Review Article

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Aplastic anemia in China

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ABSTRACT

Aplastic anemia (AA) is a hematologic disease characterized by pancytopenia. Up to now, severe aplastic anemia (SAA) has been recognized by international and domestic scholars as an autoimmune disease with bone marrow (BM) failure mediated by the hyperfunctional T lymphocytes. The incidence of AA is more in China compared with other countries. In the recent years, both the pathogenesis and treatment of AA have made a great progress in our country. Thus, the therapeutic effect of AA was much better than before. Here, we conclude the researches of AA in China.

Key words: aplastic anemia, hematologic disease, T cell, China

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INTRODUCTION

In the recent years, our studies have demonstrated that T cells were hyperfunctional in patients with acquired aplastic anemia (AA). The excessive apoptosis of hematopoietic stem cells caused by cytotoxic T cells and/or lymphokines is the main pathogenesis of acquired AA. Up to now, acquired AA has been recognized by some scholars as an autoimmune disease with bone marrow (BM) as target organ attacked by the activated T lymphocytes. Therefore, immunosuppressive therapy (IST) has become the best choice for the treatment of acquired AA if there is no sibling donor.

EPIDEMIOLOGY

The annual incidence of AA is 7.4/10^5 population in China, with equal frequency in both genders. The incidence of acquired AA has a bimodal distribution curve, with one peak between 15 and 25 years of age and a second peak at older than 60 years of age.

PATHOGENESIS

Until the 1980s, people usually considered AA as "a bone marrow failure syndrome caused by physical, chemical and biological factors." The pathogenesis of AA is complex and involves abnormal hematopoietic microenvironment, hematopoietic stem cell/progenitor cell deficiencies, and immunity disorders. Shao detected the CD34 positive BM cells of patients with AA and healthy controls and cultured in vitro for CFU-GM, BFU-E, and CFU-E. Finally, they found that the BM CD34 positive cells from patients with AA appear to be normal in percentages and in vitro proliferation/differentiation capacities. Thus, there may be no deficiencies in the hematopoietic stem cell/progenitor cells of patients with AA.[1] With the deepening of research, more and more evidences suggested that AA is a immune-regulated disease characterized by severe pancytopenia and BM failure, caused by destruction of hematopoietic cells by the antigen-specific T lymphocytes.[2] Our previous studies have demonstrated that suppressor T lymphocytes (mainly $CD8^+$ T cells) have a dramatic increase and hyperfunction in the majority of patients with AA. Those activated T lymphocytes have obvious inhibitory effect on the growth of BM cells in in vitro experiments. Meanwhile, the quantity of activated effector T cells ($CD8^+$ HLA-DR^+) was elevated in patients with AA.[3]

While after IST [antithymocyte globulin (ATG)+ cyclosporine (CSA)], the cytotoxicity of $CD8^+$ HLA-DR^+ T cells was reduced and then reached the normal state. Moreover, the expression of perforin,[4] granular enzyme,

TNF-β, and FasL, as well as many other hematopoietic negative regulatory factors, were elevated obviously in these effector T cells in patients with AA,[5] suggesting that hematopoietic stem and progenitor cells might be destroyed through lymphokine-induced apoptosis.[6] Particularly worth mentioning is the expression of linker for activation of T cells (LAT) in $CD3^+$ T cells was positively associated with the function molecules (perforin and granzyme B) of $CD3^+$ T cells. Dysregulation of LAT expression and activation may contribute to overfunction of T cells and imbalance of Th1/Th2 subsets and thus lead to hematopoiesis failure in severe aplastic anemia (SAA). [7]

Recently, Th1/Th2 imbalance in peripheral blood has been found to be closely related to patients with SAA. The imbalance of myeloid dendritic cells (mDCs) subsets might promote Th0 cells to Th1 cells and cause the overfunction of T lymphocytes and induction of apoptosis of hematopoietic cells in SAA.[8] It is noteworthy that Th1 cells decreased gradually with hematopoietic function recovery, which might contribute to the immunopathogenesis of SAA. Furthermore, both immature and activated mDCs increased in the BM of patients with SAA.[9]

Myeloid dendritic cells secrete IL-12, which is the major stimulator of Th0 cells to Th1 cells. Thus, we infer that the pathogenesis of SAA is related to the increased number and enhanced function of mDCs, which might stimulated by unknown antigen. Then the stimulated mDCs lead hyperfunction of Th1 cells and cytotoxic T lymphocytes and thus ultimately led to the apoptosis of hematopoietic cells.

