Hypersplenism: History and current status (Review)

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Abstract. Hypersplenism is a common disorder characterized by an enlarged spleen which causes rapid and premature destruction of blood cells. This review summarizes the history of hypersplenism, discuss its classification and pathogenesis, and examines its diagnosis and treatment options. We performed a comprehensive literature search using PubMed, Web of Knowledge and the China National Knowledge Infrastructure (CNKI) database, reviewed hypersplenism-related articles and summarized the major findings. According to its etiological causes, hypersplenism is characterized by splenomegaly and peripheral cytopenias. It can be classified into three categories: i) primary hypersplenism; ii) secondary hypersplenism; and iii) occult hypersplenism. A number of mechanisms causing hypersplenism have been identified, and mainly involve retention in the spleen, phagocytosis, and autoimmunity. Treatment options for hypersplenism include etiological treatment, non-surgical treatment, total splenectomy and liver transplantation. In any case, treatment should be individualized for each patient.

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1. Introduction

Hypersplenism refers to a group of syndromes that involve splenomegaly and peripheral cytopenia of various causes. Hypersplenism can be caused by many diseases which, in turn, affects the prognosis of hypersplenism. Thrombocytopenia may exacerbate liver fibrosis (1,2) and a severe decrease in platelet counts is a major risk factor of hypersplenism (3). Not surprisingly, the more severe the hypersplenism is, the worse is the prognosis (4). Current knowledge regarding hypersplenism is not sufficient, and relatively few studies have been reported. We herein performed a comprehensive literature search on PubMed, Web of Knowledge and the China National Knowledge Infrastructure (CNKI) database, and reviewed 60 hypersplenism-related articles published between 1954 and 2015. Major information and findings in this area were summarized.

2. History

The term 'hypersplenism' first appeared in the thesis of Anatole Chauffard in 1907 (5), and subsequently in the study of Morawitz and Denecked (6).

In 1955, Dameshek (7) summarized that hypersplenism should be diagnosed in the presence of four conditions: i) monolineage or mutilineage peripheral cytopenias; ii) compensatory hyperplasia of bone marrow; iii) splenomegaly; and iv) correction of cytopenias after splenectomy. Although these four conditions do not always apply to all cases, they have been commonly cited in the literature, and are important in the diagnosis of hypersplenism.

3. Classification of hypersplenism

Hypersplenism can be classified into three categories by its etiological causes as follows.

Primary hypersplenism. The cause is not clear. Examples are primary splenic hyperplasia, non-tropical idiopathic splenomegaly, primary splenic granulocytopenia, primary splenic pancytopenia, and splenic anemia or thrombocytopenia.

Secondary hypersplenism. The cause is clear. Examples include i) infections such as viral hepatitis, brucellosis,

subacute or chronic diseases (7), infectious mononucleosis syndrome and malaria; ii) alcohol use such as long-term or excessive drinking; iii) portal hypertension (PH), such as liver cirrhosis of various causes including post-hepatitic cirrhosis, alcoholic cirrhosis, and biliary cirrhosis, fatty liver cirrhosis, post-hepatitic autoimmune cirrhosis, schistosomiasis-induced cirrhosis, and drug-induced cirrhosis, as well as hemosiderosis and portal vein thrombosis; iv) granulomatous inflammation such as systemic lupus erythematosus, rheumatoid arthritis, chronic syphilis, chronic tuberculosis, Felty's syndrome, and sarcoidosis; v) malignancies such as splenic lymphosarcoma, leukemia, and cancer metastasis; vi) chronic hemolytic diseases such as hereditary spherocytosis, autoimmune hemolytic anemia, and thalassemia; vii) lipidosis such as Gaucher's disease, and Niemann-Pick disease; viii) myeloproliferative disorders such as polycythemia vera, chronic myeloid leukemia, and myelofibrosis; and ix) other diseases such as hemophagocytic syndrome (HPS), relatively benign hamartoma, splenic cyst, splenic artery aneurysm, and cavernous hemangioma. The most common hypersplenism is secondary to post-viral hepatitis cirrhotic PH.

