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Original Research Article

Clinical and Etiological Characteristics of Patients with Bicytopenia

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Abstract

Background: Erythrocytes, leukocytes, or platelets are only a few of the two types of blood cells that are reduced in bicytopenia. There are numerous studies on pancytopenia, however, there are very few that examine the range of etiologies for bicytopenia. The objective was to examine the clinical-hematological characteristics of patients with bicytopenia and to look into the various causes of bicytopenia.

Method: 200 patients with bicytopenia were selected for the study using systematic random sampling from those admitted to Indira Gandhi Institute of Medical Sciences, Patna between March 2022 and February 2023. Their hematological markers and clinical characteristics were assessed.

Results: All ages were found to have bicytopenia, with a mean age of 30.6 years. Bicytopenia was present in 5% of newborns, 6% of infants, 24% of children, 16% of teenagers, 84% of adults, and 10% of the elderly across various age groups. Anemia with leukopenia (25%) and leukopenia with thrombocytopenia (12%) were the two bicytopenias that were seen most frequently. There were 1.5 times as many men as women. Bicytopenia was shown to have non-malignant (55%) as its most frequent aetiology, followed by infectious (31.6%), malignant (8.2%), and drug-induced (3%). In the non-malignant group, immune thrombocytopenic purpura, alcoholic liver disease, and megaloblastic anemia were the most common aetiologies. Dengue (11% of all infectious diseases) was the most prevalent. The hematological malignancies were most substantially linked with symptoms such lymphadenopathy, splenomegaly, and hepatomegaly ($P \leq 0.002$). The most prevalent non-malignant symptoms were pallor, hemorrhage, hepatomegaly, and splenomegaly ($p < 0.002$). In the infectious category, fever and lymphadenopathy were most prevalent ($p < 0.002$). Lymphadenopathy, hepatomegaly, and splenomegaly were the most prominent symptoms in drug-induced aetiology ($P < 0.002$).

Conclusion: Many benign and malignant disorders can be detected by bicytopenia, a reliable hematological sign. Understanding its causes can aid in the diagnosis and effective treatment of patients.

Keywords: Anemia, Leukopenia, Thrombocytopenia, Bicytopenia, and Leukaemia.

Introduction

The word "blood" dates back to 1000 AD and is derived from the Old English word "blod." It is described as the fundamental idea [1]. It is a cause of numerous ailments, though. A person's health state can be tracked with current technology by measuring blood

counts and other data. As a result, any alteration in blood counts may serve as a sign of particular disorders [2]. Pancytopenia has been the topic of much research. There are numerous studies on the causes and effects of pancytopenia in various age groups. Bicytopenia is still uncharted area, though. There aren't many research in the literature that examine the range of aetiologies that lead to bicytopenia in various age groups. Understanding these aetiologies can help the doctor recognize an approaching illness and diagnose it. Bicytopenia research is important since different cytopenia's even have distinct therapy strategies.

Bicytopenia has a variety of aetiologies in children, from temporary marrow viral suppression (0.3%) to marrow invasion by cancers that are life-threatening (69.5%). Secondary effects of some medications (12.37%), chemotherapy, or radiotherapy for various cancers may be the source of these [3]. Evaluation of the causes of bicytopenia can aid in patient diagnosis and effective treatment [3; Figure 1].

