# Pancytopenia Adult Patients At Baghdad Teaching Hospital

**Khudair Abbas Al-Khalisi*,Azher Sebieh Al-Zubaidy**,Majid Rhaima*****


## ABSTRACT:

**BACKGROUND:**

pancytopnia is a triad of findings caused by different diseases affecting bone marrow primarily or secondarily, causing manifestations of anemia, thrombocytopenia, and/ or leucopenia

**OBJECTIVE:**

To identify causes, and presenting symptoms of pancytopnia in patients attending Baghdad teaching hospital.

**PATIENTS AND METHODS:**

One hundred and five patients, found on complete blood count having Pancytopenia were included, excluding patients that had been exposed to chemotherapy, and/or radiotherapy

**RESULTS:**

Causes in decreasing frequency were acute leukemia (30.47%), aplastic anemia (17.14%), megaloblastic anemia (13.33%), NHL (14.47%), MDS (8.57%), PNH (4.76%), TB, SLE, HD (2.58%) for each, and kalazar, and MM and HCL (1.9%) for each.

Manifestations were fatigability (67.6%), bleeding tendency (55.8%), and fever (48%).

**CONCLUSION:**

Incidence of Pancytopenia may vary according to geographical, and genetic factors, and depending on parameters, and criteria of inclusion and exclusion. Acute leukemia was found the most common cause, followed by megaloblastic anemia.


***KEY WORDS*:** pancytopenia, acute leukemia, aplastic anemia

## INTRODUCTION:

Pancytopenia is a simultaneous decrement of hemoglobin, leukocytes, and thrombocytes. These findings may result from many processes affecting bone marrow primarily or secondarily [(1)].

The resulting symptoms are usually attributable to anemia, or thrombocytopenia, but leucopenia may cause serious manifestation during the course of the disorder [(2, 3, 4)]

Pancytopenia exists in adults when hemoglobin (Hb.) concentration is less than 135 gm/L in male or 115 gm/L in female, the leukocyte count is less than $4x10^9$/L and platelet count is less than $150x10^9$/L[(2, 5)].

The initial clinical picture in patients with Pancytopenia varies widely. The onset often is insidious. Manifestations depend on the severity of pancytopenia[2]. Initially pancytopenia may become symptomatic only during times of stress or demand (e.g. bleeding or infection) [(4)]**.** More severe degrees of cytopenia can be manifested by symptoms of anemia, neutropenia and/or thrombocytopenia depending on the degree of reduction of blood cells[(2, 6)].

The platelet count is first to be affected, mucocutaneous bleeding is typical of thrombocytopenia with petechial hemorrhages in skin and mucous membranes, and the presence of spontaneous bleeding with platelet count less than $20x10^9$/L indicates severs marrow failure. Retinal bleeding is common and may lead to blindness, but interestingly its presence correlates more with the presence of anemia rather than with thrombocytopenia[(2, 4)].

Next to be affected is the myeloid series. Infection usually occurs with commensal organism of the skin or gastrointestinal tract, and typically shows incomplete response to antibiotics [(4)]. septicemia may occur without any focal signs of infection , the only clinical features being malaise and fever [(2,4)] .

Other clinical features may reflect the underlying diseases process [2, 6]. For example the presence of splenomegaly and lymphadenopathy make the diagnosis of aplastic anemia (AA) unlikely[(2)].

*Bagdad College of Medicine.
** Senior Specialist of Medicine –Baghdad Teaching Hospital.
*** Specialist of Medicine Baghdad Teaching Hospital.

**Causes of pancytopenia**

The incidence of various disorders causing Pancytopenia widely varies due to geographical distribution, environmental factors and genetic disturbances [1].