Although understanding of the immune pathogenesis of SAA gradually improved after many years of research, which antigen activated mDCs and even T cells was still unclear. Actually, the immune-initiating antigen has become the focus of our further research. Newly, we have investigated the proteome of mDCs to further explore the possible antigen that leads to immune activation in SAA. Our research have demonstrated that there are changes in protein expression levels in the SAA group, including PKM2, cofflin protein, and the G-6-PD.[10] But the specific mechanism still needs further validation.

Moreover, researches on the heredity of patients with AA have been conducted recently. Patients with SAA have short telomeres and decreased POT1 expression. TNF-α and IFN-γ are found at high concentrations in patients with SAA and may be the effectors that trigger apoptosis through POT1 and ATR.[11] The research conducted doctor Song showed that the patients with AA and abnormal telomere length have no effect after IST. And these patients should be given other treatments at the initial diagnosis.[12]

DIAGNOSIS

Many years ago, diagnosis of AA mainly depends on the morphology of BM, excluding other hematopathologies. AA diagnosed by this method is essentially a symptom of BM failure containing many different diseases, such as myelodysplastic syndrome (MDS) and paroxysmal nocturnal hemoglobinuria (PNH). With the improvement of examination, we gradually distinguished several other diseases with BM failure from AA and purified AA into a kind of independent disease system with relatively clear pathological mechanism. Some MDS was also obvious dysplasia and should be distinguished from AA. We have found that the basic difference in MDS from SAA was malignant clonal proliferation. Cytogenetics maybe helpful and abnormal chromosomes can be considered as an exclusion criterion. Currently, the emergence of new diagnostic methods, namely, CD55 and CD59, made the diagnosis of PNH more precise, but there are still some PNH called SAA-PNH syndrome that cannot be distinguished from SAA. Actually, if more than 10% of the PNH clone can be found in the patient with obviously abnormal hematopoiesis and decrease in mature hemocytes, it can be diagnosed as PNH. Meanwhile, we should exclude the fanconi anemia (FA) caused by congenital anomaly and AHA caused by some incentive. In addition, with the long-term research on AA, we purified a new disease from AA, and we called it immuno-related hemocytopenia (IRP), which was characterized by hyperfunction of B lymphocyte.[13] In the recent years, we observed that these patients responded well to corticosteroid and high-dose intravenous immunoglobulin treatment, indicating cytopenia might be mediated by autoantibodies. We retrospectively analyzed 166 patients with idiopathic cytopenia of undetermined significance (ICUS), some of which were detected as autoantibodies on BM hematopoietic cells BM mononuclear cell (BMMNC)-Coombs test, flow cytometry, western blot, and immunofluorescence (IF).[14]

We found that 25.9% (43/166) of patients had positive BMMNC-Coombs test or FCM analysis and 72.1% (31/43) of which had IgG-autoantibody positive by western blot. More than half of the patients had hyper-BM cellularity with a higher percentage of nucleated erythroid cells in the sternum. Therefore, by our clinical experience, we suggested the following points during the diagnosis of AA. First, take the evidence of hyperfunction in T lymphocyte. Next, different parts of the BM puncture were required to judge the state of hematopoiesis, especially including sternal BM puncture. Third, BM biopsies, which mainly reflect the structure of the BM and special ingredients such as fiber and "stone bone," were of similar importance. We should combine the two examinations to evaluate the hyperplasia of BM in patients.[15]