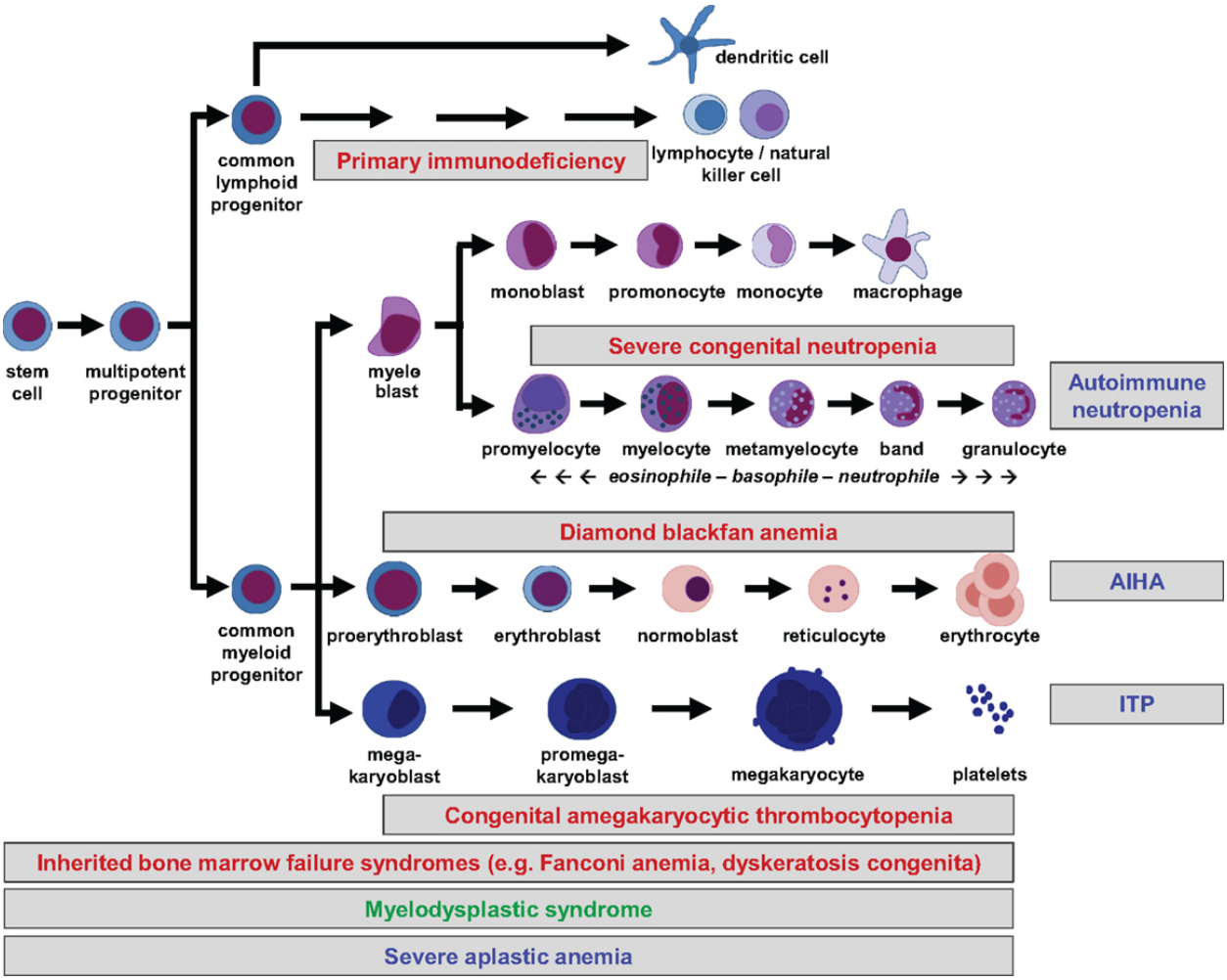

Figure 1: The causes, symptoms, and treatment of pancytopenia in children

Two investigations found that 40% and 45% of children who were referred for a bone marrow evaluation had bicytopenia [3,4]. Bicytopenias in adults are not yet known to be common. There are also not many investigations on the causes, clinical

characteristics, and hematological profiles of bicytopenic patients across the age spectrum.

Thus, research into the clinico-haematological profile of patients with bicytopenia is necessary.

Method

All the patients taking part in the study provided written informed consent. The institutional ethics committee gave its approval for the use of human volunteers in the study. A thorough history and clinical examination were recorded using a pre-structured proforma or through an in-person interview with the patient. The shape of the cells in peripheral smears was examined, together with the platelet counts and the presence of hemiparasites like malaria. Wright's stain had discolored the smears.

According to the clinical recommendation, a trephine biopsy and bone marrow aspiration were performed. Wright's stain was used to stain all of the bone marrow aspirate smears, and H&E was used to stain the trephine biopsies [5-7]. On aspirate smears, when necessary, special stains such myeloperoxidase, periodic acid-Schiff (PAS), and Perl's' stain were applied. The medical records contained other pertinent investigations that were noted.

All inpatient patients with bicytopenia met the inclusion criteria. All patients with pancytopenia and those with isolated cytopenia met the exclusion criteria. Anemia with thrombocytopenia, anemia with leukopenia, and leukopenia with thrombocytopenia were the three combinations that were considered to be the most common causes of bicytopenia. Bicytopenia is characterized by a decrease in the counts, or less than normal for that age and sex, of any two cell lineages. To determine the most typical cytopenia combination and to determine the prevalence of bicytopenia, peripheral smears and blood counts were examined.