Occult hypersplenism. In both primary and secondary hypersplenism, if the underlying disease is not serious, together with benign bone marrow hyperplasia and sufficient bone marrow compensation, peripheral cytopenias may not occur. In this case, hypersplenism becomes occult with no symptoms. However, once the bone marrow hematopoietic function is suppressed by factors such as infection or drugs, monolineage or mutilineage peripheral cytopenia occurs, accompanied by clinical symptoms, which is not classified as occult hypersplenism.

4. Pathogenesis of hypersplenism

Although the exact pathogenesis of hypersplenism-induced peripheral cytopenias is still inconclusive, several mechanisms have been identified (8).

Retention in the spleen. In patients with PH, the spleen can increase 8-10 times its normal size (9). Splenic blood volume increases due to the increased venous pressure leading to congestive splenomegaly, or because of the increased splenic arterial blood flow induced by a variety of diseases, resulting in hyperemic splenomegaly. As a consequence, there is retention of a large number of leukocytes, erythrocytes and platelets in the spleen. The number of retained blood cells can be 5.5-20 times higher than the normal level, thus facilitating capture, phagocytosis or destruction of blood cells by phagocytes resulting in peripheral cytopenias.

In 1965, Aster (10) found by using ^{51}Cr-labeled platelets that under normal circumstances, approximately one-third of platelets are stored in the spleen, and the remaining two-thirds in the blood circulation. In hypersplenism, 50-90% of platelets are retained in the enlarged spleen resulting in a reduction of platelets in the circulating blood. Furthermore, Aster demonstrated that the distribution of platelets returned to normal after splenectomy, which eliminated the retention of platelets by the splenic blood pool (8). The Wiskott-Aldrich syndrome protein (WASP) is an essential cytoskeleton regulator found in the cells of the hematopoietic lineage that control the motility of leukocytes. The impact of WASP gene deficiency on mobilization of hematopoietic progenitor/stem cells in circulation remains unknown, but previous research has indicated a correlation in the context of autologous gene therapy of Wiskott-Aldrich syndrome. In one study using a murine WASP-knockout model, Charrier *et al* found the occurrence of B-cell lymphopenia, marked neutrophilia, increased counts of circulating hematopoietic progenitor cells, and splenomegaly in WASP-knockout mice in the steady state, all of which were presumably caused by retention of hematopoietic progenitor cells due to high levels of splenic CXCL12 (11).

Phagocytosis. Phagocytes are categorized as mononuclear phagocytes (including macrophages, monocytes, and immature monocytes), and neutrophils. Macrophages (MΦs) have a strong ability for immune phagocytosis, and are the major form of phagocytes in the spleen.

Enhanced MΦ phagocytosis. Li *et al* suggested that in patients with PH, MΦs are overactivated with significantly increased phagocytosis, cytokine secretion, antigen processing and presentation (12). Excessive activation of MΦs is an important cause of hypersplenism. Significantly increased counts of MΦs in the spleen and their enhanced phagocytosis have been reported in patients with PH (13). The number of erythrocytes and platelets phagocytosed was also significantly increased. These findings indicated that MΦs are involved in hypersplenism.

In the measurement of splenic size by ultrasonography and radionuclide studies, Shah *et al* (9) demonstrated that splenic phagocytic activity in cirrhosis increased as the spleen enlarged, which contributed to anemia and leukopenia.

Jiang *et al* (14) found a high expression of miR-615-3p in splenic MΦs in hypersplenism by microarray, and demonstrated its role in enhancing the phagocytic capacity of splenic MΦs. Significantly increased mRNA expression levels of toll-like receptors 2 and 4 in splenic MΦs were detected in patients with hypersplenism due to PH, consistent with the protein levels measured by immunohistochemistry. This finding further supports the possible mechanism of 'endotoxemia → activation of toll-like receptor of splenic MΦs → increased destruction of blood cells by macrophages' in hypersplenism due to PH. Cytopenia in hypersplenism may be caused by other factors in addition to excessive destruction of blood cells by MΦs.

