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Original Research Paper

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APLASTIC ANAEMIA AND HYPOPLASTIC MDS: DIAGNOSIS AND MANAGEMENT

Boskey Pancholi* Department of Zoology, Government College Kota (Rajasthan) India-324010 *Corresponding Author

Manish Gautam Shree Kalyan Cancer Hospital, Kota (Rajasthan) India

ABSTRACT Aplastic/Hypoplastic anaemia is a rare haematological disorder that results in failure of stem cell generation. The causes may be genetic, drug or viral diseases. Among several factors exact reason is still under investigation. This disorder generally affects the age group between 15 to 25 years with a smaller peak after 60 years. The cases of aplastic anaemia vary from 1.4 to 14 cases per million population (higher in developing countries as compare to west). This article gives a systematic representation of causes, diagnostic procedure and treatment criteria for Aplastic anaemia/Hypoplastic MDS chemotherapeutic agents and later on. For treatment of MDS haematopoietic stem cell transplant from matched sibling is mostly tried. As due to lack of awareness, delayed diagnosis, lack of expertise medical care system and high-cost treatment of Aplastic anaemia is still a challenge in India. Immunosuppressive therapy was now common in those patients where match sibling is not available or patient condition not support blood transfusion. Horse anti-thymocyte globulin and rabbit anti-thymocyte globulin are the options for the treatment. These drugs along with cyclosporin (CsA) and eltrombopag are consider for the treatment and better recovery of the patients of aplastic anaemia.

KEYWORDS : Hypoproliferative, Haemorrhage, Pancytopenia, Thrombocytopenia, Immunosuppressive Agents, Myelofibrosis.

INTRODUCTION

Aplastic anaemia has a long history where aplastic means to inability of bone marrow to form blood and affect diverse pathophysiologic mechanism. Hypoproliferative anaemia are normocytic or macrocytic and are characterized by low reticulocyte count.[1] Hypoproliferative anaemia is also a prominent feature of hematologic disease that are described as bone marrow failure status. Aplastic anaemia is pancytopenia with bone marrow hypocellularity hence deficient production of red blood cells (RBC's), white blood cells (WBC's) and megakaryocytes (Platelet's) occur with marrow damage and dysfunction The incidence of acquired aplastic anaemia is two cases per million persons annually. It is result due to cytopenias and ineffective haematopoiesis.[2]

In general, men and women are affected with equal frequency, but the age distribution is biphasic, with the major peak in the teens and twenties (10-25 years) and a second rise in older adults (around 65 years and more). The hereditary condition of Aplastic anaemia is known as "Fanconi anaemia" or childhood anaemia, congenital keratosis (DKC), Congenital pure red cell aplasia (DBA), Shwachman Diamond Syndrome (SDS) and the secondary adulthood Hypoplastic anaemia which may be secondary to infection, drugs, inflammatory conditions and cancer. [3,4]

Symptoms of Aplastic Anaemia

The most common symptoms are increased bleeding time, petechiae (pinpoint red spot on the skin), bruising, fatigue, mucosal haemorrhage, menorrhagia due to thrombocytopenia. Due to neutropenia recurrent bacterial and fungal infection are more common. In bacterial infections sepsis, pneumonia, urinary tract infection whereas in fungal infection aspergillosis, mucormycosis and candidiasis are frequently reported. Severe neutropenia along with bacterial and fungal infection leads to cause of death in several patients.[5] Anaemia causes fatigability same time shortness of breath, tachycardia (palpitation) and murmur.

In children short stature, microcephaly, developmental delay and skin and nail lesions are more prominent. In inherited syndrome fingernail dystrophy associated with dyskeratosis congenita reported in several cases.[6]

Diagnosis of Aplastic Anaemia

Complete Blood Count- CBC were conducted to evaluated neutropenia, thrombocytopenia anaemia and reticulocytopenia. Sometime abnormal cells such as myeloblast and atypical in peripheral blood film (PBF)/ lymphoid cells were also seen. In case of confirmation analysis Liver function test (lactate dehydrogenase test) renal function test were conducted. Serum vitamin B12 and red blood folate levels should be performed in condition of pancytopenia.[7]

Bone Marrow Biopsy- hypocellular tissue with decreased RBC, WBC and/or Megakaryocytes. The vacant space is composed of fat cells and marrow stroma. The specimen showed cytogenic, molecular and other specialized features as described below.[8]

Bone marrow is less than 25 percent with peripheral blood neutrophil count less than 500/microL (0.5×10^3/L), whereas Peripheral platelet counts noticed less than 20,000/microL.