The aetiologies were broken down into four major groups: infectious, drug-induced, malignant, and nonmalignant. All hematological cancers that appear with bicytopenia were classified as belonging to the malignant group. All non-malignant disorders, with the exception of those brought on by active infections or drug-induced aetiologies, were classified as non-malignant. All instances that have an active infection that has been detected by serological tests fall under the infectious category. All instances that showed up with bicytopenia after therapy were under the drug-induced group. The five clinical findings that were assessed were pallor, hepatomegaly, lymphadenopathy, hepatomegaly, and splenomegaly.

Statistical Analysis

Using descriptive statistics, the clinic - hematological profiles of patients with bicytopenia were reported (mean, standard deviation and percentage). The categorical variables were compared using the Chisquare test. The link between various factors and bicytopenia was judged significant if the probability (p) value was less than 0.04. Data analysis tools SPSS (IBM, USA) and Excel (Microsoft, USA) were utilised.

Results

The collected data were tallied and examined. Five age groups were watched and analyzed for bicytopenia: infants under 2 years old (7%); children aged 2 to 12 years (7.24%); adolescents aged 13 to 18 (7%); adults aged 19 to 60 (55.4%); and people over 61 years old (11.24%).

With a range of 1 day to 80 years, the average age was 30.6 years. Age had a standard deviation (SD) of 21.2 years. Males made up 61.24% of the cases, and females made up 38.74%, according to the gender distribution.There were 1.5 times as many

men as women. It was found that more males than females presented with bicytopenia across all age groups. The most frequent bicytopenia was found to be anemia with thrombocytopenia (144 cases, 60%), followed by anemia with leukopenia (45 cases, 25%) (Table 1). The least frequent condition was leukopenia with thrombocytopenia (11 cases, 12%).

Table 1: Frequency of bicytopenia

Peripheral smear	No. of cases	Percentage
Anemia with thrombocytopenia	144	60%
Anemia with leukopenia	45	25%
Leukopenia with thrombocytopenia	11	12%

Bicytopenia was shown to have non-malignant (124 cases, 55%), infectious (36 cases, 31.6%), malignant (25 cases, 8.2%), and drug-induced (15 cases, 3%) as its most common etiologies (Table 2).

Table 2: Etiologies of bicytopenia

Etiology	No. Of Cases	Percentage
Malignant	25	8.2%
Non-malignant	124	55%
Drug-induced	15	3%
Infectious	36	31.6%

The most notable bicytopenia seen in non-malignant aetiologias was anemia with thrombocytopenia (62.0%). Both anemia with leukopenia (51%) and leukopenia with thrombocytopenia (51%) were important infectious causes. The most common bicytopenia caused by drugs was anemia with thrombocytopenia (56.1%), which was followed closely by anemia with leukopenia (37.4%).

Bicytopenia in newborns and infants was most frequently caused by non-malignant conditions (84%). In this age range, neither cancer nor drug-induced bicytopenias were observed. In the age range of 2 to 12 years, infectious causes were most frequently reported (47.7%), closely followed by non-malignant causes (41%). The most frequent cause in the 13–18 age range was non-malignant (40.5%), followed by infectious (34.3%). The most frequent cause among people aged 19 to 59 was non-malignant (58.5%), followed by infectious (30.5%), malignant (13%) and drug-induced (4.4%) conditions. Non-malignant (53.2%) aetiologies were most prevalent in the old age category, followed by infectious (22.1%), malignant (19%), and drug-induced (4.3%) aetiologies. The age groups and the aetiology showed a statistically significant connection ($p < 0.002$).

Fever was the most prevalent symptom (53.4%) at the time of presentation. Pallor (42.4%), bleeding/ petechiae /purpura/ ecchymosis (21.25%), splenomegaly (12.74%), hepatomegaly (12.24%), and lymphadenopathy (7.74%) were the next most frequent symptoms. In hematological malignancies, lymphadenopathy (41.8%), splenomegaly (21.5%), and hepatomegaly (20.3%) were the most frequent clinical features. The most common non-malignant disorders were pallor (88.8%), bleeding (65.8%), hepatomegaly (61.1%), and splenomegaly (49.0%). In the infectious group, lymphadenopathy (34.0%) and fever (54.0%) were the most prevalent clinical symptoms. Lymphadenopathy (6.3%),

hepatomegaly (6.0%), and splenomegaly (6.0%) were the most common symptoms in drug-induced aetiology.

The level of significance was investigated using the chi-square test. The cause of the cytopenia and the clinical outcomes were statistically significantly correlated ($p < 0.002$).