Pancytopnia can result from damage to bone marrow evidenced by low reticulocyte count, or increase destruction of preformed blood cells peripherally with increase reticulocyte count [1, 3, 4]

Bone marrow failure may result from a decrease in or damage to the hematopoietic stem cells and their microenvironment, resulting in hypoplastic or aplastic bone marrow; this can be congenital or acquired [4].0r because of bone marrow infiltration with abnormal or malignant tissue replacing the normal hematopoietic cells. This is the case in myelofibrosis, hemopoetic malignancy, or invasion of bone marrow with malignant metastasis, and some inherited metabolic diseases [4]. Pancytopenia may also result from ineffective haemopoisis where active bone marrow fails to produce mature cells as in vitamin B-12 or folate deficiency, or myelodysplastic syndromes (MDS).

Haemophagocytic syndrome which is characterized by uncontrolled nonmalignant proliferation of histocytes and macrophages in bone marrow, lymphoid tissues or other organ, may also cause Pancytopenia

On the other hand Pancytopenia may result from peripheral consumption such as in hypersplenism, and combined immune cytopenia. [1,2,3,4]

## AIMS OF THE STUDY:

1-To identify the most common causes of Pancytopenia in patients referred to Baghdad teaching hospital.

2-To identify the most common clinical presentations of Pancytopenia.

## PATIENTS AND METHODS:

Our study was carried out over a period of 7 months from April to November-2004. One Hundred five

Criteria for inclusion where HB < 135 gm/L in male or <115gm/L in female, leukocyte count<$4x10^9$/L and platelet count<$150x10^9$/L.

Cases of Pancytopenia caused by cytotoxic drugs or radiotherapy were excluded.

A detailed history was obtained from all patients with special concentration on the presenting symptoms and the presence or absence of relevant features for the type and severity of manifestation, and features suggesting a possible cause for the illness including review of system, nutritional habits, social history, past medical, surgical and gynecological history, drug history, and family history for the specific inherited causes of pancytopenia.

The information obtained were blotted in a special form which also included the finding at complete physical examination with special concentration on signs help to assess severity and possible causes of illness.

For all patients Blood count and film examination were performed , bone marrow aspirate by Jamshidi needle was obtained from iliac crest and was examined by a lab hematologist at teaching laboratory. Trephine biopsy was performed when aspirate was found dry, or when it is indicated for specific diagnosis or staging of the cause. It was performed for 70 patients.

Hams test and antinuclear antibodies were tested for when clinical picture was suggestive of PNH or SLE respectively.

## RESULTS:

One-Hundred and five patients were included, age range was (15-75) years mean was 36 years, 58 patients (55.23%) were males, and 47 patients (44.77%) were females, (male to female ratio was 1.3:1) (table 1).

Acute Leukemia (A.L) was the most common cause 32(30.47%) among which promyelocytic leukemia (APL) type is the cause in fifty percent. Other causes in decreasing frequency were aplastic anemia (AA) 18 (17.14%), megaloblastic anemia, 14(13.33%). Non-Hodgkin lymphoma (NHL) 11 (10.47%), MDS 9 (8.57%). PNH 5(4.76%),less common causes included Tuberculosis (TB), SLE, Hodgkin's disease and Kala-Azar 3(2.85%) for each, and M.M, and Hairy cell leukemia were the cause in 2 patients (1.9%) for each (table 2).

Easy fatigability was the commonest symptom being present in 71(67.6%) patients, other symptoms in decreasing frequency were bleeding tendency (mucocutaneous bleeding) in 58 patients (55.8%), and fever in 50 patients (48%) (Table 3).

Pallor was universal among our patients, bleeding tendency, manifested as petechiae and/or echymosis was found in 54.28% of patients. Other clinical findings in decreasing frequencies were splenomegaly (40%), hepatomegaly (24.76%) and lympadenopathy (12.3%) (Table 4).

Peripheral blood examinations showed anisopiokilocytosis (36.1%), circulating blast cells (33.3%), macrocytosis (20.9%), and abnormal lymphocytosis (7.6%), being common findings (table 5).