Upregulation of cytokines. Cytokines are proteins or small-molecule peptides secreted mainly by immune cells that can regulate cell functions and are involved in inflammation, immune responses, and wound healing.

In comparing the spleen in hypersplenism due to PH with a normal spleen, Ma *et al* (15) found 26 differentially expressed cytokines, 21 of which were significantly upregulated in hypersplenism, including cytokines related to monocyte chemotaxis and MΦ activation, such as macrophage colony-stimulating factor (M-CSF), tumor necrosis factor (TNF)-β, interferon (IFN)-γ, interleukin (IL)-10, MDC/CCL22, MCP-2/CCL8, and SDF-1/CXCL12. Moreover, M-CSF, TNF-β, and IFN-γ promoted transformation of blood monocytes to MΦs and maintained activation of MΦs (16). IL-10 is mainly produced by macrophages, and plays a role in inhibiting inflamma-

tion and activating MΦs (17). MDC is mainly produced by macrophages and monocyte-derived dendritic cells and is a chemokine indicating enhanced phagocytic capacity of MΦs (18,19). In hypersplenism due to PH, significant upregulation of the above cytokines may lead to activation and enhanced phagocytosis of MΦs and other immune cells in the splenic tissues, which eventually results in hypersplenism. Five cytokines have been demonstrated to be significantly downregulated during hypersplenism, including IL-1β, BLC/CXCL13, MCP-1, EGF, and BDNF.

IL-12 activates natural killer (NK) cells and T lymphocytes with secondary synthesis and the release of IFN-γ and other cytokines. IL-12 stimulates differentiation and proliferation of hematopoietic progenitors through synergies with other cytokines *in vitro*, and decreases peripheral blood counts and bone marrow hematopoiesis.

IL-18 has pleiotropic immunological competence and is present in multiple organs and tissues throughout the body. It has been demonstrated that the most important biological effect of IL-18 *in vitro* is to induce production of IFN-γ by T cells and NK cells; IL-18 also enhances the cytotoxic activity of NK cells and cytotoxic T lymphocytes (CTLs) *in vivo*. This cytokine is an immune cytokine, and more importantly, it is involved in regulation of humoral immunity and humoral immune responses (20). If bone marrow hematopoietic capacity decreases during long-term liver inflammation and hypersplenism, IL-18 may contribute to progression.

TGF-β is a cytokine with a strong biological activity in promoting regeneration of the extracellular matrix, modulating inflammatory reactions, and suppressing immune function. TGF-β and other substances are overexpressed in hypersplenism. Therefore, the spleen may likely regulate various processes during liver cirrhosis via TGF-β (21).

Gene dysregulation. Yan *et al* screened 94 possibly dysregulated genes in splenic MΦs in hypersplenism due to PH as compared to normal splenic MΦs, including 21 upregulated genes and 73 downregulated genes (22). One upregulated gene was identified as the activator of S-phase kinase (ASK). By investigating the Dbf4-related Cdc7 kinase activity regulator gene encoded by human ASK, Yamada *et al* isolated and identified a corresponding promoter of ASK, and demonstrated that this ASK promoter was effective in stimulating cell growth (23). The significantly upregulated ASK in splenic MΦs in hypersplenism due to PH may cause enhanced activity of MΦs, including enhanced phagocytic capacity, which may be an important mechanism leading to hypersplenism due to PH.

Under normal circumstances, a mutual restriction and a dynamic balance are present between cytokine or gene upregulation and cytokine or gene downregulation. Significant changes were observed in the expression of cytokines or genes in the spleen of patients with hypersplenism in the context of PH. The differentially expressed cytokines or genes may play an important role in immune cell activation in the spleen and the changes in the immune function in patients with hypersplenism.

Autoimmunity. The spleen is the largest lymphoid organ, and is an important site for the production of antibodies. Antigens unprocessed by the liver may enter the periphery of splenic lymphoid follicles (splenic nodules), where reactions of immature lymphocytes and plasma cells occur after antigen stimulation, thus producing antibodies (24), which may destroy blood cells.

