-term response rate including all comers. However, this data was collected when splenectomies were performed in the first 6 months of ITP and most within the first 3 months of disease. Spontaneous remission occurs in up to 10% of adults with ITP and often occurs within the first 6 months, which means waiting longer prior to splenectomy may lessen the overall response rate. This assumes that the spontaneous improvers would respond to splenectomy. It is hypothesized that autoantibody-making B cells develop in the spleen; however, they may eventually migrate out of the spleen. This hypothesis would also explain why splenectomy later would not be as successful. There is a paradox: splenectomy earlier may work better but may not be needed in some patients who undergo it. Waiting longer may lessen the cure rate. Finally, patients in whom early splenectomy is needed are those who do not respond to upfront medical treatments. If a patient fails to have any significant degree of platelet increment while being treated with high dose steroids and IVIG, he/she is thought to have a substantially lower response rate with splenectomy.

This uncertainty in response (including the dilemma of not wanting splenectomy either early or late) drives trying to predict the outcome of splenectomy. If the likelihood of successful outcome was high e.g. 85-90%, patients would more likely accept it. The only well-established test, given debate in published reports, is splenic sequestration testing using autologous indium-labeled platelets.[16] It needs to be done at experienced centers who can perform the testing without damaging the platelets. The centers (London and Paris) that have performed the most sequestration testing appear to be successful at predicting response with this technique. It has been our recent practice to send patients seriously considering splenectomy to St. Bart's in London to undergo a splenic sequestration scan.

Another predictor had been previous response to therapies but this approach has not held up i.e. response to IVIG, response to steroids, response to IV anti-D. In the absence of data, only no response to any treatments may predict a negative outcome, as discussed above.

Another issue is some of the multiple causes of secondary ITP. If there is an ongoing infection, the ITP could improve substantially with successful treatment or self-resolution of that infection; therefore, the patient might not require splenectomy. The only substantial data is in HIV infection in which patients did respond to splenectomy but with some level of viral control. Other infectious agents involved are Hepatitis C Virus, Helicobacter pylori, and Cytomegalovirus (CMV). Another example is Evans syndrome, characterized by the association of ITP with autoimmune hemolytic anemia. In children, splenectomy is unlikely to be effective while mycophenolate mofetil and rapamycin, with rituximab backup, are effective in this poorly responsive condition. In adults, there may be a higher response to splenectomy.[17]

Studies of autoimmune hemolytic anemia in mice explored complement. Studies demonstrated that mice who had IgG alone on their red cells would have them cleared in the spleen; whereas, red cells targeted by IgM who then had complement bound to their red cells (since the IgM would have dissociated from the red cells) would not respond to splenectomy because their cells would be largely destroyed in the liver. Whether this translates to platelets and ITP in humans remains to be proven.

Overall, splenectomy remains an important option in ITP. If prediction of anticipated success (or of vulnerability to specific complications) was effective and readily available, it would greatly facilitate overall management of ITP. If the likelihood of spontaneous improvement could be determined, this would be very helpful as well. Similarly, better ability to predict response to other treatments would help to determine which patients might benefit the most from splenectomy. Prediction of risk for complications of splenectomy might help management as well. The first stage to likely lead to an improvement in prediction of general outcome of ITP might be whole exome sequencing but this would be just the first step.

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