Out of 32 patients with acute leukemia, 4patients (12.5%) showed no circulating blast cells (table 5). Results found in other studies are summarized in table 6

**Table 1: Age distribution of the patients**

| Disorder | No. of cases | Percentage (%) |
|---|---|---|
| Acute leukemia | 32 | 30.47 |
| Aplastic anemia | 18 | 17.14 |
| Megaloblastic anemia | 14 | 13.33 |
| Non Hodgkin lymphoma | 11 | 10.47 |
| Myelodysplastic syndrome | 9 | 8.57 |
| Paroxysmal nocturnal hemoglubinurea | 5 | 4.76 |
| Tuberculosis | 3 | 2.85 |
| Systemic lupus erythmatosus | 3 | 2.85 |
| Hodgkin disease | 3 | 2.85 |
| Kala-Azar | 3 | 2.85 |
| Multiple Myeloma | 2 | 1.9 |
| Hairy cell leukemia | 2 | 1.9 |
| Total | 105 | 100 |

**Table 2: Causes of pancytopenia**

| Age (years) | 1-20 | 21-30 | 31-40 | 41-50 | 51-60 | >60 | Total |
|---|---|---|---|---|---|---|---|
| Number of Patients | 18 | 30 | 21 | 12 | 10 | 14 | 105 |
| Percentage (%) | 17.4 | 8.57 | 20 | 11.42 | 9.52 | 13.33 | 100 |

**Table 3: Distribution of the presenting symptoms**

| Symptoms | Easy fatigability | Bleeding tendency | Fever |
|---|---|---|---|
| Number of patients | 71 | 58 | 50 |
| Percentage (%) | 67.6 | 55.8 | 48 |

**Table 4: Distribution of clinical signs**

| Disorder | Total No | Pallor No. (%) | Patechiae No. (%) | Splenomegaly No. (%) | Hepatomegaly No. (%) | LAP* No. (%) |
|---|---|---|---|---|---|---|
| Acute Leukemia | 32 | 30 (94) | 22 (67) | 14 (44) | 8 (25) | 2 (6) |
| Aplastic anemia | 18 | 18 (100) | 14 (78) | - | - | - |
| Megaloblastic anemia | 14 | 14 (100) | 8 (57) | 2 (14) | - | - |
| Non Hodgkin lymphoma | 11 | 8 (73) | 2 (18) | 8 (73) | 8 (73) | 2 (18) |
| Myelodysplastic syndrome | 9 | 9 (100) | 5 (56) | 2 (22) | 2 (22) | - |
| Paroxysmal nocturnal hemoglubinurea | 5 | 5 (100) | 2 (40) | 4 (80) | - | 2 (40) |
| Tuberculosis | 3 | 3 (100) | 2 (67) | 2 (67) | 3 (100) | 2 (67) |
| Systemic lupus erythmatosus | 3 | 3 (100) | 2 (67) | - | - | - |
| Hodgkin disease | 3 | 3 (100) | - | 3 (100) | - | 3 (100) |
| Kala-Azar | 3 | 3 (100) | - | 3 (100) | 3 (100) | - |
| Hairy cell leukemia | 2 | 2 (100) | - | 2 (100) | - | 2 (100) |
| Multiple myeloma | 2 | 2 (100) | - | 2 (100) | 2 (100) | - |
| Total No. | 105 | 100 (95) | 57 (54) | 42 (40) | 26 (25) | 13 (12) |

***** Lymphadenopathy

**Table 5: Peripheral blood findings**

| Disorders | Anisopiokilocytosis | Circulating blast | Macrocytosis | Lymphocytosis |
|---|---|---|---|---|
| Acute leukemia | 26 | 28 | -- | - |
| Aplastic anemia | 2 | - | - | - |
| Megaloblastic anemia | - | - | 14 | - |
| Non Hodgkin Lymphoma | 4 | - | - | 8 |
| Myelodysplastic syndrome | 2 | 7 | 6 | - |
| Paroxysmal nocturnal hemoglubinurea | 2 | | 2 | |
| Tuberculosis | - | - | - | - |
| Systemic lupus erythmatosus | - | - | - | - |
| Hodgkin disease | - | - | - | - |
| Hairy cell leukemia | 2 | - | - | - |
| Multiple myeloma | - | - | - | - |
| Kala-Azar | - | - | - | - |
| Total No. | 38 | 35 | 22 | 8 |
| Percentage (%) | 36.1 | 33.3 | 20.9 | 7.6 |