Discussion

The exciting topic of cytopenia and the continuous influx of bicytopenic patient samples from various medical departments prompted us to look into the many aetiologias of bicytopenia in various age groups. Many research and pharmacological study have seen bicytopenia as a symptom, however there are very few isolated studies that have looked at this issue in the literature. The clinic - hematological characteristics of 200 patients were assessed in this investigation. Via a method called systematic random sampling, these patients were chosen. To determine the ultimate aetiology, the clinical characteristics, peripheral smears, hematological parameters, and bone marrow tests (where necessary) were taken into account.

Research conducted in Chandigarh, India, found that 40% of children who were referred for a bone marrow examination had bicytopenia. Bicytopenia was shown to be prevalent in 45% of Pakistani children with cytopenia's in bone marrow studies [3,4]. The prevalence of bicytopenia in adults is unknown as far as is known. Finding the various causes of bicytopenia and researching the clinic - hematological characteristics of individuals in various age groups were thus the goals.

Bicytopenia/pancytopenia can have a wide range of aetiologies, ranging from minor viral marrow suppression to leukemia, according to research by Naseem *et al*. [3]. This variation in cytopenia-causing diseases has been attributed to the different age groups being studied, the diagnostic criteria being used and how stringent they are, the variation in geographic regions, the length of observation, genetic differences, exposure to drugs and infectious agents, and the nutritional status of that community [8]. Male to female ratios of 2.8:1 and 1.1:1 were found in studies on bicytopenic children and children in general, respectively [3, 4]. The small difference may have resulted from the inclusion of patients from all age groups in the current study.

Adults (55.4%) were found to have the highest prevalence of bicytopenia, followed by children (17.24%), the elderly (11.24%), teenagers (7% each), and then newborns (7%). As a result, bicytopenia was observed in people of all ages, from 1-year olds to 90-year-olds.

Age was 30.6 years on average. According to another study, bicytopenia affects 7.5% of children under 1 year old, 50% of children between 1 and 5 years old, and 32.5% of children between 6 and 12 years old [4]. In the current study, anemia with thrombocytopenia (60%) was shown to be more prevalent than anemia with leukopenia (25%) or leukopenia with thrombocytopenia (12%). According to Naseem *et al*study, .'s anemia and thrombocytopenia were the most frequent bicytopenias, followed by anemia and leukopenia (17.3%) and leukopenia and thrombocytopenia (5.5%). [3]. Colony-forming unit erythrocyte and megakaryocyte, or CFU-EMk, is the progenitor cell that gives rise to both erythrocytes and megakaryocytes [5,9]. Any harm to this progenitor could therefore result in bicytopenia with anemia and thrombocytopenia.

Furthermore, normocytic hypochromic anemia with leukocytosis and thrombocytopenia might be a symptom of acute leukemias. Anemia and thrombocytopenia are brought on by the

neoplastic cell lineage that induces leukocytosis and suppresses the other cell lines [6]. When the peripheral smear results and aetiologies were compared, it was shown that non-malignant aetiologies had the highest prevalence of anemia with thrombocytopenia. Instead of infections, medications, or penetration of the marrow by malignant cells, it is possible to hypothesize that CFU-EMk is more vulnerable in non-malignant situations including megaloblastic anemia, alcoholic liver disease, and immune thrombocytopenic purpura (ITP).

Both anemia with leukopenia (51%) and leukopenia with thrombocytopenia (51%) were common in viral aetiologies. Several studies have linked leukopenia and thrombocytopenia to dengue infection. They explain this bicytopenia as being caused by a virus that kills megakaryocytes and myeloid progenitor cells in the bone marrow. Leukopenia with thrombocytopenia in dengue patients might also result from the suppression of myeloid progenitor cells and peripheral death of platelets [7]. Megaloblastic anemia, acute myeloid leukemia (AML), and ITP were the most frequent aetiologies identified in bone marrow tests. Acute lymphoblastic leukemia (ALL), micro normoblastic marrow, normoblastic hypocellular marrow, and hypoplastic marrow were among the other cases that were reported. A small number of cases of chronic lymphocytic leukemia (CLL), bone marrow fibrosis, bone marrow TB, and multiple myeloma were also noted. There aren't many research that focus especially on the bone marrow results in kids with bicytopenia. The most frequent causes of bicytopenia, according to one study conducted in Chandigarh, were megaloblastic anemia, ITP, and AML [3]. Megaloblastic anemia was the most prevalent finding in bone marrow analyses of bicytopenic children, according to another study conducted in Pakistan [4].

