APLASTIC ANAEMIA: AETIOLOGY, PATHOPHYSIOLOGY, DIAGNOSTIC APPROACH, RECENT MANAGEMENT PROTOCOLS, PROGNOSIS AND THEIR COMPLICATIONS

Abstract

Aplastic anaemia is a relatively uncommon disease, with a significant proportion of cases manifesting within the initial three decades of an individual's lifespan. The prevalence of aplastic anaemia in Asia is significantly greater, ranging from two to three times higher, compared to the Western world. Approximately 20-40% of patients diagnosed with pancytopenia in specialised medical centres exhibit aplastic anaemia. The clinical manifestations most frequently observed include pallor, manifestations of bleeding, and fever. The majority of cases of acquired aplastic anaemia occur due to the immune-mediated destruction of hematopoietic stem cells, resulting in pancytopenia and hypocellular bone marrow. This condition can be effectively managed through either immunosuppressive therapy or hematopoietic stem-cell transplantation. In the case of children and young adults diagnosed with severe aplastic anaemia, hematopoietic stem-cell transplantation from a compatible sibling donor is the preferred treatment option. However, if hematopoietic stem-cell transplantation is not possible due to factors such as age, absence of a histocompatible sibling, or presence of other medical conditions, immunosuppressive therapy is utilised as a last resort. The management of AA poses a significant challenge in developing nations. Adverse consequences of aplastic anaemia can be minimized by enhancing patient and referring physician awareness, thereby minimising the time lapse between diagnosis and treatment.

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I. INTRODUCTION

Aplastic anaemia is a haematological disorder that can be recognised by pancytopenia, as observed through a complete blood count, and the presence of a significant hypocellular or acellular marrow, as identified through bone marrow examination [1].Aplastic anaemia is diagnosed based on established criteria, which include the presence of hypocellular bone marrow (as observed through trephine biopsy) without fibrosis or neoplastic infiltration, along with the presence of at least two of the following: less than 10 g/dl of haemoglobin, a platelet count of less than 50 x 10^9/L, and a neutrophil count of less than 1.5 x 10^9/L. When the aforementioned parameters are met and the absolute neutrophil count is less than 0.2 x 10^9/L, it is referred to as very severe aplastic anaemia (VSAA), and severe aplastic anaemia (SAA), when it was less than 0.5 x 10^9/L. The remaining individuals have been diagnosed with non-severe aplastic anaemia (NSAA) [2,3].The presence of anaemia can result in the manifestation of symptoms such as overall weakness, pallor, and an increased heart rate [4]. Thrombocytopenia is associated with an elevated susceptibility to bleeding, contusions, and petechiae. The presence of leukocytopenia has been shown to elevate the susceptibility to infections [4,5].

II. AETIOLOGY AND EPIDEMIOLOGY

Aplastic anaemia may arise due to immune disorders or exposure to certain chemicals, medications, radiation, or infections. However, in approximately fifty percent of cases, the aetiology remains unidentified. Aplastic anaemia is additionally linked to exposure to toxins such as benzene or the use of certain kinds of medications, including chloramphenicol, carbamazepine, felbamate, phenytoin, quinine, and phenylbutazone [6–8] [Table 1].

Table 1: Aplastic Anaemia Aetiology [6-9]

Idiopathic	Acquired Stem Cell Defects
Secondary	Chemical and drugs: Benzene, cytotoxic agents, lindane, toluene, gold salt, chloramphenicol, non-steroidal anti-inflammatory drugs Radiations Viruses: Epstein-Barr virus, Parvovirus B-19, HIV, Varicella zoster virus, Hepatitis virus, Human herpes virus-6 Pregnancy Auto-immune diseases: Eosinophilic fasciitis, systemic lupus erythematosus, Graft-versus host disease Paroxysmal nocturnal haemoglobinuria Miscellaneous: Anorexia nervosa, Hypopituitarism, Thymoma
Inherited Disorders	Dyskeratosis congenita Fanconi’s anaemia Schwachman-Diamond syndrome Telomerase defects Amegakaryocytic thrombocytopenia

The development of aplastic anaemia is also linked to exposure to ionising radiation from radioactive materials or radiation-producing devices. Marie Curie, renowned for her groundbreaking contributions to the study of radioactivity, succumbed to aplastic anaemia as a result of prolonged exposure to radioactive substances without adequate protection. It is worth noting that during that time, the detrimental consequences of ionising radiation were not yet understood [6].

An autoimmune condition in which white blood cells assault the bone marrow is one of the recognised causes [7,8]. A T-cell-mediated autoimmune disease known as acquired aplastic anaemia is characterised by a decrease in regulatory T cells and an increase in T-bet, a transcription factor and important regulator of Th1 generation and function, in afflicted T cells. Transient aplastic anaemia can also occur as a consequence of specific viral infections, such as parvovirus and seronegative hepatitis virus [9].

The incidence of aplastic anaemia ranges from 0.6 to 6.1 cases per million people. The gender distribution is equal, with a male-to-female ratio of approximately 1:1 [10]. Aplastic anaemia is observed across all age groups, with a notable incidence peak occurring during childhood. The age group of 20 to 25 years exhibits a second peak [11].

