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REVIEW

The role of splenectomy in autoimmune hematological disorders: Outdated or still worth considering?

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ABSTRACT

We discuss the role of splenectomy in the autoimmune hematological disorders immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) and thrombotic thrombocytopenic purpura (TTP). Management of these disorders has dramatically changed the past decade as increasing knowledge of the immunopathogenesis has led to the introduction of new therapies. Until 10 years ago, splenectomy was the established second-line treatment for ITP, considered when corticosteroids failed to induce a sustained response. Concurrently, novel treatments, including anti-CD20 antibodies (rituximab) and thrombopoietin receptor agonists are increasingly used. This has led to uncertainty as to when splenectomy is advisable as the next step. The lack of comparative studies of second-line treatment options further fuels this uncertainty. Splenectomy continues to provide the highest cure rate, but it is an invasive, irreversible treatment option with a downside of postoperative complications and a largely unpredictable outcome. Careful selection of patients, widespread adoption of a laparoscopic approach, perioperative thromboprophylaxis, and better approaches to prevent and mitigate sepsis have however reduced morbidity and mortality. As in ITP, splenectomy is considered the standard second-line treatment in warm AIHA as well, although its position is nowadays less robust as rituximab tends to reach approximately the same success rate in second-line treatment. The role of splenectomy in TTP has never been clarified. Although rituximab is forwarded as best second-line therapy in recent guidelines, there are some case series suggesting that splenectomy is a safe and effective option in refractory or relapsing disease as well.

1. Introduction

Immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) and thrombotic thrombocytopenic purpura (TTP) are well-defined, predominantly immune-mediated conditions with significant morbidity and mortality. Although first-line treatment induces a response in a substantial proportion of patients, refractory disease and relapse are frequently encountered. Splenectomy is a possible second-line treatment in each of these diseases, but its role has changed dramatically the past years, with the introduction of new promising therapies. Beside new therapeutic options, also the fear of important postoperative complications and the unpredictable response to splenectomy, have resulted in physicians tending to avoid or defer splenectomy, which is increasingly viewed as the last resort. This is evidenced by a decrease in the rate of splenectomy for ITP of 50–60% in older cohorts to 15–25% in more recent studies [1,2]. Nevertheless, the evolution of new therapies was accompanied by an evolution in the approach to splenectomy as well, with the adoption of laparoscopy instead of open surgery and new measures to reduce the thrombotic and infectious risk. We highlight new insights regarding the pathogenesis of ITP, TTP and AIHA, we explain novel treatment options and we investigate the present position of splenectomy in each of the three disorders while focusing on the durability of response. Finally, we discuss the current risks and preventable measures that should be undertaken.

2. Immune thrombocytopenia

2.1. Definition, classification and epidemiology

Immune thrombocytopenia is an acquired autoimmune disorder characterized by a peripheral blood platelet count $<100 \times 10^9$/l, without abnormalities in the erythroid and myeloid/lymphoid lineages [3]. ITP

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may be found in the absence of any obvious initiating or underlying cause and is then called *primary* ITP. If associated with other disorders, including autoimmune conditions (e.g. antiphospholipid antibody syndrome), infections (e.g. hepatitis C virus, HIV, H. pylori) and certain drugs, it is defined as *secondary* ITP. ITP can also be classified based on disease duration by the following definitions: *newly diagnosed* (from diagnosis until 3 months), *persistent* (3–12 months duration), and *chronic* (>12 months duration) [4]. The incidence of ITP in adults is estimated at approximately 2.2–3.9 per 10^5 persons per year [5,6].

2.2. Immunopathogenesis of ITP

ITP is a complex immune process in which cellular and humoral immunity are involved in the destruction of platelets as well as impaired platelet production. Several theories have emerged in the last decade to explain this autoimmune process. The main mechanisms are summarized in Fig. 1.

2.2.1. Role of B-cells

1.	IgG autoantibodies against GP IIb/IIIa and Ib/IX
2.	Elevated expression of BAFF and APRIL
3.	Impaired regulatory B-cells

In 1951, Harrington and Hollingsworth demonstrated that the passive transfer of plasma from ITP patients induced a transient thrombocytopenia in healthy recipients [7]. Further studies demonstrated the presence of platelet-reactive antibodies (Abs), mainly of the IgG1 subclass. The most commonly identified antigenic targets of these IgG autoantibodies are platelet glycoproteins (GP) IIb/IIIa and Ib/IX, with a number of ITP patients having antibodies directed to multiple platelet antigens [8].

There is no straightforward explanation as to why patients develop autoantibodies to several structurally unrelated platelet surface proteins. It has been theorized that proteosomal degradation of antibody-coated platelets in antigen presenting cells (APCs) may generate novel immunogenic epitopes from normal platelet proteins, leading to epitope spread. Alternative explanations, including somatic mutation of autoantibodies and crossreactivity to unrecognized sharing of structural motifs, have not been excluded [9].

