A STUDY OF CLINICAL AND ETIOLOGICAL PROFILE OF PANCYTOPENIA IN RURAL SETUP

By Dr. Pratyush Miglani

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In partial fufillment of the requirements for the degree of

M.D
IN
GENERAL MEDICINE

Under the guidance of
Dr. Srinivasa Rao
Professor, Department of Medicine

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR.

DECLARATION BY THE CANDIDATE

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Date: Signature of the Candidate

Place: Kolar Dr. Pratyush Miglani

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR

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This is to certify that the dissertation titled **"A STUDY OF CLINICAL AND ETIOLOGICAL PROFILE OF PANCYTOPENIA IN RURAL SETUP"** is a bonafide research work done by **Dr. Pratyush Miglani** in partial fulfilment of the requirement for the degree of DOCTOR OF MEDICINE IN GENERAL MEDICINE.

Signature of the Guide
Dr. Srinivasa Rao
Professor, Department of Medicine
SDUAHER,Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR

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Date:
Place: Kolar Dr. Pratyush Miglani.

LIST OF ABBREVIATIONS USED

NCPF	- Non- cirrhotic portal fibrosis
NMS	- Neuroleptic malignant syndrome
ESM	- Ejection systolic murmur
CVS	- Cardiovascular system
RBC	- Red blood corpuscules
HIV	- Human immunodeficiency virus
PNH	- Paroxysmal nocturnal hemoglobinuria
MDS	- Myelodysplastic syndrome
NSAID	- Non- steroidal anti- inflammatory drugs
BMT	- Bone marrow transplantation

ABSTRACT

Background: Pancytopenia is an important clinico-haematological entity not uncommonly encountered in our day to-day clinical practice. It refers to a reduction in all the three formed elements of blood: erythrocytes, leucocytes and thrombocytes. There are varying trends in its clinical pattern, etiology and outcome. The management and prognosis of pancytopenia depends upon the underlying etiopathology.

Objectives: To study the etiology, presentation and outcome of patients with pancytopenia presenting in a health set-up in rural South India.

Materials and Methods: A prospective study on 30 adult patients of pancytopenia was carried out at R.L.Jalappa hospital, Kolar during the year of 2010-2011. Relevant history was taken and detailed physical examination was carried out. Bone marrow aspiration study was done for all patients. Results were tabulated and data were analyzed using SPSS program, student t-test, Spearman's correlation co-efficient.

Results: 57% patients were from younger age group (less than 40 years). Male to female ratio was 1:1. Pallor (100%), fatiguability (83.3%), fever (50%) and bleeding (36.7%) were the main presenting complaints. Nutritional anemias (megaloblastic, 46.7% and dimorphic, 30%) emerged as the major cause for pancytopenia. Poor dietary intake, alcoholism in men and pregnancy and child- birth in women were found to be major causative factors for the same. Hypersplenism (10%) was another notable cause. Pancytopenia due to aplastic anemia, had a high (100%) mortality rate.

Conclusion: A high degree of suspicion and awareness is needed as etiology, presentation and differential diagnosis of pancytopenia is diverse. Nutritional deficiency is still prevalent in our society and emerged as a major cause of pancytopenia. Patients are not able to afford life- saving treatment modalities. We still need to make considerable improvement in our healthcare system in terms of awareness and availablility.

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INTRODUCTION

Pancytopenia is an important clinico-haematological entity not uncommonly encountered in our day to-day clinical practice. There are varying trends in its clinical pattern, treatment modalities, and outcome[1,2]. It refers to a reduction in all the three formed elements of blood: erythrocytes, leucocytes and thrombocytes[1,3,4]. It should be suspected on clinical grounds when a patient presents with pallor, prolonged fever and a tendency to bleed[2].

The etiology of pancytopenia varies in different populations depending on the differences in age patterns, nutritional status, climate and the prevalence of infections[2]. Various factors encompassing geographic distribution and genetic disturbances may cause variation in the incidence of disorders causing pancytopenia[4,5,6]. Underlying pathology determines the management and prognosis of the patients[5].

Pancytopenia can be due to decrease in hemopoietic cell production in bone marrow, e.g. by infections, toxins, malignant cell infiltration or suppression, or can have normocellular or even hypercellular marrow, without any abnormal cells, e.g. in ineffective hematopoiesis and dysplasia, maturation arrest of all cell lines and peripheral sequestration of blood cells[3,4]. Pancytopenia is a common hematological problem with an extensive differential diagnosis, and the optimal diagnostic approach to pancytopenia remains undefined[4,7,8,9]. The management and prognosis of pancytopenia depends on the underlying etiopathology. Hence the finding of correct etiology in a given case is crucial[6].

OBJECTIVES OF THE STUDY

GENERAL

To study the etiology, presentation and outcome of patients with pancytopenia presenting in a health set-up in rural South India during a period of 12 months.

SPECIFIC

- To study clinical presentation of pancytopenia patients in a large teaching hospital in rural south india
- To study the causes of pancytopenia in these patients
- To study the outcome of these cases

REVIEW OF LITERATURE

Pancytopenia refers to a reduction in all three formed elements of blood -- erythrocytes, leukocytes, and platelets[2-5]. The mechanism by which pancytopenia develops appears to be either associated with decrease in haematopoietic cell production as a result of destruction of the marrow tissue by toxins, replacement by abnormal or malignant tissue, or perhaps suppression of normal growth and differentiation. In some patients the marrow may be normally cellular or even hypercellular[5].

The causes of pancytopenia can be :

a) Ineffective haematopoiesis with cell death in the marrow.
b) Formation of defective cells which are rapidly removed from circulation.
c) Sequestration and/or destruction of cells by the action of antibodies or,
d) Trapping of normal cells in a hypertrophied and over-reactive reticuloendothelial system.

Variation in the frequency of disorders causing pancytopenia has been ascribed to differences in methodology, stringency of diagnostic criteria, geographic area, period of observation, genetic differences, and varying exposure to cytotoxic agents[3-5].

The presenting symptoms are usually attributable to anemia or thrombocytopenia. Leucopenia is an uncommon cause of initial presentation but can become the most serious threat to life during the course of disorder[10].

There are many causes of pancytopenia, some are curable for which an early and prompt diagnosis is required. In certain circumstances complete cure is not possible, even in these cases early diagnosis and supportive treatment can improve the quality of life by decreasing morbidity and mortality[11].

ETIOPATHOGENESIS: Pancytopenia may be due to decreased bone marrow production or bone marrow failure, clonal disorders of haematopoiesis, increased non-immune-mediated destruction or sequestration, or an immune-mediated destruction of blood cells[12,13].

Classification	Congenital/inherited	Acquired	Acquired
Mechanism	Decreased bone marrow production	Decreased bone marrow production	Increased destruction/sequestration
Common	Gaucher's disease Fanconi's anaemia	Cytotoxic chemotherapy Radiotherapy Megaloblastic anaemia Bone marrow infiltration Myelodysplasia Myelofibrosis Idiopathic aplastic anaemia	Liver disease Portal hypertension
		Connective tissue disorders (rheumatoid arthritis, SLE) Acute viral infections (CMV, EBV, HIV) HIV disease Mycobacterial infection	
Uncommon	Various childhood metabolic, or complex multisystem disorders (e.g., dyskeratosis congenita, congenital amegakaryocytic thrombocytopenia, Shwachman's syndrome)	Paroxysmal nocturnal haemoglobinuria Anorexia nervosa Transfusion-associated GVHD Heavy-metal poisoning Infection (parvovirus B19 infection, HHV6 or CMV in transplant recipients, legionnaire disease)	Hypersplenism secondary to myelo/lymphoproliferative disorders Haemophagocytic syndromes Drug-induced immune pancytopenia Evans' syndrome with tricytopenia Infection (brucellosis, visceral leishmaniasis)

Table 1- Etiology for pancytopenia[12,13]

Pancytopenia is a common feature of many illnesses. Although the medical history, physical examination, and basic laboratory studies can often point out the etilogy, the distinction is more difficult in certain hematologic diseases, and further testing is required. Causes of pancytopenia that need to be mentioned specifically include Fanconi's anemia, paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), myelofibrosis and aleukemic leukemia. Each of these conditions is briefly reviewed in the following discussion.

Fanconi's anemia. This congenital form of aplastic anemia is an autosomal recessive inherited condition in which 10% of patients present beyond childhood[14,15]. Typical physical stigmata include short stature, skin hyperpigmentation, microcephaly, thumb or radius hypoplasia, urogenital abnormalities, and mental retardation.

Paroxysmal nocturnal hemoglobinuria. PNH is an acquired disorder that is characterized by anemia caused by intravascular hemolysis and manifested by transient episodes of hemoglobinuria and life-threatening venous thromboses[16]. A deficiency of CD59, an erythrocyte surface antigen that inhibits reactive lysis, islargely responsible for the hemolysis[17]. Approximately 10% to 30% of patients with aplastic anemia develop PNH later in the clinical course[18]. It is possible that the majority of patients with PNH have an underlying aplastic process[19]. The diagnosis of PNH is currently made by demonstrating decreased expression of the cell surface antigen CD59 by flow cytometry, replacing previously used screening tests such as the sucrose hemolysis test and examination of the urine for hemosiderin[20].

Myelodysplastic syndromes. The MDSs are a group of clonal hematopoietic stem cell disorders that are characterized by abnormal bone marrow differentiation and maturation, which leads to bone marrow failure with peripheral cytopenias, dysfunctional blood elements, and probability of leukemic conversion. The bone marrow in MDS is typically hypercellular or normocellular, although hypocellularity may also be detected. It is important to distinguish hypocellular MDS from aplastic anemia because the diagnosis dictates clinical management and prognosis. A critical feature that identifies hypocellular MDS is an associated clonal cytogenetic abnormality[21].

Idiopathic myelofibrosis. The two major features of idiopathic myelofibrosis are extramedullary hematopoiesis (in spleen, liver, and other organs) and bone marrow fibrosis. The extramedullary hematopoiesis causes hepatosplenomegaly in the majority of patients. Bone marrow biopsy specimens show varying degrees of reticulin or collagen fibrosis, with prominent megakaryocytes.

Aleukemic leukemia. Aleukemic leukemia, a rare condition characterized by the absence of blast cells in the peripheral blood of patients with leukemia, occurs in fewer than 10% of all leukemic patients and is generally seen in very young children or in elderly patients. Bone marrow aspirate and biopsy demonstrate the blast cells.