III. PATHOPHYSIOLOGY

There are two interconnected explanations for the occurrence of aplastic anaemia: the first is the external immune-mediated suppression of hematopoietic stem cells, and the second is the internal abnormality of marrow progenitors [12].

Hematopoietic stem cells that have been affected undergo maturation into T-helper cells (T1) that exhibit self-reactivity. These T1 cells subsequently release cytokines, particularly interferon (IFN) and tumour necrosis factor (TNF), in order to initiate a cytotoxic cascade. The purpose of this cascade is to eliminate and inhibit the function of various hematopoietic stem cells [13,14]. The specific antigens that T1 cells selectively recognise remain uncertain; however, evidence suggests that one such antigen is the glucose phosphate inositol (GPI)-linked protein located on cellular membranes. In addition, it has been observed that the application of immunosuppressive therapy specifically aimed at T-cells results in a positive outcome in approximately two-thirds of individuals diagnosed with idiopathic aplastic anaemia [14].

According to the second theory, stem cells that possess inherent defects experience a loss of their ability to undergo differentiation and proliferation. The failure to undergo dedifferentiation has the potential to result in the development of hematologic neoplasms through clonal evolution. The presence of telomere deficiencies, which are integral to the process of cell division, can result in the premature depletion of hematopoietic stem cells and the development of marrow aplasia [15].

The bone marrow microenvironment refers to the specialised cellular and extracellular components that exist within the bone marrow and play a crucial role in supporting its development and maintenance.

The bone marrow microenvironment is a crucial determinant in the generation of viable stem cells. The key constituents encompass stromal cells, the extracellular matrix, and localised cytokine gradients [16]. The hematopoietic and non-hematopoietic components of the bone marrow exhibit close interplay, contributing to the support and regulation of hematopoietic equilibrium [17]. Aplastic anaemia patients exhibit not only reduced quantities of hematopoietic stem cells but also modifications in their hematopoietic niche. These alterations arise from the heightened presence of cytotoxic T-cells, specifically the polyclonal expansion of dysregulated CD4+ T-cells, which initiate apoptosis in bone marrow cells. Furthermore, abnormal production of interferon, tumour necrosis factor, and transforming growth factor contributes to an increase in adipocyte numbers and a decrease in pericyte numbers. These changes in the hematopoietic niche also contribute to the suppression of haematopoiesis [18,19].

IV. DIAGNOSTIC APPROACH

1. **Clinical History, Physical Examination, Biochemical Tests, and Bone Marrow Examination:** Aplastic anaemia manifests in individuals of all age groups, exhibiting an equal prevalence across genders and races. The presence of splenomegaly is not observed, and its existence indicates the possibility of an alternative diagnosis. The examination of the peripheral blood smear reveals the presence of normocytic and normochromic anaemia, along with reticulocytopenia, neutropenia, and thrombocytopenia. The bone marrow examination reveals a decrease in cellularity, accompanied by significant suppression of haematopoiesis [Figure 1]. The absence of cytologic abnormalities is indicative of the absence of an underlying haematological disorder. In order to establish a conclusive diagnosis of aplastic anaemia, it is imperative to conduct a bone marrow biopsy [20].

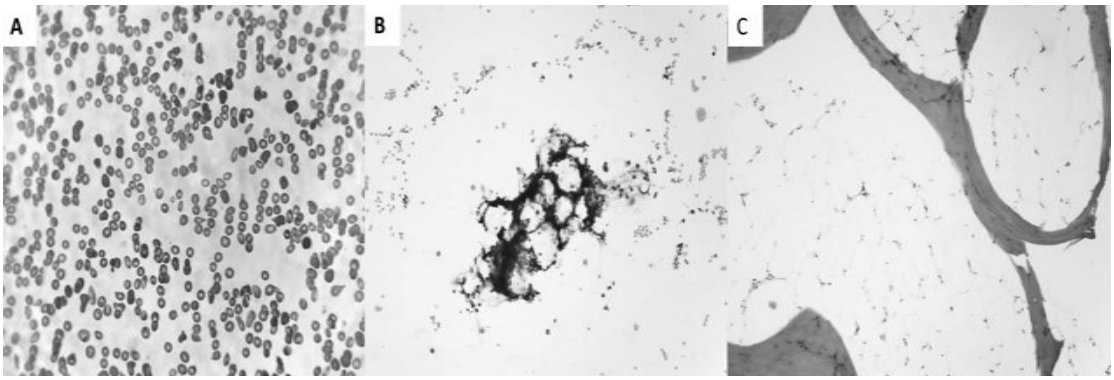

Figure 1:
(A) Peripheral blood smear of a patient with aplastic anaemia showing pancytopenia;
(B) Bone marrow aspirate smears showing hypocellular marrow fragments with marked suppression of haematopoiesis;
(C) Bone marrow biopsy of a patient with aplastic anaemia showing markedly hypocellular marrow spaces filled with fat cells.