Antibodies are only detectable in 40 to 50% of patients. This may be explained because brisk clearance of some types of antibody-platelet complexes may reduce circulating antibody titers to below the threshold of detection. Also tightly bound antiplatelet Abs may be difficult to dissociate for study. Secondly, there may be some undetected antigens, such as minor or cryptic antigens on platelets or antigens that reside primarily on megakaryocytes. Finally, there may simply be a subset of patients in which there are other mechanisms of platelet loss [10].

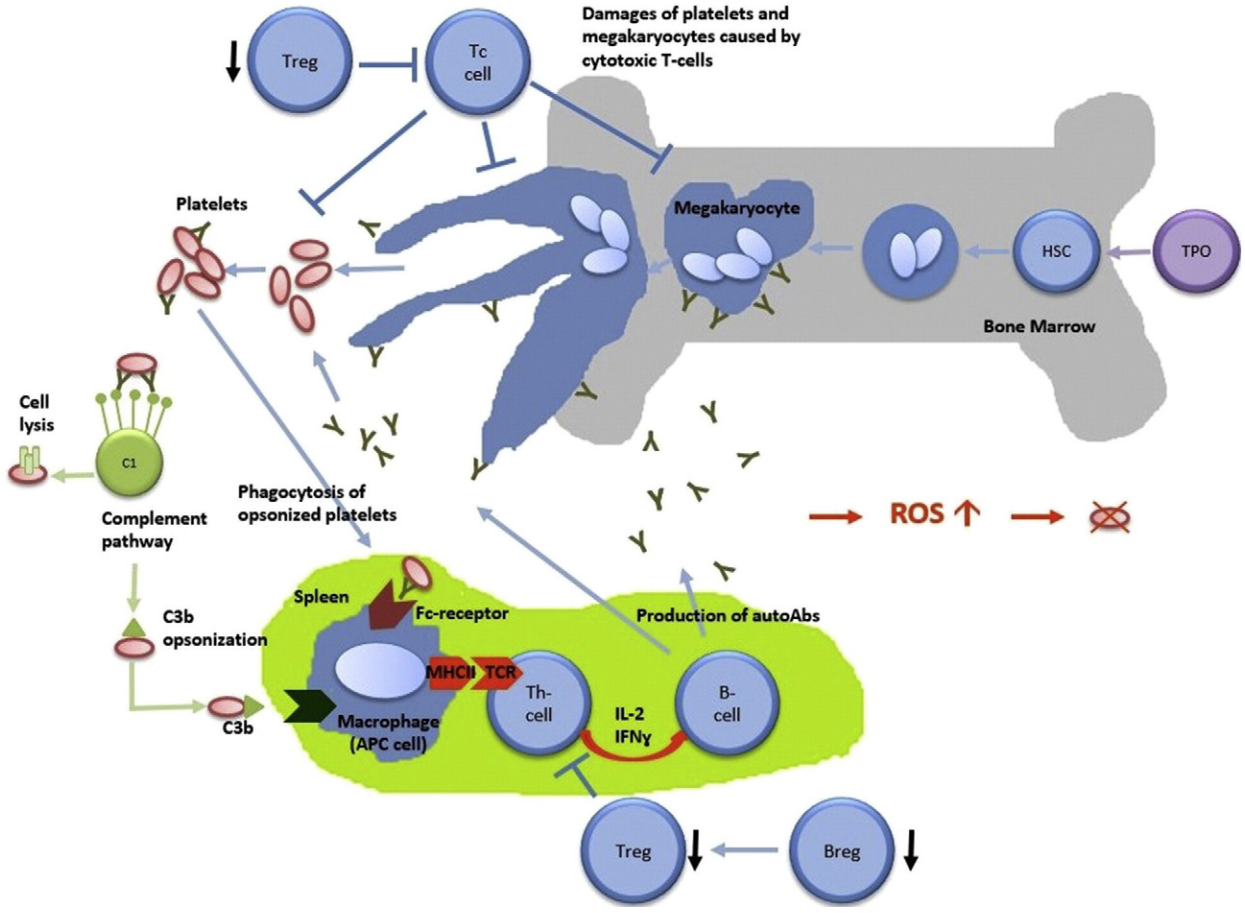

Fig. 1. Schematic representation of the pathophysiology of ITP. Platelets opsonized by autoantibodies are destroyed by macrophages in the spleen and peptide fragments expressed with MHC class II stimulate helper T-cells, that in turn activate autoreactive B-cells. Impaired regulatory T-cells (Tregs) fail to suppress this vicious cycle. Regulatory B-cells (Bregs), which induce the recruitment or differentiation of regulatory T-cells, are also impaired. Autoantibodies furthermore suppress megakaryocytopoiesis. Platelet autoantibodies may fix complement, enhancing opsonization or facilitating direct platelet lysis. They can also cause platelet destruction via induction reactive oxygen species (ROS). Autoreactive cytotoxic T-cells may play a role in the destruction of platelets and megakaryocytes. Finally, decreased levels of TPO (thromopoietin) impair an effective megakaryocytosis.
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