Combination pancytopenia

Many conditions associated with pancytopenia result from a combination of decreased bone marrow production and increased destruction or sequestration of blood cells. They include:

- Connective tissue disorders (most commonly rheumatoid arthritis and systemic lupus erythematosus)
- Acute CMV infection
- Mycobacterial infection
- Infectious mononucleosis
- HIV has also been associated with pancytopenia secondary to underproduction of blood cells
- Felty's syndrome (rheumatoid arthritis, splenomegaly, and neutropenia) may also be associated with pancytopenia

MEGALOBLASTIC ANEMIA

Megaloblastic anaemia has been recognized as a clinical entity for over a century. The first clinical description of pernicious anaemia, which is one of the known causes of megaloblastic anaemia, has been attributed to Thomas Addison in 1849[22].

Megaloblastic anaemia results from abnormal maturation of haematopoietic cells due to defective DNA synthesis. Two vitamins, cobalamin (vitamin B12) and folic acid are essential for DNA biosynthesis. Deficiency of either vitamin results in asynchrony in the maturation of the nucleus and cytoplasm of rapidly regenerating cells. In the haematopoietic system this asynchrony results in abnormal nuclear maturation with normal cytoplasmic maturation, apoptosis, ineffective erythropoiesis, intramedullary haemolysis, pancytopenia and typical morphological abnormalities in the blood and marrow cells[23-25].

This ineffective erythropoiesis is accompanied by intramedullary hemolysis causing an elevated lactate dehydrogenase and indirect bilirubin in the serum[24].

Megaloblastic anaemia leads to substantial morbidity if unrecognized or misdiagnosed. Its etiology is multifactorial and may result from dietary deficiency, impaired absorption and transport or impaired utilization of these vitamins in DNA synthesis.

In India with diverse ethnic populations, different dietary and social customs, the incidence of megaloblastic anaemia and its associated problems have not been adequately documented[26].

Megaloblastic anaemia must be an important differential diagnosis in patients presenting with pancytopenia[26,27]. Khanduri et al in a study done on 175 patients of pancytopenia found that 62% of them had pancytopenia. A study of pancytopenia in nutritional megaloblastic anaemia from northwest India, done by Sarode R. et al[28], revealed that 43.8% had pancytopenia. Quite a sizeable number of studies from Indian- subcontinent have observed similar findings.

ETIOLOGY

Nutritional

In India with her diverse ethnic populations, different dietary and social customs, the incidence and pattern of megaloblastic anaemia and its associated implications are quite different from western world[26] .

Inadequate Dietary Intake - Dietary cobalamin deficiency arises in vegans who omit meat, fish, eggs, cheese, and other animal products from their diet. The largest group in the world consists of Hindus, and it is likely that many millions of Indians are at risk of deficiency of cobalamin on a nutritional basis[25,29,30]. Subnormal serum cobalamin levels are found in up to 50% of randomly selected, young, adult Indian vegans[29,30]. Dietary cobalamin deficiency may also arise rarely in nonvegetarian individuals who exist on grossly inadequate diets because of poverty or ignorance[25]. Hence, inadequate dietary intake, over-cooking of our food, poverty and unawareness contribute to high prevalence of vitamin B12 deficiency[31,32].

Increased demand - In contrast to western studies, Indian researchers have observed peak incidence of megaloblastic anemia in age group of 20-30 years and preponderance of women. Possibly due to the increased demand during growth spurt, puberty and child-bearing age group in a population already deficient in cobalamin[26]. A 1973 study by WHO on the nutritional status of pregnant women in India documented iron, folate and cobalamin deficiency[33]. Patients are being treated in the short term with haematinics and transfusions with relief of symptoms. In most instances long term follow up and diet counselling are not being done. The fortification of diet to prevent megaloblastosis needs to be taken up as a national public health issue[26].

Folate in pregnancy - . Folate is now reviewed not only as nutrient needed to prevent megaloblastic anemia in pregnancy but also as a vitamin essential for reproductive health. It plays substantial role in the relationship between various outcomes of human reproduction i.e pregnancy, lactation and male reproduction[34]. The association of folate deficiency and neural tube defects has long been known. Folate supplementation has been widely studied. The Cochrane database included twentyone studies from various regions[35]. The results were: Folate supplementation was associated with a reduction in the proportion of women with low hemoglobin level in late pregnancy and reduction in megaloblastic erythropoiesis. There was a possible reduction in the incidence of low birth.

Pernicious anemia – Pernicious anemia is the end stage of type A chronic atrophic (autoimmune) gastritis. The gastritis results in the loss of parietal cells in the fundus

and body of the stomach. The loss of these cells is associated with the failure of intrinsic-factor production and results in vitamin B_{12} deficiency and megaloblastic anemia.

An autoimmune basis for the gastritis is supported by the presence of mononuclear-cell infiltration into the gastric mucosa with loss of parietal and zymogenic cells, autoantibodies to parietal cells and intrinsic factor, regeneration of parietal and zymogenic cells after therapy with corticosteroids or immunosuppressive drugs, familial predisposition, and association with autoimmune endocrinopathies and antireceptor autoimmune diseases[25,36].

Finding the cure for pernicious anaemia even led to the discovery of vitamin B12[37-43]. A recent population survey revealed that 1.9 percent of persons more than 60 years old have undiagnosed pernicious anemia[44].

The onset and progression of pernicious anemia are slow. The median age at diagnosis is 60 years. Slightly more women than men are affected. The usual presentation is with symptoms of anemia. Population-based studies have revealed an excess risk of gastric carcinoma as well as gastric carcinoid tumors in patients with pernicious anemia.

The presence of type A chronic atrophic gastritis can be confirmed by gastric biopsy. Total achlorhydria, the direct result of the loss of gastric parietal cells, is diagnostic of pernicious anemia because it is the only gastric lesion that results in total achlorhydria[36].

Drugs - Drugs that act by interfering with DNA synthesis, such as antimetabolites and alkylating agents, some antinucleosides used against HIV and other viruses, can all induce megaloblastic anemia[45].

Trimethoprim (in high, extended doses) and pyrimethamine, which bind with greater affinity to bacterial than human dihydrofolate reductase, have beenassociated with megaloblastic anemia, primarily among patients already at risk for folic acid deficiency. Antibiotics such as sulfasalazine and anticonvulsants such as phenytoin have been linked to folate-related changes which induce megaloblastic anemia, perhaps related to interference with absorption. Decreased cobalamin levels have been reported with term use of histamine 2-receptor antagonists and proton pump inhibitors (omeprazole)[46-49]. Khanduri et al obtained history of H_2 receptor antagonists or proton pump inhibitors intake in about 20% of patients presenting with megaloblastic anemia.

Alcohol - The impact of alcohol on the hematopoietic system can be divided into direct and indirect effects. Direct effects are primarily seen in the bone marrow and involve leucocytes, erythrocytes and platelets. Indirect effects are secondary to metabolic or physiologic alterations resulting in liver disease and to nutritional abnormalities, such as folate deficiency[50-53].

Direct - The most striking indication of alcohol's toxic effects on bone marrow cells is the appearance of numerous large vacuoles in early RBC precursor cells. The vacuoles usually appear in the pronormoblasts 5 to 7 days following the initiation of

heavy alcohol consumption. To a lesser extent, vacuoles also develop in the granulocyte precursors also[50,51]. This impaired hematopoiesis affects mainly erythrocytes. It also affects the function of the leukocytes and platelets. Hence, considerable number of patients present with pancytopenia[52,53].

Indirect - Haematological functions are also affected indirectly from nutritional deficiency, chronic alcoholic liver disease and other metabolic derangement[51]. Nutritional deficiency occurs not only due to poor dietary habits practised by alcohol abusers but also by the effects of alcohol on the consumption, storage and neutralization of folate and other vitamins[52,53]. Reasons for folate deficiency in alcoholic patients include an antifolate effect of ethanol, intestinal folate malabsorption, interruption of normal enterohepatic circulation, and ethanol-induced increased urinary folate excretion[54].

Blood cell precursors require folic acid and other B vitamins for their continued production. Under conditions of folic acid deficiency, precursor cells cannot divide properly and large immature and nonfunctional cells (i.e., megaloblasts) accumulate in the bone marrow as well as in the bloodstream. Megaloblasts occur frequently in the bone marrow of alcoholics; they are particularly common among alcoholics with symptoms of anemia, affecting up to one-third of these patients[53,54].

Gastrointestinal diseases –

Total or partial gastrectomy

Intestinal stagnant loop syndrome

Ileal resection and Crohn's disease

Selective cobalamin malabsorption with proteinuria (Imurslund-Grasbeck syndrome)

Tropical sprue

Fish tapeworm infestation

Zollinger- ellison syndrome

Clinical features

- Evidence of anemia can include patients presenting with pallor and generalised weakness, but otherwise asymptomatic, particularly if the anemia had developed gradually and is compensated. In severe anemia, patients may have dyspnea, tachycardia, and cardiopulmonary distress.
- Thrombocytopenia, leading to bruising, gum bleeding , epistaxis, per rectal or pervaginal bleeding can be a presenting feature[31].
- Patients can have symptoms of neutropenia, like fever, particularly related to respiratory tract, urinary tract and skin infections.
- Gastritis, anorexia, nausea and vomiting can be present in considerable number of patients. The lining epithelium of the gastrointestinal tract becomes atrophic in megaloblastosis. A vicious cycle of megaloblastosis leading to atrophy of mucosa, and subsequent malabsorption of the two vitamins, worsens megaloblastic anaemia[26].
- Patients may have icterus, caused by accumulation of unconjugated bilirubin in plasma due to the death of nucleated red cells in the marrow (ineffective erythropoiesis)[24,25].

- Glossitis, characterized by a smooth tongue due to loss of papillae, occurs in patients with cobalamin deficiency.
- Cobalamin deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the posterior and pyramidal tracts of the spinal cord and, less frequently, optic atrophy or cerebral symptoms. The patient, more frequently male, presents with paresthesias, muscle weakness, or difficulty in walking and sometimes dementia, psychotic disturbances, or visual impairment[24].
- Abdominal scars may suggest a blind loop syndrome due to gastric surgery or a lack of ileal absorption of cobalamin in a patient who had an ileal resection.

Heamtologic findings

Peripheral blood - Oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main feature. The MCV is usually >100 fL unless a cause of microcytosis (e.g., iron deficiency or thalassemia trait) is present. Some of the neutrophils are hypersegmented (more than five nuclear lobes)[25].

