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Diagnosis, Pathophysiology and Management of Aplastic Anemia

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Abstract

Aplastic anemia is a clinical syndrome characterized by fatty replacement and decreased hematopoietic precursors of the bone marrow, which results in peripheral blood pancytopenia. Severe aplastic anemia is defined by at least two of the following peripheral blood count criteria: (1) absolute neutrophil count 500/mL, (2) absolute reticulocyte count60,000/L, and (3) a platelet count 20,000/L. Aplastic anemia has been associated with exposures to drugs, chemicals, and toxins, as well as certain viral infections. Standard treatment for patients who have a matched sibling donor is Hematopoietic Stem Cell Transplantation that provides a cure in about 90 % of patients. This treatment can be applied to patients aged below 50 years although age limit can be increased to below age 60 if the patient is medically fit. Survival has progressively ameliorated over the last 30 years thanks to improvement of immunosuppressive treatment and of Hematopoietic Stem Cell Transplantation. The improvement of supportive care also contributed to ameliorate the outcome, especially for patients who do not respond the upfront therapies

Keywords: Aplastic animi; Diagnosis; Pathophysiology; Management.

Introduction

Aplastic anemia is defined as pancytopenia associated to a persistent hypo cellular bone marrow in the absence of major dysplastic signs and marrow fibrosis. The involvement of at least two lineages in peripheral blood cells is required to confirm diagnosis. Values have to lower than <10 gr/dl for hemoglobin, than 1.5 × 109/L for neutrophils and lower than 50 × 109/L for platelets. Aplastic anemia (AA) is a life-threatening bone marrow failure disorder which, if untreated, is associated with very high mortality [1-3]. Aplastic anemia is now increasingly recognized as being closely related to other hematologic diseases. Erythrocytes, granulocytes, and platelets, which are normally produced in the bone marrow, decrease to dangerously low levels [5]. Historically, aplastic anemia has been strongly associated with exposure to chemicals and drugs in the environment, giving the disease a social impact disproportionate to its incidence. Aplastic anemia, acquire or congenital anemia associated with hypo plastic "fatty or empty" bone marrow and global dyshematopoiesis [6].

Diagnosis and clinical manifestations of aplastic anemia

Acquired AA can occasionally be traced to a distinct trigger such as seronegative hepatitis, drugs, toxins or pregnancy, but the vast majority of cases are classified as idiopathic. Clinical manifestations are proportional to the peripheral blood cytopenia and may include dyspnea on exertion, fatigue, easy bruising, petechiae, epistaxis, gingival bleeding, heavy menses, headache and fever. A complete blood count, leukocyte differential, reticulocyte count and a bone marrow aspirate and biopsy can establish the diagnosis. Peripheral blood flow cytometry to detect cells missing glycosylphosphatidylinositol anchored proteins (GPI-AP), bone marrow karyotyping and FISH to help exclude hypo plastic myelo dysplastic syndromes (hMDS) should be performed on all patients [7-11].

Differential diagnosis

Blood counts can be decreased in overwhelming infection (eg, bacterial sepsis) and secondary to a few diseases (eg, cirrhosis

with hypersplenism, systemic lupus), but severe persistent pancytopenia has a limited differential diagnosis and almost always implies BM involvement [12,13].

Pathophysiology

Multiple etiologies for AA have been proposed which in due course lead to an immune- mediated destruction of hematopoietic stem cells (HSCs) residing in the bone marrow, but the bulk of cases remain idiopathic [14]. Severe aplastic anemia (SAA) is regarded as the result of an immune-mediated destruction of hematopoietic cells, at least in a proportion of patients. Cytokine over expression in bone marrow T lymphocytes of AA patients also play an important role, and the expansion of polymorphisms in promoting regions of cytokine genes may also suggest a genetic influence on the immune response with a more prompt activation possibly leading predisposed subjects to a marrow inhibition. Genetic predisposition may also be postulated due to the frequent association with HLA genes. Recovery of autologous hematopoiesis in patients who failed to engraft after stem cell transplant and responsiveness to immunosuppressive therapies are the major clinical evidences supporting an immune pathophysiology underlying acquired AA. Although a nonimmune pathophysiology has been inferred from a failure to respond to immunosuppression, refractoriness to therapy is also consistent with very severe stem cell depletion, a "spent" immune response, or immunological mechanisms resistant to current therapies. The mechanism of activation of cytotoxic T-cells is unclear, but several potential factors which are associated with antigen recognition, susceptibility of immune response, and secretion of cytokines are found. The pathophysiology is believed to be idiopathic or immune-mediated phenomenon with active destruction of haematopoietic stem cells. The abnormal immune response may be elicited by environmental exposures, such as to chemicals, drugs, viral infections and endogenous antigens generated by genetically altered bone marrow cells. A small fraction of the genes involved in pancytopenia has been represented by the congenital BM failure syndromes (relatively rare) which lately develop in clinical syndromes as Fanconi's anemia, Dyskeratosis Congenital, and Shwachman-Diamond syndrome. Hepatitis-associated aplastic anemia (HAAA) is a well-recognized and distinct variant of clinical syndrome, acquired aplastic anemia, in which an acute attack of hepatitis leads to the marrow failure and pancytopenia [15-20] (Figure 1).