**Table 6: Summary of other studies**

| Study | Country | Year | No. of cases | Commonest cause | 2nd common cause |
|---|---|---|---|---|---|
| International Agranulocytosis* | Europe and "Israel" | 1987 | 319 | Aplastic anemia | Myelodysplastic syndrome |
| Keisu M | Europe and "Israel" | 1990 | 100 | Neoplastic disease | Aplastic anemia |
| Hossain et al* | Bangladesh | 1992 | 50 | Aplastic anemia | Chronic malaria |
| Vermal et al* | India | 1992 | 202 | Aplastic anemia | Megaloblastic anemia |
| Tilak et al* | India | 1999 | 77 | Megaloblastic anemia | Aplastic anemia |
| Kishor et al* | India | 2000 | 50 | Megaloblastic anemia | Aplastic anemia |
| Kumar et al | India | 2001 | 166 | Aplastic anemia | Acute leukemia |
| Ishtiaq et al* | Pakistan | 2002 | 100 | Megaloblastic anemia | Hypersplenism |
| Mussarrat et al* | Pakistan | 2002 | 89 | Aplastic anemia | Megaloblastic anemia |
| Current study | Iraq | 2004 | 105 | Acute leukemia | Aplastic anemia |

- These studies excluded cases of Pancytopenia with blast cells in peripheral blood.

## DISCUSION:

Although Pancytopenia is a common laboratory finding , and many diseases are known to be potential causes, there are limited number of studies to determine the relative frequencies of these causes, we are not aware about such a study performed in Iraq.

Table (6) shows a comparative information obtained from several studies concerning this aspect. Some of these studies have been reported from the Indian subcontinent, most of them found that aplastic anemia[1,7,8,9,10] or MA[1,4,11,12] being the commonest cause of Pancytopenia, Keisu ,M study which was done in Europe and "Israel" in 1990 found neoplastic diseases as the most common cause[15].

In our study the most common cause was acute leukemia 32 (30.47%), of which Acute myelogenous leukemia (AML) constituted 22 (68.75%) with acute promyelocytic leukemia being the most common subtype (72,7%) while Acute lymphoblastic leukemia (ALL) in 10( 31.25%). The second and third common causes were aplastic anemia and megaloblastic anemia respectively.

The differences between our study and 0ther studies may be attributed to the following causes:

Many of these studies excluded cases of Pancytopenia with blast cells in peripheral blood dismissing the majority of leukemic patients. Differences in environmental, social and genetic factors between our society and other societies may influence the frequency of causes in different studies.

The high prevalence of acute leukemia in our study may be attributed to the high referral rate of patients with hematological malignancies to the Hematological department in Baghdad teaching hospital where our study is performed; this may cause selection bias in assessing the actual prevalence in the general population Iraq.

Because our study involved adult patients only it is expected to show a relatively high prevalence of AML since this type of leukemia accounts for

about 90%of acute leukemia in adults[2, 3,14] , especially acute promyelocytic leukemia[15].

The high prevalence of aplastic anemia in Indian subcontinent may be attributed to environmental factors such as exposure to toxic chemical rather than genetic factors[1].

Internationally:

aplastic anemia occurs more frequently in the East than in the west, e.g., in Japan and the Far East, its incidence is at least 3 times higher than in the USA and Europe, where environmental factors and use of Insecticide have been implicated as a common cause of this disease, yet some Studies from Thailand also implicated

Pesticide exposure as a common etiological agent for aplastic anemia[1]

In Indian subcontinent megaloblastic anemia had been found common cause of pancytopenia in many studies [1,4,9,11,12] (it was the commonest cause in some of studies and 2nd most common cause in others), this may be attributed to the high prevalence of nutritional anemia in that part of the world[1,4].