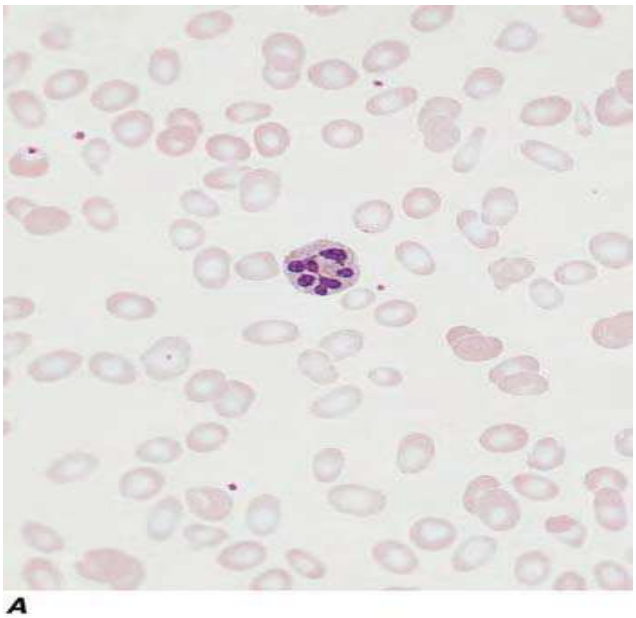

Figure 1. The peripheral blood in severe megaloblastic anemia

Bone marrow (figure 2) - In the severely anemic patient, the marrow is hypercellular with an accumulation of primitive cells due to selective death by apoptosis of more mature forms. The erythroblast nucleus maintains a primitive appearance despite maturation and hemoglobinization of the cytoplasm. The cells are larger than normoblasts, and an increased number of cells with eccentric lobulated nuclei or nuclear fragments may be present[25].

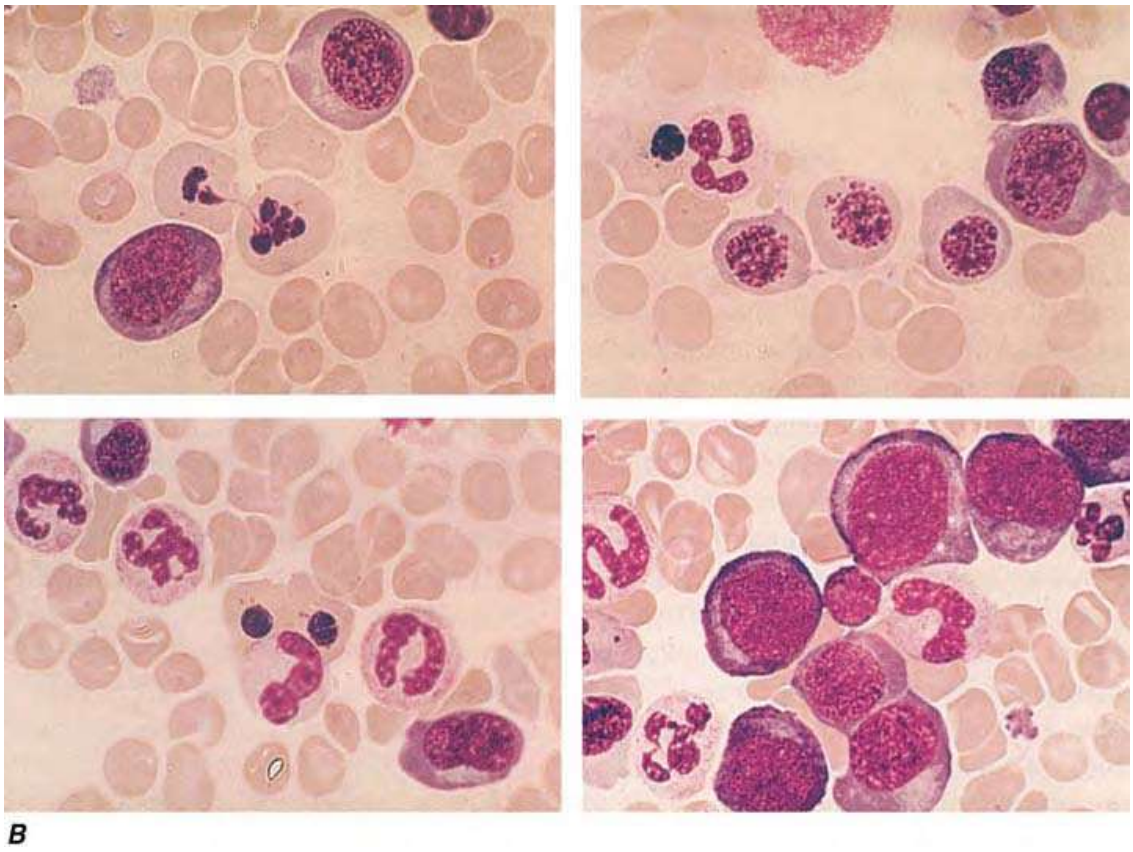

Figure 2. The bone marrow in severe megaloblastic anemia

APLASTIC ANEMIA

Aplastic anemia is defined as the failure of bone marrow to produce blood cell components. The hallmarks of the disease are pancytopenia and a hypocellular bone marrow. Aplastic anemia is a rare disease, and its incidence in Asia is two to three times higher as compared to west. This geographic variation is more likely caused by environmental rather than genetic elements[55,56].

Etiology

The most common causes of aplastic anemia are discussed below. Inherited forms of the disorder are rare and consist of Fanconi's anemia, dyskeratosis congenita, and Schwachman syndrome. Among patients with the acquired disorder, idiopathic aplastic anemia, in which no cause is apparent, accounts for approximately 65% of all cases of aplastic anemia[57].

Secondary aplastic anemia

Secondary aplastic anemia occurs after exposure to environmental factors and in certain disorders. The following factors have been implicated as causes of secondary aplastic anemia:

Chemicals. A definitive linkage between benzene and aplastic anemia has been established from clinical and epidemiologic data, as well as from animal and in vitro studies[58,59].Despite this association, benzene is still widely used as a solvent and in the manufacture of other chemicals, drugs, dyes, explosives, leather goods, and rubber.

Drugs- Chloramphenicol was, at one point, the most common cause of drug-induced aplastic anemia. Anticonvulsant medications, in particular carbamazepine and hydantoins, are also associated with the development of aplastic anemia. Treatment with antineoplasticcytotoxic agents carries a high risk of aplastic anemia, and drugs such as gold salts, D-penicillamine, phenylbutazone, quinacrine, and acetazolamide have also been implicated.

Infectious agents. Some viral infections, notably infectious mononucleosis caused by Epstein-Barr virus, have been associated with aplastic anemia. Whether anemia results from a direct effect by the virus on the bone marrow or from a host immunologic response is unclear. The association between hepatitis and aplastic anemia is also strong[60].

Radiation. Repeated exposure to low doses of radiation has been associated with aplastic anemia. Single exposure to high doses of radiation (such as after a nuclear explosion) is more likely to lead to leukemia rather than aplastic anemia[57].

Rheumatic diseases. Connective tissue disorders such as rheumatoid arthritis and systemic lupus erythematosus have been associated with aplastic anemia. However, it is not certain whether the drugs used to treat these disorders (NSAIDs, gold salts, allopurinol, D-penicillamine) cause the anemia or whether the activated immune system, which is a feature of these diseases, is the responsible factor[57].

Pregnancy. Many cases of aplastic anemia have also been found in association with pregnancy.

Pathophysiology

The pancytopenia in aplastic anemia reflects failure of the hematopoietic process manifested as a severe decrease in the numbers of all hematopoietic progenitor cells. Two mechanisms have been suggested for bone marrow failure. The first mechanism is direct hematopoietic injury by chemicals (eg, benzene), drugs, or radiation to both proliferating and quiescent hematopoietic cells. The second mechanism, supported by clinical observations and laboratory studies, is immune-mediated suppression of marrow cells[61]; examples of this mechanism are bone marrow failure after graft-versus-hostdisease (GVHD), eosinophilic fasciitis, and hepatitis. The mechanism for idiopathic, pregnancy-associated, and some cases of drug-associated aplastic anemia is not clear but may involve immunologic processes as well. Cytotoxic T cells are thought to mediate the suppressive effect on hematopoietic cells through the production of hematopoiesis-inhibiting cytokines such as interferon-γ and tumor necrosis factor-α[62].

Clinical presentation

The signs and symptoms of patients presenting with aplastic anemia are typically related to the decrease or absence of peripheral blood cellular components[63]. The clinical presentation ranges from insidious to dramatic. Because platelets are depleted early in the process of the disease, dependent petechiae, bruising, gum bleeding, buccal hemorrhage, epistaxis, or retinalhemorrhage may be among the first presentations. Because of anemia, patients may complain of shortness of breath, fatigue, or chest pain. Neutropenia or leukopenia may result in fever, chills, or infections. Hepatosplenomegaly, lymphadenopathy, or bone pain are less common in patients with aplastic anemia.

Differential diagnosis

Pancytopenia is a common feature of many illnesses. Although the medical history, physical examination, and basic laboratory studies can often exclude aplastic anemia, the distinction is more difficult in certain hematologic diseases, and further testing is required. Causes of pancytopenia that need to be considered in the differential diagnosis include Fanconi's anemia, paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), myelofibrosis, aleukemic leukemia, agranulocytosis, and pure red cell aplasia. Each of these conditions is briefly reviewed in the etiology section.

Diagnostic Evaluation

The hallmark of aplastic anemia is pancytopenia and a hypocellular bone marrow[56]. A complete blood count is the initial diagnostic study, and this study reveals varying degrees of anemia, thrombocytopenia, and leukopenia. Because of the hypoproliferative marrow, the reticulocyte response is low or absent despite the anemia. Aplastic anemia is classified as mild, moderate, or severe on the basis of the severity of the pancytopenia. Criteria for classifying aplastic anemia as severe are listed in table below[64]. The most important prognostic factor is the absolute neutrophil count (ANC). Patients with an ANC less than 0.5 x 109/L have a high risk of developing infection and patients with an ANC less than 0.2 x 109/L have a poor prognosis[64].

Diagnostic Criteria for Severe Aplastic Anemia*	
At least two of the following:	**One of the following:**
Absolute neutrophil count <0.5 x 109/L Platelet count < 20 x 109/L Anemia with corrected reticulocyte count < 1 %	Bone marrow cellularity < 25 % Bone marrow cellularity < 50 % with fewer than 30% hematopoietic cells
***According to the International Aplastic Anemia Study Group**	

Table 2. Diagnostic criteria for aplastic anemia

Bone marrow aspiration and biopsy must be performed to rule out other possible causes for pancytopenia, such as MDS or leukemia. In normal bone marrow, 40% to 60% of the marrow space is typically occupied with hematopoietic cells (depending on the age of the person) (figure 3- A); by contrast, the bone marrow in patients with aplastic anemia typically contains very few hematopoietic cells and consists primarily of fatty space and stromal cells **(**figure 3- B). Human leukocyte antigen (HLA) typing should be performed on all patients as soon as the diagnosis of aplastic anemia is entertained. Tests for exposure to viruses, especially cytomegalovirus, should also be performed early because these tests assist in the choice of blood products for transfusion[57].