TREATMENT

Once AA is diagnosed, we should take treatment measures as soon as possible. For young patients with SAA and HLA-matched sibling donor, hematopoietic stem cell transplantation (HSCT) becomes the preferred treatment for granted. Also in the recent years, the unrelated donor HSCT and haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) were considered as an alternative therapy for SAA if there is no suitable donor for matched sibling donor allogeneic hematopoietic stem cell transplantation (MSD-HSCT).[16] However, because of the donor, economic, graft-*versus*-host disease (GVHD), the use of HSCT to treat SAA was restricted. For those patients older than or younger than 40 years with no HLA-matched sibling donor, IST should be the first choice.[17] IST could inhibit the hyperfunction of T lymphocytes, reduce the negative hematopoietic regulatory factors, and remove the damage of hematopoietic cells. This regimen has become the first-line treatment for AA (especially SAA) and has been included in the guidelines of China and domestic. There was a significant risk of relapse with rapid tapering of cyclosporine, and the treatment should be continued for a long time until the immunoreaction is completely back to normal. It generally takes a small dose (as small as 25 mg) for several years. Meanwhile, IST often combines with hematopoietic stimulating factor (HGF), thrombopoietin (TPO), and androgen in case to promote hematopoietic function of BM. An adequate course of HGF leads to lower rates of early infection and mortality, shorter duration of cytopenia and blood transfusion dependence, and faster recovery of BM hematopoiesis. The addition of HGFs to sequential intensive immunosuppressive therapy (SIIST) was well tolerated in all patients.[18] We observed that granulocyte transfusions combining with G-CSF to treat severe infections in patients with SAA increase the response rate of antifungal and antibiotic therapies. The survival rate at 30, 90, and 180 days were 89%, 70%, and 66%, respectively, which were longer than that before.[19] Study by doctor Wang showed that the time to platelet and red blood cell transfusion independence was shorter in patients with SAA who received TPO than in those who have not received TPO treatment.[20] Thus the use of TPO could improve hematologic response and promote BM recovery in patients with SAA receiving IST. Androgen can promote hematopoiesis by stimulating the secretion of erythropoietin (EPO) of kidney and increasing the sensitivity of immature red cell to the EPO. Before the ATG/CSA, androgen has already been used in the treatment of AA; now it has became an aid drug in the treatment of AA.[21] IST is the "fundamental treatment" of AA, and immune support treatment was equally important and helpful. Most patients with AA have extremely low immunity with the lack of granulocyte; powerful immune support therapy can improve the humoral immunity. As symptomatic treatment, appropriate dose of gamma-globulin or thymosin can be used for patients with AA.[22]

PROGNOSIS

SAA occurs urgently and had an extremely high mortality rate earlier. Nearly, a decade, the prognosis of SAA significantly improved as a result of better treatment.[23] The effective rate of sib-HSCT is about 80%, but only 30% of patients with SAA can obtain the HLA-matched sibling donor. The therapeutic effect of IST also improved in the recent years, almost same as the sib-HSCT. Research by the Beijing Children Hospital on the rabbit ATG showed that the total effect was 77%, and in the study by doctor Cao, it was 83.3%.[24] In China, the use of horse ATG is limited, but the pig ATG was frequently used because of its less cost. The research of Han summarized the clinical data of 48 patients who received treatment with pig ATG, the total therapeutic effect was 82.2%, almost the same as rabbit ATG.[25] The study of doctor Wei obtained the same result, revealing that the pig ATG was the same in effectiveness compared with that of the rabbit or horse ATG.[26] Meanwhile, the commission AA patients still have the opportunity of relapse and clonal evaluation. Cui reported 7 patients who had monosomy 7 malignant clonal evolution in the Tianjin General Hospital. Ma also reported 19 patients who evoluted to MDS/AML after treated with IST, and the main clonal abnormal was monosomy 7.[27] Only 1 person have the evaluation of plus 8; 2 persons have the abnormal of complicated karyotypes. Research by doctor sun showed that PNH clone are detectable in patients with AA after treatment with IST.[28] And the appearance of PNH clone had not affected the therapeutic efficacy of patients with AA.

General aspect, during the nearly 20 years, not only the pathogenesis and diagnosis but also the treatment of SAA has made a great progress in China. And the guideline of the diagnosis and treatment about AA in China has been published in the Chinese Journal of Hemotology. For the great efforts made by all hematologic doctors in China, the therapeutic effect of AA was better than before. But there are still more questions about the pathogenesis of AA that have to be explored. The treatment of SAA should also be modified in the future.

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Conflict of Interest

The authors declare no competing financial interests.

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