These syndromes include clonal diseases (paroxysmal nocturnal hemoglobinuria, myelodysplasia, and large granular lymphocytosis); and single hematopoietic lineage deficiency diseases (agranulocytosis, pure red-cell aplasia, and amegakaryocytic thrombocytopenia), note especially the areas of overlap between aplastic anemia and paroxysmal nocturnal hemoglobinuria and myelodysplasia.

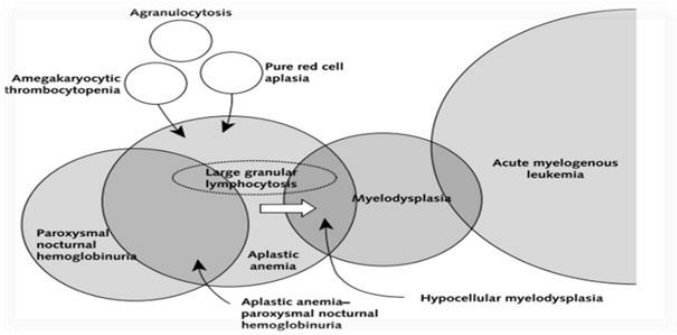

Figure 1: *Venn diagram showing possible relationships among bone marrow failure syndromes.*

Primary supportive care

Before initiating more definitive therapies for acquired SAA, the clinician must consider the significant supportive care required for these patients. An individual patient's requirement for supportive care will depend upon the severity of symptoms and pancytopenia. Throughout the diagnostic and treatment process, patients must be provided aggressive supportive care. Generally, restrictive transfusion targets (hemoglobin > 7 g/dL, platelets > 10,000 cells/μL) are preferred, especially in potential transplant candidates, given the risk of alloimmunization and transfusional iron overload [21].

Transfusions

Patients with severe cytopenias require urgent support with blood products. Blood products should be irradiated to prevent transfusion associated graft-versus-host disease (GVHD), and filtered to reduce the incidence of viral infections and prevent all immunization [22, 23].

Growth factors

The use of HGFs to support blood counts is of limited value in SAA, as predicted by both in vitro studies and measurement of endogenous serum levels of HGF, which are markedly elevated. There may be a limited role for granulocyte colony stimulating factor (G-CSF) administration in an attempt to stimulate a neutrophil response in the presence of severe infection, although there have been no prospective randomized studies showing a benefit for G-CSF in SAA patient [24-26]. Irradiated blood products should be used to prevent transfusion-associated graft-versus-host disease (GVHD). Because of the high mortality due to invasive mold infections, particularly Aspergillus species, antifungal prophylaxis with voriconazole or posaconazole should be used in patients with severe neutropenia (absolute neutrophil count < 500 cells/μL). Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be used during the period of lymphopenia following ATG therapy, ideally selecting an alternative to trimethoprim-sulfamethoxazole because of its myelosuppressive effects. Antimicrobial prophylaxis with quinolone antibiotics in patients with VSAA can reduce the risk of gram-negative sepsis, but routine use of prophylactic antibiotics in patients with higher

neutrophil counts is not advised in order to limit antibiotic resistance [27].