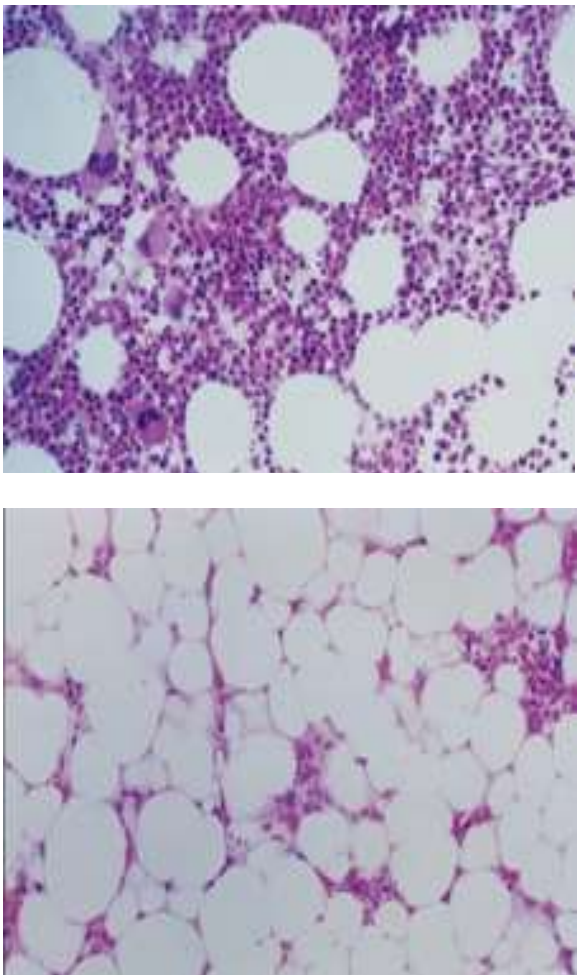

Figure 3. Bone marrow specimens from a, A. Healthy patient B. Patient with aplastic anemia

Treatment Considerations and Supportive Care

The severity of aplastic anemia and the age of the patient are, in general, the two major considerations that guide treatment[65]. Occasionally, patients with mild to moderate aplastic anemia respond to treatment with androgens, which act by stimulating erythropoiesis[66].

While diagnostic testing for aplastic anemia is being undertaken and treatment options are being contemplated, patients may require transfusions of blood products. It is important that patients, particularly potential candidates for bone marrow

transplantation, receive as few blood products as possible in order to decrease the risk of sensitization. Also, blood donations from a family member should be avoided during this time period[57].

Platelet transfusions should be given when the patient has an active bleeding episode or when the platelet count is severely depressed. Precautions for neutropenia should be followed in patients with aplastic anemia. These patients should focus on careful mouth and dental care, wash hands frequently and thoroughly, minimize invasive procedures.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) from an HLA matched sibling is the treatment of choice for severe aplastic anemia in patients age 60 years or younger. HLA typing of the patient and any potential sibling donor should be performed as soon as BMT has been identified as a treatment option. Survival rates of 70% to 90% after BMT have been reported in a number of studies, with higher survival rates in patients younger than 40 years who receive HLA identical BMT[56].

Immunosuppressive Therapy

The risk of morbidity and mortality after BMT increases with age. Hence, immunosuppressive treatment is considered first-line treatment for older patients and for younger patients for whom a matched sibling donor is not available[57].

HYPERSPLENISM

Pancytopenia is one of the well-known hematologic manifestations of hypersplenism. Banti (1800) and Gristel (1866) explained the idea that spleen may produce ill effects through exaggeration of its normal activities. Chauffard (1907) introduced the term hypersplenism to refer to this concept[67,68].

Hypersplenism is a clinical syndrome characterized by enlargement of spleen, reduction of at least one cell line in the blood in the presence of normal marrow function and evidence of increased release of premature cells such as reticulocytes or immature platelets from the bone marrow into the blood. In hypersplenism there is peripheral destruction of cells resulting in cytopenias and if the condition is quite severe then it causes pancytopenia[69].

The bone marrow picture is either of normocellularity or hypercellularity in hypersplenism.Erythropoiesis is usually normoblastic. A disease process that has been responsible for enlargement of spleen may infiltrate the bone marrow[70].

Since hypersplenism is treatable cause of pancytopenia in most cases, timely intervention can reduce patient morbidity and mortality to great extent[69]. The criteria to diagnose hypersplenism include splenomegaly, a peripheral blood picture of anaemia, neutropenia,and thrombocytopenia (either singly or in combination), a cellular bone marrow, and significant improvement in peripheral blood picture following splenectomy[71,72].

Etiology

Recent studies conducted in indian sub-continent have proven strong corelation between pancytopenia, hypersplenism and chronic liver disease. Pancytopenia in chronic liver disease can be due to hypersplenism, megaloblastic anemia and primary marrow suppression[69].

Ashraf et al studied 150 patients of chronic liver disease presenting with pancytopenia and found hypersplenism as cause of pancytopenia in 68% of patients[69]. Sundaresan et al observed hypersplenism in 28 of 100 patients with splenomegaly and found that majority (60.7%) of them had splenomegaly of congestive origin i.e. due to Non- cirrhotic portal fibrosis (NCPF) and cirrhosis of liver[72]. The causes of hypersplenism in these patients were as follows:

1. Non-cirrhotic portal fibrosis (NCPF)
2. Cirrhosis of liver
3. Hyper-reactive malarial splenomegaly (HMS)
4. Chronic hepatitis
5. Idiopathic

Some of the westren researchers have also found liver disorder as a major cause of hypersplenism in their studies[73,74].

Non-cirrhotic portal fibrosis (idiopathic portal hypertension) and hypersplenism

IPH is a rare disorder, characterized clinically by portal hypertension, splenomegaly, and hypersplenism accompanied by pancytopenia[75]. The underlying

etiology and pathogenesis are poorly understood. It has been proposed that infectious, toxic (exposure to trace metals or chemicals), immunological and immunogenetic factors may play a role[76].

As hepatosplenomegaly is the leading symptom, other causes of organomegaly such as infections, malignancy, malformations and metabolic disorders, must be ruled out. IPH is not associated with hepatic cirrhosis but portal vein thrombosis, non-thrombotic causes, and parenchymal atrophy of the liver secondary to portal malperfusion[75,76]. Although the etiology remains obscure, either presinusoidal or extrahepatic vasculopathy lead to elevatedintrahepatic portal resistance[77-79]. The overall prognosis is generally benign, although catastrophic cases related to bleeding from esophageal varices may occur[78,80].

Splenectomy in NCPF

Various studies have reported overwhelming results in patients who underwent splenctomy. Johnson HA et al in a review of 391 splenectomies performed over a sixteen-year period, observed that pancytopenia and haemolytic complications of the disease processes were the commonest indications for splenectomy[81]. Sundaresan et al have observed improvement in all three cell lines occuring in all the patients undergoing splenectomy[72]. Letoquart observed a positive response in 94% of 47 patients[82] .

Of late, alternatives to splenectomy have been suggested for hypersplenism. These include splenic embolisation to reduce splenic volume[83,84] and transjugular intrahepatic portosystemic shunt (TIPS) for cirrhotics developing hypersplenism[85] .

DRUG - INDUCED PANCYTOPENIA

Drugs are one of the commonest, though quite often less well recognised, cause of pancytopenia[86]. Pancytopenia sometimes-and quite unexpectedly-resultsfrom treatment with a commonly used drug thought to be "safe." When a single drug has been used and the bloodpicture returns to normal on its withdrawal there can be little doubt about the association. Identifying the causative agent is much more difficult when several drugs have been given,even when a complete drug history is available[87,88]. Drugs effects may be predictable (i.e., dose dependent) or unpredictable (possibly immune mediated or idiosyncracy)[86].

Benestad first distinguished between conditional (or idiosyncratic) responses and immunological effects. Conditional effects are probably due to abnormal target cells or drug metabolism and are present before, during, and after administration of the drug. Immunological 'sensitisation" to a particular drug is seen only after more than one dose has been given; though the predisposition may be present before treatment it cannot be detected experimentally[89].

Linn et al published their experience of 25 cases of methotrexate induced pancytopenia over a period of 5 years. Majority of their patients were elderly. Delayed drug clearance in the elderly due to prolonged enterohepatic circulation, possibly would have placed them at higher risk of pancytopenia. Additionly, the elderly are more likely to have poor nutritional status[90].

Hematologic side effects of psychotropic drugs are quite well reported[91]. But pancytopenia is not very commnly encountered with. Bautista-Quach et al have reported a case of pancytopenia associated with clonazepam use[92]. Several hypotheses have been illustrated in drug-induced aplastic anemia including direct toxic effect to hematopoietic elements, and immune-mediated destruction secondary to idiosyncratic reaction to a drug[93]. Additionally, benzodiazepine-induced thrombocytopenia has been shown to be mediated by platelet specific antibodies[94]. Elouni et al have observed three cases of pancytopenia induced by use of the newer anti-epileptic drug levetiracetam[95].

Sodium valproate is a commonly used anticonvulsant. Valproate is increasingly being used in the treatment of psychiatric conditions, particularly bipolar affective disorder[96]. Hematologic toxic effects of valproate vary in type and severity, ranging from marrow failure with fatal aplastic anemia to an incidental finding of RBC macrocytosis. The cause for the thrombocytopenia is unclear[97]. Immune-mediated peripheral destruction has been suggested by some authors as the underlying mechanism based on marrow morphologic findings and platelet autoantibody studies[98]. Dysmyelopoietic effects can occur years after starting the drug also[99]. It is postulated that this these toxic effects may be dose-related and much more common than is recognized.

Opatrny et al have reported pancytopenia in a patient who was being treated with albendazole for pulmonary echinococcal cyst[100]. Erie et al have reported a case of amiodarone induced bone marrow granuloma presenting as pancytopenia[101].

Oral hypoglycemic agents have also been reported to present with pancytopenia. Patients taking pioglitazone, rosiglitazone, metformin have been found to have pancytopenia[102,103].

All these experiences stress the need for monitering of hematologic parameters of patients who are on these drugs and points us to keep a high degree of suspicion since in majority of these cases pancytopenia is reversible after withdrawl of the drug.

MATERIALS AND METHODS

SOURCE OF DATA

This study was conducted at R.L.Jalappa Hospital and Research Centre, Tamaka, Kolar, attached to Sri Devaraj Urs Academy Of Higher Education And Research (SDUAHER) during the year 2010-2011.

The study was done on thirty patients who presented with pancytopenia.

INCLUSION CRITERIA

- Patients aged above 18 years.
- Patients having pancytopenia on routine hemogram.
- Patients consenting to bone marrow aspiration.

EXCLUSION CRITERIA

- Patients less than 18 years of age.
- Patients on chemotherapy drugs.

Selection of subjects

- Pancytopenia was defined as reduction in all three blood elements, Haemoglobin - less than 10 g/dl, Total leukocyte count - less than 3,500/ mm^3, Platelets - less than 100,000 / mm^3.
- Complete hemogram is a routine investigation in R.L.Jalappa hospital for both inpatients and outpatients. The patients having pancytopenia were identified by going through hemogram reports.
- The identified patients underwent relevant detailed history taking and those who were confirmed to have pancytopenia and satisfied inclusion and exclusion criteria were included in the study.