Significant increases in anti-platelet GPIIb-IIIa antibody and the B-cell-producing GPIIb-IIIa antibody were found in patients with cirrhosis, suggesting that anti-platelet autoantibody-mediated platelet destruction may be an important cause of cirrhotic thrombocytopenia (25). Increased platelet-associated GP antibodies have been detected in 64% of patients with chronic liver diseases of different causes. Such antibodies could lead to decreased platelet counts by themselves or in combination with the GPIIb-IIIa antibody, or by binding to the platelet glycoprotein GPIb-IX complex (26). With progression of hepatitis C, GPAIg levels increase gradually. Consequently, thrombocytopenia often occurs in patients with chronic hepatitis C (27).

Granulocyte colony-stimulating factor (G-CSF) is used for hematopoietic progenitor cell mobilization. Platelet counts decrease during G-CSF administration. Platelets entering the spleen are cleared rapidly from the blood stream in the hypersplenic state. Thrombopoietin (TPO) is almost specifically produced by liver cells. Eissa *et al* found low levels of TPO in patients with cirrhosis (28). The balance between production and destruction of TPO was not maintained. A decrease in TPO secretion from functional hepatocytes was also reported (29). However, Sanjo *et al* (30) and Rios *et al* (31) suggested that thrombocytopenia was not directly related to serum TPO levels in patients with hepatitis liver cirrhosis, but with splenic size and certain platelet-associated immunoglobulin hormone (PAIgG).

PAIgG is a class of platelet autoantibodies bound to the platelet surface glycoprotein and mainly produced by the spleen. It was shown that significantly higher PAIgG was presented in patients with thrombocytopenic purpura and cirrhotic hypersplenism. PAIgG-bound platelets were easily captured and phagocytized by MΦs while flowing through the spleen with mediation by antibodies. In addition, PAIgG can also bind to and destroy megakaryocytes and their precursors, thus inhibiting their differentiation and platelet formation (32). T helper (Th) cells can be differentiated into Th1, Th2, and Th17 subsets. Th1 cells primarily secrete IL-2, IFN-γ, TNF-α, and other cytokines, and mediate cellular immune responses, such as delayed-type hypersensitivity (DTH) and macrophage activation. Th2 cells primarily secrete IL-4, IL-5, IL-10, IL-13 and other cytokines, promote proliferation and differentiation of B cells into plasma cells, secrete specific antibodies, improve mucosal immunity, and mediate humoral immunity and type I hypersensitivity. The balance between Th1 and Th2 cells is an important factor in maintaining immune balance. Immune responses with an increased Th1/Th2 ratio tend to lead to Th1-dominant diseases, and immune responses with a decreased Th1/Th2 ratio tend to lead to Th2-dominant diseases. One previous study demonstrated that autoimmune diseases are Th1-dominant (33).

Thrombocytopenia may also be related to excessive consumption of platelets. Accelerated renewal of fibrinogen and plasminogen was found in patients with chronic liver disease, suggesting increased consumption of platelets (34).

Liver cirrhosis-related hypercoagulability was considered to be a pathological factor of excessive consumption of platelets (35).

5. Treatment options

Peripheral cytopenias caused by hypersplenism often affects prognosis, and should therefore be closely monitored during treatment.

Non-surgical treatment. This category of treatment primarily includes etiological treatment and treatment of concomitant diseases.

Etiological treatment. Hypersplenism has many causes, and treatment should be administered in light of the specific cause. In clinical practice, any deficiencies should be supplemented; for example, transfusion of erythrocytes and platelets should be given for erythropenia and thrombocytopenia, respectively, and transfusion of whole blood should be carried out for leukopenia. After transfusion, treatment including traditional Chinese medication can also be administered to promote restoration of decreased blood cell counts to normal or near normal levels. Kalambokis and Tsianos (36) observed an increased incidence of peripheral cytopenias in patients with liver cirrhosis, which may be related to hypersplenism, and the activation of monocytes and promotion of the release of pro-inflammatory cytokines, such as serum IL-1, leukocyte IL-6, TNF-α, and IFN-γ, by endotoxin produced by intestinal bacteria. In this case, antibiotic therapy should be prescribed for endotoxemia in patients with cirrhosis to increase blood cell counts. Zuchini *et al* (37) found that electromagnetic hyperthermia was effective in treating thrombocytopenia in a rat model of cirrhotic hypersplenism. Chernykh *et al* (38) reported satisfactory outcomes achieved by autologous stem cell transplantation in the treatment of peripheral cytopenias due to cirrhotic PH. Zhang *et al* (39) proposed that phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1) may play an important role in the pathogenesis of PH and regulating the inhibition of MΦ activity, and that inhibition of PIK3R1 expression may potentially be useful for the treatment of PH and hypersplenism.