Before looking at the bone marrow, a full history of iatrogenic exposure, cytotoxic treatment, and current and past illnesses with or without lymphadenopathy is

needed. Blood tests are usually requested in order to obtain diagnostic clues. Commonly asked blood tests include those assessing renal function, liver enzymes, thyroid function, vitamin B12 levels, folic acid level and complete blood count. These biochemical tests, in conjunction with the patient's medical history and the results of an examination, could be helpful in establishing the cause of aplastic anaemia [1,21].

Studies of immunophenotyping and cytogenetic testing with the use of flow cytometry and fluorescence in situ hybridization (FISH) are helpful when attempting to rule out hematologic illnesses as the cause of pancytopenia [21,22].

V. TREATMENT

The treatment of aplastic anaemia is based on the primary cause. Certain medications have been withdrawn from the market in the United States due to their links with aplastic anaemia, such as Ticlopidine, a platelet aggregation inhibitor utilised for primary or secondary stroke prevention, as well as dual antiplatelet therapy after percutaneous coronary intervention, and phenylbutazone, a nonsteroidal anti-inflammatory drug employed as an analgesic and antipyretic [23]. The occurrence of aplastic anaemia in relation to pregnancy is typically of a temporary nature and resolves upon the completion of delivery [24,25].

The treatment approach for patients who do not exhibit any reversible cause is contingent upon several factors, including the patient's age, severity of the disease, availability of a suitable donor, and their performance status. According to previous research, it is recommended that individuals who are under the age of 50 years and in good overall health but are afflicted with a severe illness receive allogeneic hematopoietic cell transplant (HCT) as a priority before commencing initial immunosuppressive therapy [23]. The administration of full-dose immunosuppressive therapy is employed for older patients aged 50 years or older who are in a state of good health, as well as for young patients who do not possess a hematopoietic cell transplant (HCT) donor. This therapeutic approach involves the utilisation of eltrombopag, horse/rabbit anti-thymocyte globulin (ATG), cyclosporine A, and prednisone. This combination can be customised to include either single-agent eltrombopag, anti-thymocyte globulin (ATG), or cyclosporine A for individuals with compromised health conditions. Eltrombopag is a pharmacological agent classified as a non-peptide agonist of thrombopoietin. Its primary mechanism of action involves augmenting platelet counts and stimulating intracellular signal transduction pathways, thereby promoting the proliferation and differentiation of progenitor cells in the bone marrow [24]. The administration of anti-thymocyte globulin (ATG) results in the eradication of T-lymphocytes that are responsive to antigens, leading to the stimulation of hematologic reactions in individuals with aplastic anaemia. Cyclosporine A effectively suppresses the synthesis and secretion of interleukin-II (IL-2), thereby impeding the activation of quiescent T-lymphocytes induced by IL-2. Ongoing clinical trials are currently being conducted to investigate the efficacy of alternative therapies as secondary treatment options [25,26].

Supportive care encompasses the administration of infection prophylaxis and treatment, as well as the blood transfusions. It is recommended to closely observe individuals for the development of secondary hemochromatosis and, when appropriate, administer iron chelators. The utilisation of growth factors, such as erythropoietin or granulocyte colony-

stimulating factors, is prohibited due to insufficient precursor cells available to elicit adequate responses [27].

1. **Follow-Up:** Regular monitoring of complete blood counts is necessary to assess the ongoing remission status of the patient. A significant proportion of individuals diagnosed with aplastic anaemia exhibit cellular clones that possess distinct characteristics associated with paroxysmal nocturnal haemoglobinuria (PNH), an uncommon disorder characterised by anaemia accompanied by thrombocytopenia and/or thrombosis [28]. The potential coexistence of aplastic anemia and paroxysmal nocturnal haemoglobinuria has been postulated as a mechanism employed by the bone marrow to evade immune-mediated destruction [28-30].

2. **Prognosis:** The prognosis of individuals with aplastic anaemia is significantly influenced by factors such as age, the severity of the disease, and the patient's response to initial treatment. Individuals who experience a cessation of drug use or receive treatment for an underlying condition exhibit a clinically stable trajectory, as do those with processes that resolve on their own [31]. The survival rate for patients who receive a bone marrow transplant from a compatible donor exceeds 75% over a period of five years. A significant proportion of patients who do not receive treatment experience mortality within a year due to complications directly associated with the disease, such as bleeding, infections, or the development of lymphoproliferative disorders [31–33].

VI. COMPLICATIONS

The prevailing complications associated with aplastic anaemia encompass haemorrhage, infections, or progression to lymphoproliferative disorders. The management of these conditions involves the implementation of surveillance measures and the administration of symptomatic treatments, such as transfusions, antibiotics, and/or chemotherapy. The management of patients diagnosed with aplastic anaemia is a collaborative effort involving an interprofessional team [34]. The disorder has the potential to impact multiple organ systems. In addition to the primary disease, various complications may arise as a consequence of immunosuppressive therapy and hematopoietic cell transplantation. It is imperative to closely monitor these patients for the occurrence of infections and bleeding. Premenopausal women may experience heavy menstrual bleeding, and it is recommended that they consider hormonal therapy as a potential treatment option. In conclusion, it is imperative to provide comprehensive education to all patients regarding the importance of upholding proper hand and personal hygiene practises, as they are particularly susceptible to infections [35].

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