Classification	Criteria	Cell count
Severe aplastic anaemia	Peripheral blood neutrophil count	<500/microL
	Peripheral blood platelet count	<20,000/microL
	Peripheral blood reticulocyte count	<60,000/microL
Very severe aplastic anaemia	Peripheral blood neutrophil count	<200/microL
Non- severe aplastic anaemia	Does not match the above criteria	

Blood Film Examination– macrocytosis and anisopoikilocytosis (different size and shape of red blood cells) were frequently seen. Blood cells demonstrate abnormal behaviour such as dysplastic neutrophil, hairy cells, abnormal platelets (small in size) and white blood cells (Figure 1). High power image of haematoxylin-stained bone marrow biopsy section demonstrating peculiar hypocellularity. Few hematopoietic cells i.e. lymphocytes, plasma cells, macrophages with marked pigments in their cytoplasm (Figure 2). The bone marrow aspirate smear with hypocellular particle with prominent stromal elements including fat cells and capillaries lined with residual hematopoietic cells such as lymphocytes, macrophages and endothelial cells (Figure 3a, b, c).

In the normal marrow biopsy section of a young adult. The marrow biopsy of young adult devoid of hematopoietic cells that contains only scattered lymphocytes and stromal cells. Hematopoietic spaces are replaced by pre-adipocytic fibroblast or reticular cells converted to adipocytes (Figure 1A, B).

Figure 2 A, B, Blood film examination showing different abnormal behaviour (haematoxylin stain).

DEB Test (Peripheral Blood Chromosomal Breakage Analysis) in case of falconi anaemia patients diepoxybutane test is conducted. Patients with transplant candidate and FA patient sibling also show positive results.

Flow Cytometry: It is used to detect GPI anchored proteins in paroxysmal nocturnal hemoglobinuria (PNH) patients.

Vitamin B12 and Folate: Level of Vitamin B12 and folate deficiency monitored for correct analysis.

Viral Studies: After recurrent infection of Hepatitis aplastic anaemia is reported in young male patients so screening of Hepatitis A/B/C, parvovirus B19, cytomegalovirus, Epstein Barr virus must be conducted.

Systemic Lupus Erythematosus: Screening of SLE conducted due to autoimmune response with cellular bone marrow. Myelofibrosis or hypocellular marrow are the characteristic features of autoimmune related blood disorders.

Chest X-ray and Other Radiology Patients suffers from Inherited bone marrow failure syndrome (IBMFS) and Dyskeratosis congenita (DC) showed abnormal chest X ray profile. This syndrome is characterized by abnormal nails, reticular cell pigmentation, oral leukoplakia and in some cases aplastic anaemia.[9]

Abdominal Ultrasound Scan and Echocardiogram Enlarged lymph nodes and spleen give a positive signal for haematological disorder or pancytopenia.

Pancytopenia With Hypocellular Bone Marrow
Acquired aplastic anaemia
Inherited aplastic anaemia
Hypoplastic MDS
Hypoplastic AML

Pancytopenia With Cellular Bone Marrow
Primary bone marrow disease

PNH: Paroxysmal nocturnal hemoglobinuria (PNH) is rare disease that have symptoms like haemolytic anaemia, haemoglobinuria, fatigue and shortness of breath. Some cases thrombosis, renal insufficiency and in worst cases renal failure were also reported.[10]

Myelopathies Due to apathy of spinal cord like spinal stenosis, disc regeneration, herniation, auto immune disorders and trauma. It may be cervical, thoracic and lumber.[11]

Hairy Cell Leukaemia Rare and chronic disease of B cell malignancy involving spleen, bone marrow and peripheral blood. Suffers from fatigue, weakness and cytopenia.[12]

Hypersplenism in this condition spleen become overactive and filtered too many blood cells and leads to deficiency or cytopenia condition. Hypersplenism may result in anaemia, leukopenia, thrombocytopenia and related serious underlying disease.[13]

Overwhelming Infection overwhelming post splenectomy infection (OPSI) is rare and fatal due to permanent dysfunction of spleen that can progress to flu-like symptoms and sepsis. In most of the cases it is rare but leads to high mortality rate if being untreated.[14]

Brucellosis Sarcoidosis it is a zoonotic infection transmitted to human through cattle sheep goats, camel, pigs and other animals.[15]

Hypoplastic Anaemia can be Divided into Below:

Pure Red Cell Aplasia (PRCA): It is a form of hypoplastic anaemia in which suppression of erythropoiesis and inappropriate immune response. The causes may be because of viral illness like parvovirus infection in immuno-compromised patients or in HIV infection. Other conditions related to PRCA are ABO mismatch or bone marrow transplant, Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or any other autoimmune disorders. Some medicines such as antiseizure medicines, recombinant erythropoietin and tranquilizers may leads to this condition. Chronic lymphoid leukaemia, chronic myeloid leukaemia, Hodgkin lymphoma, non- Hodgkin lymphoma and multiple myeloma are some rare causes of PRCA. Sometime Organic phosphates toxins consumption may lead to PRCA.[16]

Myelodysplastic Syndrome (MDS) The myelodysplastic syndrome (MDS) is a disorder characterised by peripheral cytopenia, dysplastic hematopoietic progenitors, hypercellular or hypocellular bone marrow which may later convert to acute myeloid leukemia. In MDS syndrome group of clonal hematopoietic stem cells showed mutation (common in genes involved in RNA splicing). Common features of MDS are:

1. Refractory anaemia with excess blast (RAEB): Hypercellular marrow with dyserythropoiesis and dysgranulosis: abnormal immature white blood cells 5 to 9% or 10 to 19% of nucleated marrow cells. this condition shows more than 2 cell lines with morphologic abnormality.[17]
2. Refractory anaemia: reticulocytopenia normal or hypercellular marrow with erythroid hyperplasia and dyserythropoiesis; abnormal immature white blood cells more than 5% of nucleated morrow cells.
3. Refractory anaemia with ringed sideroblastic: reticulocytopenia with ringed sideroblast in more than 15% nucleated marrow cells.
4. Refractory cytopenia with multilineage dysplasia and ringed sideroblast: more than 15% ringed sideroblast.
5. Myelodysplastic syndrome, unclassified: not defined to category
6. MDS with isolated del(5q): severe anaemia, thrombocytosis and deletion of long are of chromosome no. 5.[18]
7. Chronic myelomonocytic leukemia (CMML): Mixed with absolute monocytosis (>1000/mcL) in blood; significant increase in blood; significant increase in marrow monocyte precursors.
8. Chronic neutrophilic leukaemia: neutrophilia and absence of Philadelphia chromosome and fusion of BCR-ABL1 fusion gene.[19]

Myelophthisic Anaemia: The causes are replacement of bone marrow by metastatic cancer. Primary myelofibrosis granulomatous disease, lipid storage disease such as Gaucher disease and patients may suffer from two or three related disease simultaneously, or one diagnosis may appear to evolve into another. Many of these syndromes share an immune mediated mechanism of marrow destruction and some element of genomic instability resulting in a higher rate of malignant transformation.[20]

Drugs: Environmental toxins such as insecticide, benzene, nitrogen mustard, several medications such as chloramphenicol (Chloromycetin), phenylbutazone (butazolidine), sulfonamides (gantanol) some anticonvulsant, cimetidine causing Aplastic anaemia in several patients.[21]

Bone Marrow Lymphoma: Lymphoma is a type of cancer that originates in white blood cells called lymphocytes. Hodgkin's lymphoma involved in number of extra nodal anatomic sites such as CNS, testicles, skin. The main characteristic is the

bone marrow involvement without focal bone lesion. The patients present with the symptoms with fevers, night sweats, weight loss with prominent cytopenia.[22]

Non-Hodgkin's Lymphoma is a type of cancer in which white blood cells called lymphocytes grow abnormally forms tumours through the body. Diffuse large B-cell lymphoma and follicular lymphoma are among the most common subtypes.[23]

Systemic Lupus Erythematosis, Sjogren's Disease it is a chronic inflammatory disease that primarily occurs in lacrimal and salivary glands resulting in reduction of salivary and lacrimal flow. This disease is also associated increased CD+T cells production. These T cells maintain peripheral immune tolerance through suppression of proliferation and release of proinflammatory cytokines in immune cells.[24]

Vitamin B12 and Folate Deficiency the inability to make intrinsic factor chronic gastritis, gastrectomy (removal of part of stomach), autoimmune condition and other types of megaloblastic anaemia such as type 1 diabetes, thyroid disease and family history.[25]

Alcoholism Folate deficiency is the main reason for the development of megaloblastic haematopoiesis. The toxic effect of alcohol on erythrocyte production also reflected in several patients with megaloblastic anaemia. Excess of alcohol consumption Another important effect of alcohol is in haematopoiesis where marrow might be hypoplastic or aplastic.[26]

Hypocellular Bone Marrow Failure (BMF) acquired bone marrow failure results of drugs, toxins or virus infection. Acquired BMF is an idiopathic aplastic anaemia that become life threatening caused by autoimmune destruction of haemopoietic progenitor stem cell.[27]