METHOD OF COLLECTION OF DATA

- Detailed physical examination was made of the patients included in the study and their clinical profile was documented as per a systematic proforma.

- Other relevant investigations were carried out, to confirm the diagnosis, including etiology.

- **Complete hemogram**

  Two ml of anticoagulated blood was collected for complete hemogram. Complete blood count was performed using an automated blood counter. In cases of very low counts and abnormal cells, a manual review of the instrument's results was performed using the improved Neubauer counting chamber (Hausser Scientific, Blue Bell, PA, USA). Peripheral smear was studied after staining with leishman's stain. Special satins – Periodic acid schiff reagent stain, Myeloperoxidase, Sudan black and Pearl's stain were used when indicated.

- **Bone marrow aspiration study**

  This was done in all patients to identify the etiology. An informed consent was obtained. A Jamshidi needle was used to aspirate material from the Posterior iliac crest in adults. Local infiltration anaesthesia was used after administering a test dose. Sterile precautions were observed.

The needle and stillete were placed in position and the cap was closed. After piercing the skin and subcutaneous tissue, the periosteum and cortex were pierced with a drilling action. Once in the marrow cavity, the stillete was removed and 0.2-0.3 ml of marrow fluid was aspirated with a sterile disposable 10ml syringe. The aspirate was transferred to a set of slides and smeared. The needle was withdrawn and a tincture benzoin seal applied. Slides were stained with Leishman's stain. In case of failure, bone marrow aspirations were done at different sites.

- Pancytopenia was defined as Hb < 10 gm%, leucocyte count < 3,500/mm^3 and platelet count < 1,00,000/mm^3. Anaemia was defined as mild (Hb 9–12 gm%), moderate (Hb 5–9 gm%) and severe (Hb < 5 gm%). Leucopenia was defined as mild (leucocyte count > 3,000/mm3), moderate (leucocyte count 1,000–3,000/mm3) and severe (leucocyte count < 1,000/mm3). Thrombocytopenia was defined as mild (platelet count > 50,000/mm3), moderate (platelet count 20,000–50,000/mm3) and severe (platelet count < 20,000/mm3).

- Other investigations were performed in selected cases according to their provisional diagnosis, including malarial parasite and antigen, blood culture, liver function test, iron profile, enzyme-linked immunosorbent assay for the human immunodeficiency virus (HIV) I and II, the hepatitis B surface antigen (HBsAg) and ultrasound scanning of abdomen.

- The patient's history, physical examination results and haematological parameters were recorded on the study proforma and the data was tabulated.

- **Statistical Methods**

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on the data is made,

1**.** Dependent variables should be normally distributed.

2. Samples drawn from the population should be random.

3. Cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

RESULTS

Thirty adult patients of pancytopenia fulfilled the criteria according to our study protocol, and were selected for inclusion into the study during the year of 2010-2011. Following data was recorded.

Demography

Age in years	Number of patients	%
18-20	5	16.7
21-30	7	23.3
31-40	5	16.7
41-50	6	20.0
51-60	4	13.3
>60	3	10.0
Total	30	100.0

Mean ± SD: 39.17±17.69

Table 3: Age distribution of the patients studied

Gender	Number of patients	%
Male	15	50.0
Female	15	50.0
Total	30	100.0

Table 4: Gender distribution of the patients studied

Maximum number of patients were in age group 20-30 years, followed by age group of 40-50 years. Mean age of patients was 39 years, range 18- 67 years. There were fifteen male patients and fifteen female patients, ratio of 1:1.

Clinical manifestations

Clinical manifestation	Number	Total	Percentage
Fatiguability	25	30	83.3%
Fever	15	30	50%
Bleeding	11	30	36.7%
Anorexia	05	30	16.7%
Respiratory distress	04	30	13.3%
Bone pain	03	30	10%
Abdominal distension	04	30	13.3%
Diarrhea	04	30	13.3%
Pallor	30	30	100%
Icterus	11	30	36.7%
Edema	08	30	26.7%
ESM on CVS exam.	12	30	40%
Splenomegaly	07	30	23.3%
Hepatomegaly	06	30	20%

Table 5- Frequency of observed clinical manifestations

The commonest presenting complaint was fatiguability in 83% (25/30) followed by fever in 50% (15/30). Bleeding from various sites was encountered by 36.7% of the patients (11/30). Five patients had per- rectal bleeding in form of blood in stools. Two patients had excessive loss of blood during pregnancy and child birth. Two patients had intra- cranial bleeding. One patient had epistaxis and another bleeding gums.

Pallor was universally present in all the patients on examination. Splenomegaly was seen in 23% (07/30) and hepatomegaly in 20% (06/30) of patients. 40% (12/30) patients had an ejection systolic murmur on CVS examination.

Severity of cytopenias

Anemia	Number	Total	Percentage
Mild	01	30	3.3%
Moderate	06	30	20%
Severe	23	30	76.7%

Table 6- Frequency and severity of anemia among patients

Leucopenia	Number	Total	Percentage
Mild	07	30	23.3%
Moderate	21	30	70%
Severe	02	30	6.7%

Table 7- Frequency and severity of leucopenia among patients

Thrombocytopenia	Number	Total	Percentage
Mild	20	30	66.7%
Moderate	04	30	13.3%
Severe	06	30	20%

Table 8- Frequency and severity of thrombocytopenia

Bone marrow cellularity

Bone marrow	Number of patients	Percentage
Cellular	27	90%
Hypo cellular	3	10.0%
Total	30	100.0%

Table 9- Bone marrow cellularity of the patients

Etiology

Etiology	**Number**	**Total**	**Percentage**
Megaloblastic anemia	14	30	46.7%
Dimorphic anemia	09	30	30%
Hypersplenism	03	30	10%
Aplastic anemia	02	30	6.7%
Drug- induced pancytopenia	01	30	3.3%
AML	01	30	3.3%

Table 10- Etiology of pancytopenia in patients

The commonest cause of pancytopenia was megaloblastic anaemia and was seen in 14/30 patients (46.7%), followed by dimorphic anaemia (30%), and hypersplenism (14%). The other causes of pancytopenia were aplastic anemia (6.7%), drug- induced pancytopenia and AML.

Outcome

Outcome	Number	Total	Percentage
Discharged	27	30	90%
Expired	03	30	10%

Table 11- Outcome of the patients studied

Correlative observation

	Diagnosis					
	Megaloblastic anemia (n=14)	**Dimorphic anemia (n=9)**	**Hypersplenism (n=3)**	**Aplastic anemia (n=2)**	**Drug induced pancytopenia (n=1)**	**AML (n=1)**
Age in years						
• <40	10 (71.4%)	3 (33.3%)	2(66.7%)	1 (50.0%)	0	1(100.0%)
• >40	4 (28.6%)	6 (66.7%)	1(33.3%)	1 (50.0%)	1(100.0%)	0
Gender						
• Male	6 (42.9%)	5 (55.6%)	0	2 (100.0%)	1(100.0%)	1(100.0%)
• Female	8 (57.1%)	4 (44.4%)	3 (100.0%)	0	0	0

Table 12- Frequency of various etiologies of pancytopenia according to age and gender

Clinical manifestation	Diagnosis						P value
	Megaloblastic anemia (n=14)	Dimorphic anemia (n=9)	Hypersplenism (n=3)	Aplastic anemia (n=2)	Drug induced pancytopenia (n=1)	AML (n=1)	
1.Fatiguability	14 (100.0%)	7 (77.8%)	2 (66.7%)	2 (100.0%)	0	0	0.013*
2.Fever	2 (14.3%)	5 (55.6%)	0	1 (50.0%)	1 (100.0%)	1 (100.0%)	0.474
3.Bleeding manifestation	4 (28.6%)	4 (44.4%)	0	2 (100.0%)	0	1 (100.0%)	0.142
4.Anorexia	4 (28.6%)	1 (11.1%)	0	0	0	0	0.770
5.Respiratory distress	2 (14.3%)	0	1 (33.3%)	0	1 (100.0%)	0	0.162
6.Abdominal distension	0	1 (11.1%)	3 (100.0%)	0	0	0	0.002**
7.Bone pain	1 (7.1%)	0	1 (33.3%)	1 (50.0%)	0	0	0.184
8.Diarrhea	1 (7.1%)	3 (33.3%)	0	0	0	0	0.556
9.Pallor	14 (100.0%)	9 (100.0%)	3 (100.0%)	2 (100.0%)	1 (100.0%)	1 (100.0%)	1.000
10.Icterus	4 (28.6%)	5 (55.7%)	2 (66.7%)	0	0	0	0.484
11.Edema	2 (14.3%)	3 (33.3%)	2 (66.7%)	0	1 (100.0%)	0	0.170
12..ESM on CVS exam.	8 (57.1%)	2 (22.2%)	1 (33.3%)	1 (50.0%)	0	0	0.479
13.Splenomegaly	2 (14.3%)	2 (22.2%)	3 (100.0%)	0	0	0	0.060+
14.Hepatomegaly	3 (21.4%)	1 (11.1%)	2 (66.7%)	0	0	0	0.477

Table 13- Correlation between clinical manifestations and etiology

Outcome	Diagnosis						P value
	Megaloblastic anemia (n=14)	**Dimorphic anemia (n=9)**	**Hypersplenism (n=3)**	**Aplastic anemia (n=2)**	**Drug induced pancytopenia (n=1)**	**AML (n=1)**	
Discharged	14 (100%)	09 (100%)	03 (100%)	0	0	01 (100%)	<0.001**
Expired	0	0	0	02 (100%)	01 (100%)	0	