Immunosuppressive therapy

ATG and Ciclosporin (CSA) represent the most commonly used agents in first line immunosuppressive therapy. Their combined uses have been demonstrated to be much more effective than ATG alone. Horse anti-thymocyte globulin (ATGAM (R); h-ATG) is the only drug approved by the Food and Drug Administration for the treatment of AA. While it is generally believed that hATG administration leads to depletion of immune competent cells, its exact mechanism of action remains unclear. H-ATG preparations contain a variety of antibodies recognizing human T-cell epitopes, many directed against activated T-cells or activation antigens. Although the decline in circulating levels of lymphocytes is transient, the number of activated T -cells is decreased for more prolonged periods of time; this effect is also reflected in decreased lFN-γ and possibly TNF production after h-ATG [28-30]. CSA should be started at day +1 at the dose of 5–15 mg/ kg/die divided in 2 daily doses for 12 months then slowly tapered over 12 further months. CSA levels should be maintained around 200ng/ml. The duration of CSA administration represents a crucial point in the management of responders to immunosuppression. Controversial results have been obtained in different studies on pediatric and adult population. In an Italian retrospective study on children, slow tapering of CSA (0.3–0.7 mg/kg/month) was correlated to a lower relapse incidence compared to a rapid one (>0.8 mg/kg) [31]. The use of G-CSF has shown to increase neutrophils count and to reduce both infections and days of hospitalization. Its use also demonstrated to have a prognostic impact in terms of response, since patients who experienced a neutrophil count ≥0.5 × 109 /L at day + 30 had the higher chances to respond. Due to these concerns G-CSF could be used during the first 30 days of treatment and beyond in case of infective episodes in neutropenic patients [32].

Stem cell stimulation therapy

Anemia does not respond to erythropoietin or neutropenia to G-CSF, which is unsurprising because levels of the endogenous growth factors are very elevated in patients' blood. Therefore, improvement with eltrombopag of patients with refractory severe aplastic anemia was entirely unexpected. Eltrombopag is a thrombopoietin mimetic, a small molecule designed to trigger the mpl surface receptor and signal transduction pathway, and developed to avoid the problem of (neutralizing) antibody formation to intact thrombopoietin protein and iatrogenic idiopathic thrombocytopenia. Eltrombopag is approved for use in idiopathic thrombocytopenic purpura and has an excellent toxicity profile; in addition, it is administered orally. Eltrombopag should not be effective in aplastic anemia because in this disease, in contrast to idiopathic thrombocytopenia, blood levels of thrombopoietin are extremely high [33].

Matched sibling donor (MSD)

HSCT European Blood and Marrow Transplantation (EBMT) recommended Conditioning regimen for MSD HSCT includes Cyclophosphsamide (Cy) (200 mg/kg) given in 4 days, and ATG (7.5 mg/kg). However, the use of ATG may be considered optional since a prospective study comparing patients receiving Cy with or without ATG showed similar results [35]. Fludarabine at the dose of 150 mg/m2 has also been used as an alternative option to be associated to lower Cy doses in order to prevent fertility impairment. Graft-versus-Host Disease (GvHD) prophylaxis includes the use of both Methotrexate and CSA that provided with a superior effect when compared with CSA alone [34].

Unrelated donor HSCT

Currently Unrelated Donor (UD) HSCT is reserved to patients lacking a matched sibling donor and who do not respond to first line IS treatment. In the last few years, the outcome of this procedure has been progressively improved. Conditioning regimen included low dose irradiation or fludarabine. Low-dose Total Body Irradiation (TBI) regimen resulted to have a good outcome but a higher GvHD incidence [35].

Haploidentical HSCT

Patients who failed immunosuppressive treatment and lack an unrelated donor might be considered eligible to undergo a haploidentical HSCT. Many experiences have been published with the use of different conditioning regimen but the limited number of patients and absence of prospective trials make difficult to suggest any recommendation, since results where similar in all cases. Both unmanipulated and ex vivo T-Cell depleted transplants have been used in this setting. The first platform was used in patients conditioned with different TBI doses and Cy [36, 37].

Conclusion

Aplastic anemia (AA) is a life-threatening bone marrow failure disorder which, if untreated, is associated with very high mortality. Severe aplastic anemia (SAA) is regarded as the result of an immune-mediated destruction of hematopoietic cells, at least in a proportion of patients. Cytokine over expression in bone marrow T lymphocytes of AA patients also play an important role, and the expansion of polymorphisms in promoting regions of cytokine genes may also suggest a genetic influence on the immune response with a more prompt activation possibly leading predisposed subjects to a marrow inhibition. ATG and Ciclosporin (CSA) represent the most commonly used agents in first line immunosuppressive therapy. Their combined uses have been demonstrated to be much more effective than ATG alone.

Horse anti-thymocyte globulin (ATGAM (R); h-ATG) is the only drug approved by the Food and Drug Administration for the treatment of AA.

Abbreviations

AA: Aplastic anemia; ATG: Anti-thymocyte globulin; BM: Bone marrow; CSA: Ciclosporin; GVHD: Graft-versus-host disease; G-CSF: Granulocyte colony stimulating factor; GPI-AP: Glycosylphosphatidylinositol anchored proteins; HSCT: Hematopoietic Stem Cell Transplantation; HAAA: Hepatitis-associated aplastic anemia; hMDS: Hypoplastic myelo dysplastic syndromes; SAA: Severe aplastic anemia

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