Legionnaires Disease legionnaires disease is the type of lung infection which occurs on the interaction with legionella bacteria. With common symptoms like fever, cough, diarrhoea and confusion. In several patients' legionnaires disease show marked inhibition of myelopoiesis and granulopoiesis. Hence, the infection of Legionella pneumophila may be the cause of aplastic anaemia.[28]

Anorexia Nervosa Patients with anorexia nervosa showed gelatinous marrow transformation (GMT) or malnutrition bone marrow. Some studies indicate anorexia nervosa associated with pancytopenia and other types of idiopathic aplastic anaemia.[29]

Aplastic Anaemia (AA) Therapy

Many patients with AA may present stable blood count for years, but pancytopenia may worsen over time in some patients who progress to serve pancytopenia and meet the criteria for SAA or become transfusion dependent, can then be treated according to current algorithms.

Treatment- treatment for aplastic anaemia depending upon severity, age and stage at the time of presentation. There are several options are available including blood transfusion, medications and at last bone marrow transplantation.

Blood Transfusion: as the blood is not produced properly blood transfusion can relieve the symptoms in diseased patients.[30]

a) **Red Blood Cells** relieve anaemia and fatigue by improving R.B.C. count
b) **Platelets** important blood clotting factor so replenishment help excessive bleeding.

Multiple transfusion can create complications such as excess of iron in the body that will damage vital body parts. Counter medication is given to get rid of side effects.

Stem Cell Transplant help in rebuilding of the required stem cells for R.B.C. production but this option is only applicable with younger patients with matched sibling donor (sibling donor in most of the cases). In this therapy diseased marrow is irradiated using chemotherapy. The healthy stem cells filtered from the blood of donor and injected to the diseased patient where they are migrated to the required area and repair cell damage. This process required long hospitalization and sometimes rejection treat. In several cases this rejection leads to life threating situations. The probability of donor matching is also rare.[31]

Immunosuppressive Drug Therapy

Anti-thymocyte Globulin (ATG)- In aplastic anaemia the patient's immune system is reacting against the bone marrow, interfering with its ability to make blood cells. ATG works by killing cells of immune system (T lymphocytes) that attacking bone marrow stem cells. The immunosuppressive drug therapy allows patient's bone marrow stem cells to make blood cells. ATG is given intravenously for 8-12 hours a day (for 4 days). ATG maintain blood supply in 50% cases, ATG along with cyclosporin improve blood counts in 70% cases. Anti-thymocyte globulin therapy reduces or stops blood transfusion in three months whereas complete recovery takes about 9 months.[32]

Advantages

Well tolerated by most of the patients. Cheap and easily affordable and patient required brief hospitalization. In most of the studies reported response rate (complete response (CR) + partial response (PR)] is approximately 50-70%. Most recent studies have shown improved overall survival (above 80% at 1 year), regardless of the initial response to IST (immuno-suppressive therapy).[33]

Side Effects- Some patients complain about chills, fever, hives (urticaria or itchy raised welts that are found on the skin), nausea, vomiting, diarrhoea, dizziness and headache.[34]

Indication: Immunosuppressive Therapy

1) Patients with non-severe aplastic anaemia who are dependent on red cell and/or platelets transfusion.
2) Patients with non-severe aplastic anaemia who, although not transfusion dependent may have significant neutropenia and be at risk of infection
3) Patients with severe or very severe aplastic anaemia who are >40 years of age and
4) Younger patients with severe or very severe disease and unable to meet HLA- compatible donor.

Non-transplant Therapy of Aplastic Anaemia

- For patients older than 40 years with newly-diagnosed severe or very severe aplastic anemia, young patients (without MSD), ATG immunosuppression and cyclosporine A (CsA) therapy should be maintained as frontline therapy, offering outcomes comparable to allogeneic BMT with reduced morbidity in older patients.[35]
- Horse ATG is the recommended ATG source, based on a randomized-controlled trial of 120 patients showing a superior overall response (68% compared to 37%) and OS (96% compared to 76%) for horse ATG-based IST compared to rabbit ATG-based IST.[36]

Salvage Therapy for Relapsed and Refractory AA

- In the Aplastic anemia, overall patient improvement, ~33–35% of patients relapse after initial recovery, while another 35% will be refractory to frontline IST.
- Most patients (~60–68%) who relapse following an initial response to IST can be salvaged with full-dose CsA monotherapy and/or a second course of IST with rabbit ATG and CsA or transplant.