Table 14- Outcome of patients according to etiology of pancytopenia

DISCUSSION

Demographical analysis

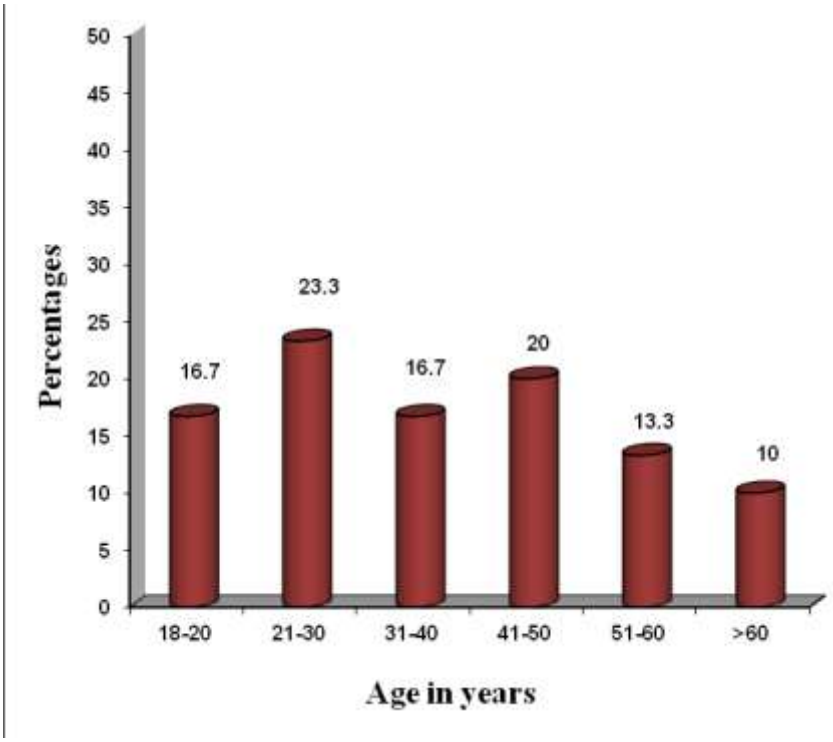

Figure 4- Age distribution among cases of pancytopenia

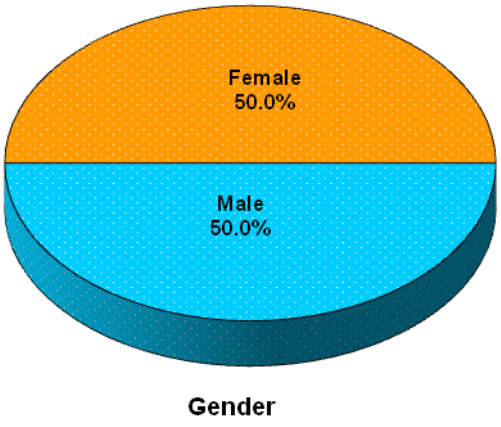

Figure 5- Sex distribution among cases of pancytopenia

Majority of cases were in younger age groups, 18-45 years of age. Incidence was similar among males and females, male: female ratio was 1:1. This was in contrast to number of other studies conducted in Indian sub- continent that observed more incidence among males. Jalbani et al[1] studied forty patients of pancytopenia in a teaching hospital in Pakistan and observed that male: female ratio was 2.6: 1. Similar observations were made by Santra et al[2], Khodke et al[5] and Kumar et al in india.

Probable reasoning behind this observation has been thought to be our social rituals, customs and their implications. Ours being a male dominated society, and the increased exposure of men to industrial, agricultural and other occupational toxins and pollutants has been proposed as a reason behind increased noted incidence of pancytopenia among men[1].

But the equivocal incidence observed among men and women in this study could actually be an indicator of high burden of nutritional anemia among women, especially pregnant or lactating females.

Clinical manifestations

The commonest presenting complaint was fatiguability in 83% (25/30) followed by fever in 50% (15/30) and bleeding manifestations in 36.7% of the cases (11/30). Five patients had per- rectal bleeding in form of blood in stools. Two patients had excessive loss of blood during pregnancy and child birth. Two patients had intra-cranial bleeding. One patient had epistaxis and another bleeding gums.

Pallor was universally present in all the patients on examination. Splenomegaly was seen in 23% (07/30) and hepatomegaly in 20% (06/30) of patients. 40% (12/30) patients had an ejection systolic murmur on CVS examination. This study has found a correlation between pancytopenia and pallor, fever, and easy fatigability; this is in accordance with other studies[4,7] .

Clinical manifestation	Number	Total	Percentage
Fatiguability	25	30	83.3%
Fever	15	30	50%
Bleeding	11	30	36.7%
Anorexia	05	30	16.7%
Respiratory distress	04	30	13.3%
Bone pain	03	30	10%
Abdominal distension	04	30	13.3%
Diarrhea	04	30	13.3%
Pallor	30	30	100%
Icterus	11	30	36.7%
Edema	08	30	26.7%
ESM on CVS exam.	12	30	40%
Splenomegaly	07	30	23.3%
Hepatomegaly	06	30	20%

Etiology

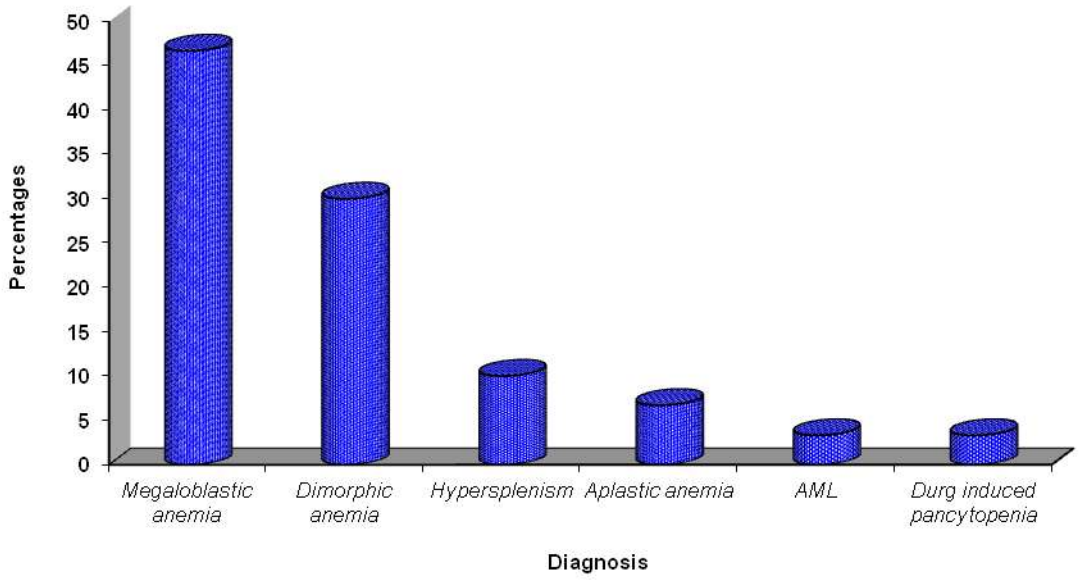

Figure 6- Etiological distribution of our subjects

The commonest cause of pancytopenia in our study was megaloblastic anemia and was seen in 14/30 patients (46.7%), followed by dimorphic anaemia (30%). Kodke et al studied 50 patients of pancytopenia in Delhi and made similar observations. This increased incidence of megaloblastic and dimorphic anaemia correlates with the high prevalence of nutritional anemias in our country[5]. Diagnosis in these patients was established by bone marrow findings and they responded well to the appropriate vitamin B_{12} and adjunctive iron therapy.

There was significant history of alcohol intake in seven patients and all of them were found to have nutritional anemias leading to pancytopenia. All patients were males. Three patients had megaloblastic anemia and other four had dimorphic picture on peripheral smear and bone marrow examination. Alcohol abuse, causing

impaired hematopoiesis through its direct and indirect (anti-folate) effects, leading to pancytopenia has been ascertained by many studies throughout the world[36-40].

Another major group identified was post- partum women. There were seven post- partum patients who presented with pancytopenia. Six patients had megaloblastic anemia and one patient had dimorphic anemia.

This observation has immense importance as it stresses upon a major public health issue. Importance of folate in pregnancy is widely and long known. The WHO study on the nutritional status of pregnant women in India[21] and the Cochrane database[42] , among other studies, have observed the magnitude of this problem in our society. This observation in current study suggests that we still need to take strong steps in improving education and awareness among women. Additionally, fortification of food might need to be taken up as national health issue, as suggested by other researchers also[14].

Hypersplenism was the next most common cause of pancytopenia in this study. 10% (3/30) of patients were diagnosed to have hypersplenism, leading to pancytopenia. All three patients were females. Splenomegaly was evident on clinical examination. Bone marrow aspiration study showed a cellular marrow. Ultrasound scanning of abdomen revealed features suggestive of portal hypertension, with normal liver.

The incidence of hypersplenism as cause of pancytopenia is subject to enormous geographical variation, as has been observed by other studies[4]. Sundaresan et al too, in their study on patients of hypersplenism in South India, found idiopathic portal hypertension as most frequent cause of hypersplenism[35]

Present study identified two patients of aplastic anemia who presented with pancytopenia. Both were males. One was 24 years old and another 80 years. Both patients expired after suffering massive intra- cranial bleed.

One patient of bipolar disease, a 55 year old gentleman, on regular treatment for the same, was found to have pancytopenia on routine complete hemogram. Bone marrow was normocellular. On carefully eliciting the drug history it was found that patient had been taking sodium valproate since seven years for bipolar disorder. Patient expired while platelet autoantibody studies were being contemplated.

Hematologic toxic effects of valproate vary in type and severity, ranging from marrow failure with fatal aplastic anemia to an incidental finding of RBC macrocytosis[57]. Valproate intake causing pancytopenia is not uncommonly reported[57-60]. Researchers have suggested that these hemato- toxic effects of the drug are dose-related and much more than is recognised[59].

Outcome

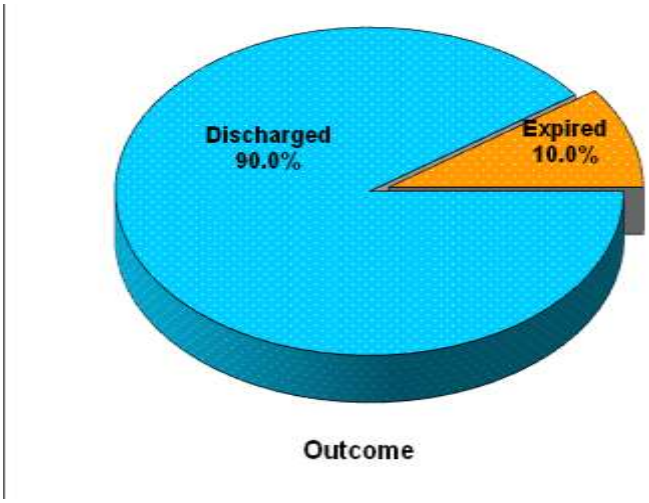

Figure 7- Outcome of patients of pancytopenia

Ninety percent (27/30) patients got discharged from hospital after appropriate treatment. They were provided diet- counselling, wherever necessary and were advised to follow- up regularly. Ten percent of patients (3/30) expired.

Two patients of aplastic anemia, expired after suffering massive intra- cranial bleed. They were on supportive therapy, immunosuppressive agents and transfusion of blood elements, but they could not afford bone marrow transplantation.