Among nutritional anemia, vitamin B-12 deficiency is more prevalent than folate deficiency.

NHL is also a common cause of Pancytopenia due to bone marrow infiltration by malignant lymphoid cells[2,3,5] or due to hemophagocytic syndrome[16].

Our study also showed non Hodgkin lymphoma as a cause of pancytopenia in a lesser number of patients, Most of other studies showed myelodysplastic syndrome less frequently than our study where it was found 5th common cause of Pancytopenia and this also may be due to high referral rate of leukemic patients to our hospital decreasing relatively other causes.

Pancytopenia has been reported occasionally in association with tuberculosis; it has been more consistently documented in patients with milliary tuberculosis, and suggests the possibility of granulomatous infiltration of bone marrow, hypersplenism, proliferation disorder of reticulo-endothelial system, hemophagocytic syndrome, or some unrelated disease processe[17].

In our study we found that 3 patients with tuberculosis presented with Pancytopenia, two of them presented with milliary type and the other case presented with fever and generalized lymphadenopathy and diagnosed by lymph node biopsy. This may be attributed to the fact that our country is endemic with this disease.

Pancytopenia in SLE may be due to immune mechanism, cytotoxic drugs, and hypersplenism or hemophagocytic syndrome. In our study, three cases of SLE presented with arthritis, anemia and positive serological markers.

Leishmaniasis needs to be considered as possible differential diagnosis of Pancytopenia [18], particularly in our country where many areas are endemic with this disease. Leishmaniasis was the cause of pancytopenia in three patients that was diagnosed by bone marrow examination. Paroxysmal hemoglubinurea and hairy cell leukemia are rare conditions but usually presented with pancytopenia[2].

In this study, Paroxysmal hemoglubinurea diagnosed by Hams test and was found positive in five patients.

The initial manifestations of Pancytopenia varies widely and depend on severity of Pancytopenia and can be manifested by symptoms of anemia, neutropenia or thrombocytopenia, which occur either singly or in combination depending on degree of reduction[2,6].In our study easy fatigability (manifestation of anemia) was the commonest presentation found in 67.6% of patients and this correlate with finding of Niazzi and Razaq[1] who also found that anemia is the commonest presenting symptoms present in 68.2%.The second most common presenting features in our study was bleeding tendency in form of mucocutaneous hemorrhage found in 55.8% while fever was found in 48%,

Niazzi and Razaq[1] found fever as the 2nd most common presentation, this may be attributed to high prevalence of acute myelogenous leukemia particularly acute promyelocytic leukemia in our study.

It's known that up to 90% of patients with promyelocytic leukemia present with bleeding tendency and which is the presenting manifestation in up to half of patients with acute leukemia, this may be due to thrombocytopenia or DIC while fever present in 15- 20% of patients which may result from infections secondary to neutropenia or from leukemia itself[5].

Also in aplastic anemia the most common early presentation is bleeding tendency. Symptoms of anemia are also frequent. Infection is unusual first symptoms of aplastic anemia[2, 3].

## CONCLUSIONAND ECOMMENDATIONS:

1-Acute leukemia, aplastic anemia, and megaloblastic anemia are the major causes of Pancytopenia, in the current study however, uncommon and rare causes like myelodysplastic syndrome, Lymphoma, TB, paroxysmal nocturnal hemoglubinurea, SLE, hairy cell leukemia, and Kala-Azar …etc. should also be kept in mind .

2-Variation in the prevalence of disorders causing Pancytopenia may be attributed to the differences in inclusion and exclusion criteria, Geographic areas, Genetic differences and environmental exposure to chemicals, and toxic agents.

3-General weakness and easy bruising is the major presenting symptoms of Pancytopenia.

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