External irradiation and ablation. Kenawi *et al* treated eight patients with liver cirrhosis, splenomegaly and hypersplenism by externally irradiating the spleens using radioactive Co-60. Laboratory data showed that the hemogram returned to completely normal in two patients and partially normal in three patients. Moreover, remission of chronic splenic pain was obtained in all patients and no significant complications were reported (40). Ismail *et al* (41) also observed increased platelet counts and improved splenic pain in patients treated with splenic irradiation. Feng *et al* (42) treated patients with hypersplenism using radiofrequency ablation which gave effective symptom relief while maintaining normal blood Tuftsin levels essential for the anti-infective and antitumor functions of the body.

Partial splenic artery embolization. In 1979, Spigos *et al* used partial splenic artery embolization for the first time to treat hypersplenic patients with success (43). Thereafter, it has been applied in the treatment of PH, hypersplenism, and bleeding esophagogastric varices (44). This procedure not only increases platelet and leukocyte counts (38), but also reduces splenic size, improves pancytopenia (45), and stimulates the immune system (46). Despite some clinical success in treating splenomegaly and hypersplenism, the indications for partial splenic artery embolization are limited due to serious complications, such as splenic infarction and abscess, which could result in a high risk of death (47).

Total splenectomy. In secondary hypersplenism, the underlying disease must be treated to prevent further sequestration or destruction of blood cells, and possible spleen enlargement. These therapies should be tested prior to splenectomy - removal of the target organ of hypersplenism (48). In severe cases of splenomegaly and hypersplenism, splenectomy is performed to correct the effects of low blood cell and platelet counts (49,50). As well, it can effectively improve liver function (51). In particular, laparoscopic splenectomy has several advantages (52) and is superior to partial splenic artery embolization (53). Although splenectomy is commonly used and effective for the treatment of hypersplenism (48), some risk factors and side effects do exist. For instance, the treatment of all future infections in patients who underwent a complete splenectomy became more complicated, as a key component of the body's normal defense system is not longer present (54). These individuals will be more susceptible to sepsis and other infections, and should receive, pre-operatively, proper immunization for pneumococcus, influenza, hepatitis, and meningococcemia. For this reason, total splenectomy should be avoided if possible.

Liver transplantation. While liver transplantation for the treatment of hypersplenism has not been reported, hypersplenism is often developed from liver cirrhosis. Severe cirrhosis is often associated with serious hypersplenism. For patients with severe cirrhosis, concurrent early cancer or liver failure, liver transplantation may be suggested. In addition to restoring the liver function, liver transplantation may reduce the splenic size and the portal pressure, decrease the risk factors of bleeding, and eventually eliminate hypersplenism (55). Chu *et al* (56) reported that liver transplantation plus concurrent splenectomy did not increase the risk and could provide better outcomes in patients with liver cirrhosis and hypersplenism.

6. Conclusion

Hypersplenism, classified as primary, secondary, or occult types, is a common clinical disorder with a long history. The pathogenesis varies considerably from patient to patient. Primary hypersplenism is brought on by a disorder within the spleen itself, while secondary hypersplenism is caused by a variety of other diseases. Management and treatment should therefore be administered taking into account the specific etiology and be individualized for each patient. Available treatment options include non-surgical and surgical methods. Surgical outcome following splenectomy is usually satisfactory; however, total splenectomy should be avoided if possible.

Continuous basic and clinical studies will advance our understanding of the underlying mechanisms of the development of hypersplenism, and provide better management strategies for the treatment of patients with hypersplenism.

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