Correlative analysis

	Megaloblastic anemia (n=14)	Dimorphic anemia (n=9)	Hypersplenism (n=3)	Aplastic anemia (n=2)	Drug induced pancytopenia (n=1)	AML (n=1)
Age in years						
<40	10 (71.4%)	3 (33.3%)	2(66.7%)	1 (50.0%)	0	1(100.0%)
>40	4 (28.6%)	6 (66.7%)	1(33.3%)	1 (50.0%)	1(100.0%)	0
Gender						
Male	6 (42.9%)	5 (55.6%)	0	2 (100.0%)	1(100.0%)	1(100.0%)
Female	8 (57.1%)	4 (44.4%)	3 (100.0%)	0	0	0

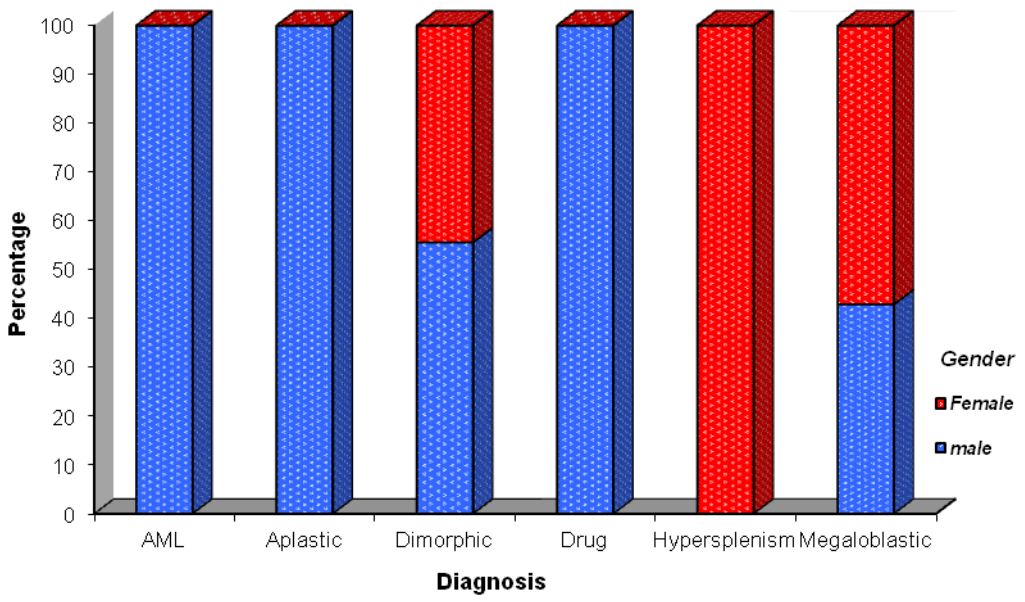

Figure 8- Distribution of etiology of pancytopenia according to gender

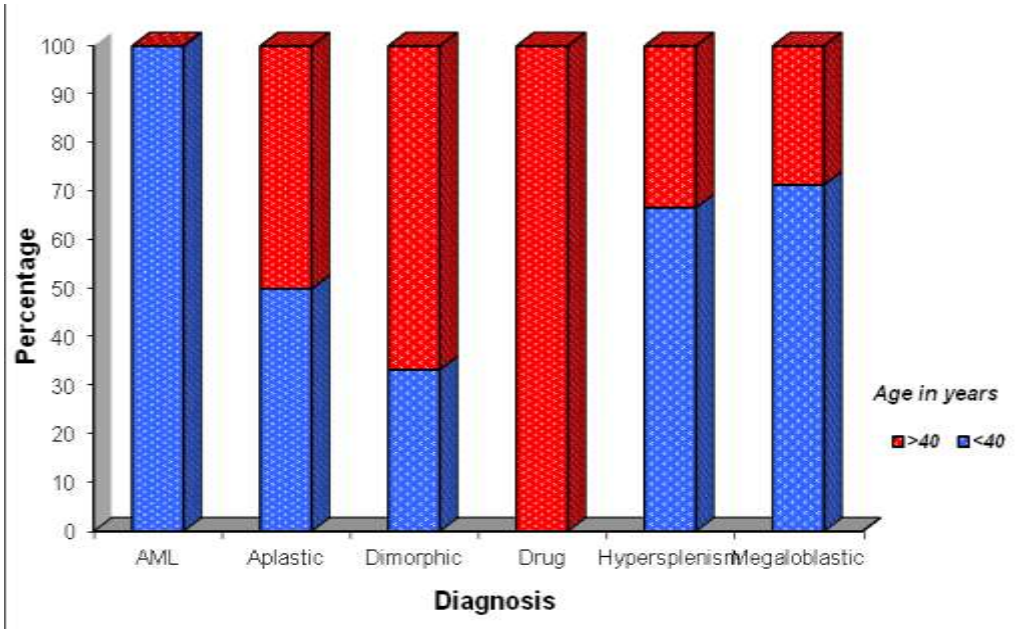

Figure 9- Distribution of etiology of pancytopenia according to age

Majority (71.4%) of patients of megaloblastic anemia were in younger age-group, less than 40 years. Additionally, prevalence of megaloblastic anemia was more in women (57.1%). Other Indian researchers too, in contrast to western studies, have observed peak incidence of megaloblastic anemia in younger age groups and preponderance of women. Possibly due to the increased demand during growth spurt, puberty and child-bearing age group in a population already deficient in cobalamin[14].

All three cases of hypersplenism were women. Although there is no literature directly linking preponderance of hypersplenism towards either sex, but Sundaresan et al observed female to male ratio of 1.6: 1 in their study on hypersplenism in South India[35].

Both patients of aplastic anemia were men. There is no proven male preponderance for the disease but some researchers have suggested increased exposure to occupational and environmental toxins as a possibility.

Clinical manifestation	Diagnosis						P value
	Megaloblastic anemia (n=14)	Dimorphic anemia (n=9)	Hypersplenism (n=3)	Aplastic anemia (n=2)	Drug induced pancytopenia (n=1)	AML (n=1)	
1.Fatiguability	14 (100.0%)	7 (77.8%)	2 (66.7%)	2 (100.0%)	0	0	0.013*
2.Fever	2 (14.3%)	5 (55.6%)	0	1 (50.0%)	1 (100.0%)	1 (100.0%)	0.474
3.Bleeding manifestation	4 (28.6%)	4 (44.4%)	0	2 (100.0%)	0	1 (100.0%)	0.142
4.Anorexia	4 (28.6%)	1 (11.1%)	0	0	0	0	0.770
5.Respiratory distress	2 (14.3%)	0	1 (33.3%)	0	1 (100.0%)	0	0.162
6.Abdominal distension	0	1 (11.1%)	3 (100.0%)	0	0	0	0.002**
7.Bone pain	1 (7.1%)	0	1 (33.3%)	1 (50.0%)	0	0	0.184
8.Diarrhea	1 (7.1%)	3 (33.3%)	0	0	0	0	0.556
9.Pallor	14 (100.0%)	9 (100.0%)	3 (100.0%)	2 (100.0%)	1 (100.0%)	1 (100.0%)	1.000
10.Icterus	4 (28.6%)	5 (55.7%)	2 (66.7%)	0	0	0	0.484
11.Edema	2 (14.3%)	3 (33.3%)	2 (66.7%)	0	1 (100.0%)	0	0.170
12..ESM on CVS exam.	8 (57.1%)	2 (22.2%)	1 (33.3%)	1 (50.0%)	0	0	0.479
13.Splenomegaly	2 (14.3%)	2 (22.2%)	3 (100.0%)	0	0	0	0.060+
14.Hepatomegaly	3 (21.4%)	1 (11.1%)	2 (66.7%)	0	0	0	0.477

Figure- Clinical manifestations of different etiology of pancytopenia

Majority of patients presented with fatiguability. All patients of megaloblastic anemia and 77.8% (7/9) patients of dimorphic anemia had fatiguability as a presenting complaint. Since p value is significant (0.013) for this observation, it was concluded that there is a co-relation between fatiguability and pancytopenia.

Bleeding manifestations were recorded in eleven patients, and it was significant for patients of aplastic anemia (100%).

Abdominal distension was observed in all patients of hypersplenism, and thus it is also a significant factor, p value of 0.002.

Pallor was universally present, in all patients, on examination. Icterus was seen in 55.7% (5/9) of patients of dimorphic anemia and 66.7% patients of hypersplenism.

In 66.7% (2/3) patients of hypersplenism and 21.4% (3/14) patients of megaloblastic, hepatomegaly was observed on examination. Significantly, splenomegaly was noted in all patients of hypersplenism.

On examination of cardiovascular system, an ejection systolic murmur was observed in 57.1% (8/14) patients of megaloblastic anemia, and 22.2% (2/9) patients of dimorphic anemia.

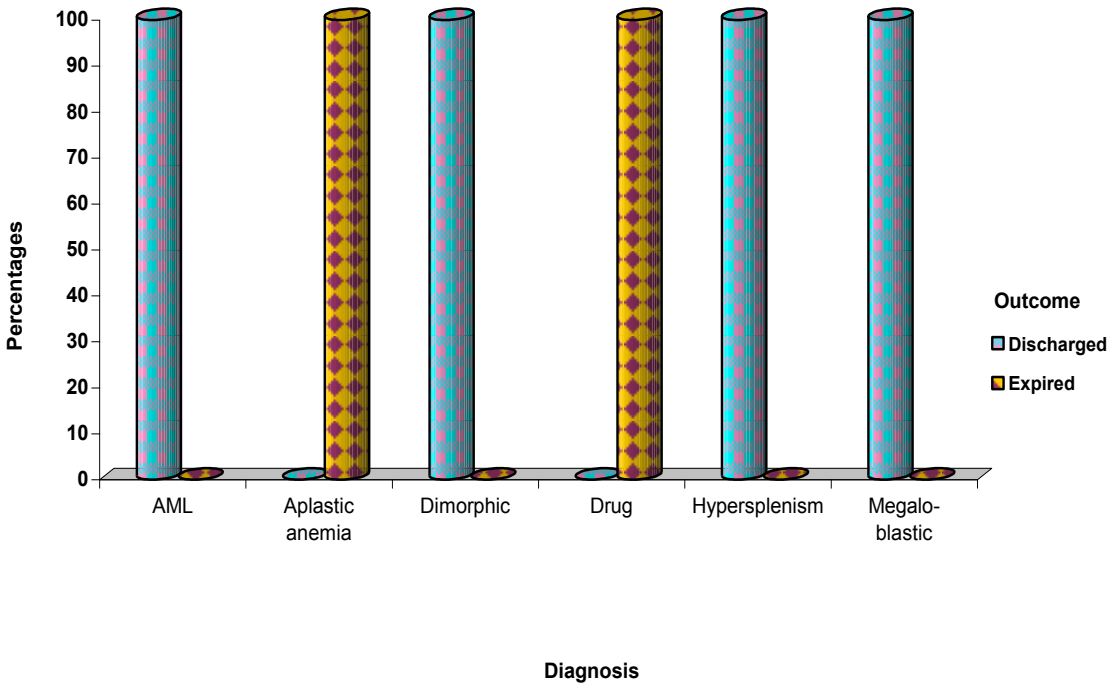

Figure 10- Outcome of patients according to etiology

Ninty percent (27/30) patients got discharged from hospital after appropriate treatment. They were provided diet- counselling, wherever necessary and were advised to follow- up regularly. Ten percent of patients (3/30) expired.