In order to distinguish between malignant and non-malignant diseases, bone marrow tests are essential. They are adequate for detecting megaloblastic anemia and cancers like acute leukemia and multiple myeloma, which can fundamentally alter the patient's course of treatment.

According to Naseem *et al*., malignancy (241 cases) accounted for the majority of the causes of bicytopenia in children, followed by non-malignancy (64 cases), non-specific causes (42 cases), and secondary to therapy (49 cases). Three Bone marrow procedures are clinically required in cancers; however, this investigation was done exceptionally on the bone marrow of children. The variances may exist because bicytopenia is prevalent in all age groups and bicytopenia patients, regardless of the disease's severity, in the current investigation.

In their examinations of children's bone marrow, Ayub and Khan also found that the most frequent cause of bicytopenia (57.5%) was megaloblastic anemia. They proposed that malnutrition and frequent infections in poor socioeconomic areas could be the root causes of megaloblastic anemia [4]. All three lineages are typically impacted by vitamin B12 deficiency since it influences nuclear maturation, but anemia may not manifest for years. In actuality, macrocytosis happens before anemia [10].

None of the research on bicytopenia indicate alcoholic liver disease as a contributing factor; this may be because the investigations were only conducted on children. Although all age groups were represented in the current investigation, excessive alcohol use appeared to be one of the causes of bicytopenia. Anemia was more common in 69% of non-alcoholics than it was in 51% of alcohol abusers, according to a study by Latvala *et al*. (p 0.05). They claimed that coupled cytopenia's (34–38%) and thrombocytopenia (41% each) were frequent findings in patients

with alcoholism [11]. Another study suggested that alcoholic cirrhosis frequently co-occurs with hematological abnormalities and that alcohol, hypersplenism, malnutrition, and liver failure were the causes of combined or isolated cytopenia's [12]. ITP by itself just reduces platelet count, but associated anemia may be caused by a different nutritional shortage, which is relatively common in this area [3].

Megaloblastic anemia, marrow hypocellularity, and ITP were shown to be the most frequent conditions in non-malignant cases by Naseem *et al*. [3]. 84.1% of the patients in the 18 cases of iron deficiency anemia that also included bicytopenia had anemia with leukopenia. The research indicates that iron shortage results in reactive thrombocytosis and microcytic hypochromic anemia in the peripheral blood. Nonetheless, there is modest granulocytopenia in the later stages of iron deficient anemia [13].

Leukopenia or thrombocytopenia may also be brought on by hypersplenism [14] Moreover, as a side effect of combined iron chelation therapy, neutropenia or thrombocytopenia may develop [15]. Bicytopenia in newborns is not mentioned in any studies in the literature.

The incidence of thrombocytopenia was higher in preterm and LBW infants, according to research by Charro *et al*. [16]. Maternal anemia, which is known to result in low birth weight and prematurity, may be the source of the associated anemia [17]. Moreover, pregnant anemia is a typical occurrence in India. In the current study, a few intriguing examples with non-malignant aetiologies were found. After a bone marrow examination, a patient who initially had bicytopenia was found to have primary myelofibrosis. There was no such case in the literature. Almost 61% of the patients exhibit anemia, 10 to 50% do so with leukopenia, and 51% do so with thrombocytosis. Thrombocytopenia develops as the illness progresses [18]. Gaucher disease was determined to be the diagnosis based on b-glucosidase levels and a bone marrow aspiration. Gaucher disease was linked to anemia and thrombocytopenia in several investigations by Binesh *et al*. and Kaplan *et al*. [19,20].

The aetiology of this syndrome's development of bicytopenia is excessive vasoconstriction brought on by hypertension, which damages endothelial cells and fragments red blood cells. A reduction in platelet life span and chronic intravascular coagulation syndrome causes associated thrombocytopenia [21].

Conclusion

An important hematological finding known as bicytopenia can be used as a diagnostic cue to investigate a number of hematological illnesses. It can assist the practitioner manage various illness situations effectively by directing them to offer additional investigations in a more targeted manner and avoiding superfluous diagnostic testing. Bicytopenia is a clinical indicator for a variety of benign and malignant disorders, it can be said. To aid in quick evaluation and early identification of patients presenting with bicytopenia, the various aetiologias along with the symptoms in various age groups identified in this study have been divided systematically, in tabular form. Understanding the causes of the condition can aid in diagnosis and effective care. In bicytopenic individuals, it may assist dramatically lower morbidity and mortality.

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