Horse ATG in Aplastic Anemia

- ATG is a heterologous anti-serum obtained by injecting

human lymphocytes in animals.[37]
- Most available data from large randomised clinical trials refer to polyclonal ATGs obtained from horse (h), which have to be considered the gold standard for AA treatment.
- hATG is the recommended first line IST for patients ineligible for HLA identical sibling haemopoietic stem cell transplantation (HSCT) as stated by the British Committee for Standards in Haematology (BCSH) guidance following the results obtained from a prospective randomised trial comparing hATG versus rATG for the treatment of AA.

ATG is created by injecting human white blood cells (T cells) into horse and rabbit after generation of immune response antibodies were extracted. On comparison horse derived ATG (hATG) results in better survival response and increased blood count.[38]

Action of ATG in Aplastic Anemia:
- hATG targets the T-lymphocytes, the cells that are responsible for destroying or suppressing the stem cells in patients with aplastic anemia
- hATG also stimulates haemopoiesis

ATG in Aplastic Anemia:
- Improves long term survival in sAA at standard recommended doses.
- When used along with cyclosporine, the response rate increases to 70%.
- Safer as compared to high dose cyclophosphamide.
- 2nd course of immunosuppression is less frequently required.
- High response rate and survival regardless of severity of AA.

hATG dose
- Practical dose: The normal daily dose of ATG is 40mg/kg over 4 hours, for 4 days. Prophylactic treatment for serum sickness may be initiated on day 1 with Prednisone 1 mg/kg, which may be continued for 2 weeks
- Dosage in Pack Insert: 10 to 20mg/kg daily for 8-14 days followed by alternate day therapy for a total of 21 doses. Patients reports thrombocytopenia in several cases so regular monitoring for CBC count should be carried out.
- Conventional premedication prior to every ATG dose involves acetaminophen and diphenhydramine.

Role of Cyclosporine:
- Cyclosporine is another immunosuppressive drug that targets T-lymphocytes
- Studies have shown that cyclosporine used alone is not as effective as ATG
- The combination of cyclosporine & ATG has been found to be more effective than either drug alone

Dose and Adverse Effects of Cyclosporine A (CsA):
- CsA may be initiated on day 1 at a daily dose of 10 mg/kg (15 mg/kg per day in children) to a target trough level between 200 and 400 ng/mL. CsA should be given for the period of 6 months.
- Two of the most serious side effects are high BP & kidney damage Patient frequently develop hypertension during CsA treatment
- Irreversible nephrotoxicity in renal transplant patients
- Convulsions
- Gingival hyperplasia
- Hepatotoxicity in renal transplant patients

ELTROMBOPAG Eltrombopag (Promacta/Revolade) increased the number of platelets and decrease the bleeding time. It is a lab synthesized platelet growth factor that promote bone marrow to synthesize more platelets. After approval by U.S. Food and Drug Administration (2014) Eltrombopag was approved to treat refractory aplastic anaemia. Whereas in 2018, FDA approved the same for treatment of aplastic anaemia. It comes as a tablet and as a powder for oral suspension (liquid) to take by mouth.[39]

Side Effects OF Eltrombopag (Promacta)
- Some allergic reaction such as hives, difficult breathing, swelling of your face, lips, tongue, or throat.
- Pain or burning on urination.
- Fever, chills, body aches, flu symptoms, unusual weakness or tired feeling.
- Nausea, upper stomach pain, itching, loss of appetite.
- Dark urine, clay-coloured stools.
- Jaundice (yellowing of the skin or eyes);
- Pain, swelling, warmth, or redness in one or both legs.

CONCLUSION
Severe and very severe Aplastic anaemia were more common than non-severe aplastic anaemia in many studies. The assessment of degree of disease severity is important in treatment decisions. In the current study current assessment procedure and criteria for severity is discussed. Depending upon the severity various treatment procedure is given. Bone marrow transplantation is considered best treatment option if matched sibling donor is available if not then immune suppressive therapy is considered next best option. knowledge of clinical and hematological parameters will certainly aid in early diagnosis of Aplastic anemia and sub-categorization of the disorder for better treatment. But in a developing country financial constraints and lack of awareness forms a major drawback in providing an apt patient management. Thus, management of aplastic anemia in a developing country is definitely a challenging task. It is the need of the hour that tertiary centers such as ours create awareness amongst the general population and more studies for affordable alternative treatment options should be established.

Ethical Approval
The Institutional Review Board Approval is not required.

Declaration of Patient Consent
Patient's consent is not required as patients' identity is not disclosed or compromised.

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Conflicts of Interest
There are no conflicts of interest.

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