Two patients of aplastic anemia, expired after suffering massive intra- cranial bleed. They were on supportive therapy, immunosuppressive agents and transfusion of blood elements, but they could not afford bone marrow transplantation.

One patient, having drug- induced pancytopenia had developed neuroleptic malignant syndrome (NMS) and eventually expired. NMS was attributed to clonazepam therapy which he was taking for bipolar disorder since seven years.

SUMMARY

- Thirty patients of pancytopenia were studied.
- Relevant history was taken and detailed physical examination was carried out.
- Bone marrow aspiration study was carried out for all patients.
- Mean age of cases was 39 years with a male to female ratio of 1:1.
- Most common clinical manifestations were pallor(100%) and fatiguability (83.3%), followed by fever (50%) and bleeding manifestations (36.7%).
- Most common causes of pancytopenia were nutritional anemias (megaloblastic anemia, 46.7% and dimorphic anemia, 30%) followed by hypersplenism (10%).
- Ninety percent of patients had a cellular bone marrow.
- Ten percent of patients expired.
- Aplastic anemia had a high mortality rate (100%), due to intra- cranial bleed.
- Study showed a correlation between pancytopenia and fatiguability, fever and pallor.

CONCLUSION

This study showed that etiology of pancytopenia in majority of patients, in a tertiary care health setup in South India, was nutritional deficiency viz. megaloblastic anemia and dimorphic anemia. Significant number of these patients were post- partum and lactating women, and alcoholic men.

Main presenting clinical manifestations were fatiguability, fever, bleeding manifestations and pallor. So, there is a correlation between these clinical features and pancytopenia. Majority of patients had a cellular bone marrow.

Most patients responded to treatment and showed considerable improvement. But a minority of patients succumbed to bleeding manifestations and expired.

Hence, awareness and high degree of suspicion is required to identify etilogy and clinical presentation of pancytopenia. Furthermore, major steps need to be taken to increase awareness and availability of healthcare measures among our patients.

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PROFORMA

TITLE OF THE STUDY

"A STUDY OF CLINICAL AND ETIOLOGICAL PROFILE OF PANCYTOPENIA IN RURAL SETUP".

1. **Name & Address of the patient**:

D.O.A: ..... D.O.D: .....

IP/ O.P No. _____ Age: _____ Sex: Male/ Female

Occupation: _____

2**. Chief Complaints**:

3. **History Of Presenting Illness**:

a. Fever

b. Weight loss

c. Jaundice

d. Bleeding

3. **Past History**:

a. Drugs

b. Radiation

c .Chemical

d. H/o blood transfusions

e. Any other reliable history

5. **Family History**:

Malignancy/ Congenital abnormalities

a. Parents

b. Sibling

6. **Personal history**:

a. Alcohol consumption

7. **General Examination**

a. Pallor - mild / moderate / severe

b. Jaundice -

c. Skin - purpura / petechiae

d. Bony Tenderness

e. Lymph nodes

f. Edema

8. Cardiovascular system examination

9. Respiratory system examination

10. Abdominal examination

a. Liver

b. Spleen

11. Central nervous system examination

12. Laboratory Investigations

A. Hemogram

Hb%

RBC count

WBC count

Platelet count

PBS

B. Bone Marrow Study

FINAL DIAGNOSIS

SIGNATURE OF GUIDE **SIGNTURE OF CANDIDATE**

KEY TO MASTER CHART

M	-	Male
F	-	Female
CVS	-	Cardiovascular system
ESM	-	Ejection systolic murmur
N	-	Normal
LFT	-	Liver function tests
MCV	-	Mean corpuscular volume
AML	-	Acute pro- myelocytic leukemia

SL NO	NAME	AGE	SEX	FEVER	FATIGUABILITY	RESPIRATORY DISTRESS	BLEEDING MANIFESTATION	BLOOD TRANSFUSION	ANOREXIA	ABDOMINAL DISTENSION	BONE PAIN	ALCOHOL	OTHERS
1	Srinivas	40	M	-	+	-	PER RECTAL	+	-	-	-	+	-
2	Jayamma	60	F	+	+	-	-	-	-	-	-	-	loose stools
3	narayanamma	70	F	+	-	-	-	-	-	-	-	-	Loose stools
4	anjanamma	20	F	-	+	-	PERI PARTUM	+	-	-	-	-	Post partum
5	varalakshmi	23	F	-	+	+	PERI PARTUM	+	-	-	-	-	Post partum
6	Rani	32	F	+	+	-	-	-	-	-	-	-	-
7	Lakshmamma	35	F	-	-	-	-	-	-	+	-	-	Portal Hypertension
8	Mahesh	18	M	+	+	-	-	-	-	-	-	-	-
9	Lokesh reddy	23	M	+	-	-	EPISTAXIS	-	-	-	-	-	-
10	Manjula	19	F	-	+	-	-	+	+	-	-	-	Post partum
11	Narayaswamy	81	M	-	+	-	INTRACRANIAL	+	-	-	+	-	-
12	Rajgopal	55	M	+	-	+	-	-	-	-	-	-	BPD
13	Manjunath	19	M	+	+	-	-	+	-	-	-	-	-
14	Kamalamma	50	F	-	+	-	PER RECTAL	-	-	-	-	-	Loose stools
15	Chandrappa	24	M	+	+	-	INTRA CRANIAL	+	-	-	-	-	
16	Shilpa	20	F	+	-	-	PER RECTAL	+	-	-	-	-	Post partum
17	Radamma	41	F	-	+	-	-	-	+	-	-	-	Post partum
18	Mune gowda	45	M	+	+	-	-	-	+	-	-	+	-
19	Shivappa	30	M	+	+	-	-	-	-	-	-	+	-
20	Savitha	21	F	+	+	+	-	-	-	-	-	-	Post partum
21	Venkatesh	50	M	-	+	-	PER RECTAL	-	+	-	-	+	-
22	Narayanswamy	28	M	+	+	-	-	-	-	-	-	-	-
23	Gowramma	48	F	-	+	+	-	-	-	+	+	-	-
24	Krishnappa	55	M	-	+	-	ORAL	-	-	-	-	-	-
25	Devamma	35	F	-	+	-	-	-	-	+	-	-	Portal Hypertension
26	Rani	21	F	+	+	-	-	-	-	-	+	-	Post partum
27	Nagaraj	42	M	-	+	-	-	-	+	-	-	+	-
28	Rathnamma	70	F	-	+	-	PER RECTAL	-	-	-	-	-	Loose stools
29	Narayanappa	60	M	-	+	-	-	-	-	+	-	+	-
30	Muralidhar B K	40	M	+	+	-	-	+	-	-	-	+	-

PALLOR	JAUNDICE	EDEMA	HEPATO MEGALY	SPLENO MEGALY	CVS	ANEMIA	LEUCOPENIA	THROMBOCYTOPENIA	MCV	LFT	BONE MARROW	DIAGNOSIS	OUTCOME
+	-	-	+	-	n	severe	moderate	mild	103	Normal	Hyper cellular	megaloblastic anemia	discharged
+	+	-	-	+	n	moderate	mild	mild	83	Indirect	Hyper cellular	dimorphic anemia	discharged
+	-	-	-	-	n	severe	moderate	mild	108	Normal	normocellular	dimorphic anemia	discharged
+	-	+	-	-	ESM	severe	moderate	severe	95	Normal	Hyper cellular	megaloblastic anemia	discharged
+	-	-	-	-	n	severe	moderate	severe	102	Normal	normocellular	megaloblastic anemia	discharged
+	-	-	-	-	ESM	severe	moderate	mild	96	Normal	Hyper cellular	megaloblastic anemia	discharged
+	+	+	+	+	n	severe	moderate	mild	62	Normal	normocellular	hypersplenism	discharged
+	+	-	-	-	n	severe	moderate	mild	117	Direct	normocellular	megaloblastic anemia	discharged
+	-	-	-	-	n	moderate	severe	severe	96	Normal	AML	AML	discharged
+	+	-	-	-	n	moderate	moderate	mild	92	Normal	normocellular	megaloblastic anemia	discharged
+	-	-	-	-	n	moderate	moderate	severe	-	Normal	hypocellular	Aplastic anemia	expired
+	-	+	-	-	n	mild	moderate	moderate	105	Normal	normocellular	Drug induced pancytopenia	expired
+	+	-	+	+	ESM	severe	moderate	mild	92	Indirect	Hyper cellular	megaloblastic anemia	discharged
+	-	-	-	-	ESM	severe	moderate	severe	103	Normal	Hyper cellular	megaloblastic anemia	discharged
+++	-	-	-	-	ESM	severe	severe	severe	78	Normal	hypocellular	Aplastic anemia	expired
+	-	-	-	-	n	moderate	moderate	mild	70	Normal	normocellular	dimorphic anemia	discharged
+	-	-	-	-	ESM	severe	mild	mild	110	Normal	Hyper cellular	megaloblastic anemia	discharged
+	+	-	-	-	n	severe	moderate	mild	98	Indirect	Hyper cellular	megaloblastic anemia	discharged
+	+	+	-	-	n	severe	moderate	moderate	86	Normal	Hyper cellular	dimorphic anemia	discharged
+	-	-	-	-	ESM	severe	mild	mild	108	Indirect	Hyper cellular	megaloblastic anemia	discharged
+	+	-	-	-	n	severe	mild	mild	92	Indirect	Hyper cellular	dimorphic anemia	discharged
+	-	+	+	+	ESM	severe	mild	mild	115	Normal	Hyper cellular	megaloblastic anemia	discharged
+	+	+	+	+	ESM	severe	moderate	mild	48	Direct	Hyper cellular	hypersplenism	discharged
+	+	-	-	-	ESM	severe	moderate	moderate	94	Normal	normocellular	dimorphic anemia	discharged
+	-	-	-	+	n	severe	moderate	mild	58	Normal	Hyper cellular	hypersplenism	discharged
+	-	-	-	-	ESM	severe	moderate	mild	112	Normal	normocellular	megaloblastic anemia	discharged
+	-	-	-	-	n	severe	moderate	mild	105	Normal	Hyper cellular	megaloblastic anemia	discharged
+	-	+	-	-	ESM	severe	mild	mild	72	Normal	hypocellular	dimorphic anemia	discharged
+	-	+	-	-	n	moderate	moderate	mild	79	Direct	normocellular	dimorphic anemia	discharged
+	+	-	+	+	-	severe	mild	moderate	91	Indirect	normocellular	dimorphic anemia	discharged