

Our Experience with Bicytopenia in Patients Treated at the Ankara Hospital Pediatric Clinic

Zahide Yalaki¹, Semra İçöz¹, Fatma İnci Arıkan¹, Bülent Alioğlu², Yıldız Bilge Dallar¹

¹Clinic of Pediatric Infections Disease, Ankara Training and Research Hospital, Ankara, Turkey

²Clinic of Pediatric Hematology, Ankara Training and Research Hospital, Ankara, Turkey

Abstract

Objective: Bicytopenia is a potentially life-threatening or a temporary situation that can be seen in patients. It may develop as a result of benign or malign reasons. This study performed a clinical and hematological evaluation of children with bicytopenia and determined the etiologic reasons.

Material and Methods: From 1606 patients, between 6 months and 17 years of age, hospitalized in the Ankara Research and Treatment Hospital Pediatric Clinic and intensive care unit between February 2012 and February 2013, 28 of them had bicytopenia, and they were considered in this study. The physical examination findings, total blood count findings, peripheral smear findings, viral infection findings, diagnostic findings, KI aspiration/biopsy results, and cure time of bicytopenia for each patient were recorded.

Results: We found that 57.1% of the patients were male, and the medium age was 9.2±6.9 (6 months-17 years). The etiologic causes of bicytopenia included 64.2% infection, 7.1% idiopathic thrombocytopenic purpura, 7.1% medicine use, 3.5% megaloblastic anemia, 3.5% chronic illness anemia (celiac disease), and 14.2% acute leukemia.

Conclusion: We think that in patients with bicytopenia, all viral causes should be investigated, and peripheral smears should certainly be evaluated; in case of suspicion, bone marrow aspiration/biopsy should be performed, and malignancy should be considered. (*J Pediatr Inf 2014; 8: 23-7*)

Keywords: Bicytopenia, infection, malignity

Introduction

Peripheral cytopenia is defined as the reduction of blood cells (erythrocyte, leukocyte or thrombosis). Bicytopenia is defined as the reduction of 2 cell series; pancytopenia as the reduction of 3 cell series. Etiology of bicytopenia and pancytopenia has a broad distribution in children. As it may be related to bone marrow (BM) suppression-associated viral infection, it may also develop as a result of malignity-associated BM suppression. This particular situation may arise as a result of drugs, chemotherapy or radiotherapy (1-3).

Leukocytes composed of peripheral blood cells are the cells that are originated from pluripotent stem cells in the BM and play an important role in host defense against acute inflammation response and infection agents (4).

Neutropenia is the factor responsible for the clinical statuses that proceed sometimes asymptotically, sometimes mildly and sometimes fatally from the period of newborn all the way to the childhood (3, 5). Neutropenia is the state of absolute neutrophil count being (ANC) <1500/mm³. This may be congenital or acquired. Acquired (secondary) neutropenia may develop as a result of infections, malignity and drugs (3, 6, 7). Weight of neutropenia is related to ANC. Neutropenias have been defined as follow: Mild neutropenia is 1000-1500/mm³; medium neutropenia is: ANC 500-1000/mm³; serious neutropenia is: ANC <500/mm³. Especially serious neutropenia may cause substantial morbidity and mortality (3, 7, 8). The second decreasing cell series may be hemoglobin (Hb) or thrombosis. Clinical symptoms may develop in these patients depending on the function of blood cell series.

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Correspondence

Address:
Zahide Yalaki
Ankara Eğitim ve
Araştırma Hastanesi,
Çocuk Sağlığı ve
Hastalıkları Kliniği,
Ankara, Türkiye
Phone: +90 506 407 98 66
E-mail:
dr_zahide@yahoo.com

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The decrease in the number of thrombosis ($<150000/\text{mm}^3$) or their function getting defected are the most important reasons for rashes, petechia-purpura development and bleeding tendency. Patients may have anemia-driven exhaustion, fatigue, loss of appetite; and neutropenia-caused fever and infections (9, 10).

The aim of this study is to examine children with bicytopenia clinically and hematologically and identify their etiologic reasons.

Material and Methods

Twenty-eight patients with bicytopenia out of 1776 1 month to 17 year-old, hospitalized and followed up in the intensive care unit of Pediatric Department of Ankara Hospital were included in this study between February 2012 to February 2013. Physical examination findings of the patients on admission, complete blood count, peripheral smear findings, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), acute phase reactants as cultures, viral tests (HSV, CMV, EBV, Parvo virus), diagnosis of the patients, the therapies they received, BM aspiration/biopsy results and recovery duration of bicytopenia were all recorded.

Cancer patients, congenital or acquired aplastic anemia, congenital and cyclical neutropenia cases, chronic idiopathic thrombocytopenic purpura (ITP) patients were excluded from the study.

Complete blood count was assessed by Beckman Coulter LH 780 hemogram device was used by getting EDTA-blood. Cytopenia was defined as; Hb <11 g/dL, leukocyte count $<4000/\text{mm}^3$ and platelet count $<150\ 000/\text{mm}^3$. Bone marrow aspiration and biopsy was performed to the patients if there was a clinical indication. Acute phase reactants of ESR >20 mm/sa and CRP >0.8 mg/dL were defined as meaningful.

Informed consent was taken from the parents before the study and the study was approved by the ethical committee of our hospital at the 454-numbered meeting in February 2012.

Table 1. Symptomatic and physical therapy findings of the patients (n=28)

| | n | % |
|------------------|----|------|
| Fever | 19 | 67.8 |
| Exhaustion | 4 | 14.2 |
| Petechial rashes | 4 | 14.2 |
| Short stature | 1 | 3.5 |
| Hepatomegaly | 3 | 10.7 |
| Splenomegaly | 1 | 3.5 |

Analyses of the data was performed by the SPSS (Statistical Package For the Social Sciences) for Windows 15.0. Whether the distribution of continuous and discrete numeric variables was close to normal was analyzed by the Kolmogorov Smirnov test. The variables (age, ESR) confirming to normal distribution were shown as average \pm standard deviation; non-normal distribution (CRP) medium in the form of (1st quarter-3rd quarter); categorical variables, number of cases and “%”.

Results

Bicytopenia was found in 1.57% of the patients who were hospitalized at the pediatric ward and intensive care unit and monitored at our hospital between February 2012 and February 2013. Sixteen (57.1%) patients were male and 12 (42.9%) were female; the average age of male and female patients were 9.2 ± 6.9 year (6 month-17 year of age).

Nineteen (67.8%) had fever on admission, 4 (14.2%) weakness, 4 (14.2%) rashes and 1 (3.5%) admitted for short stature (Table 1). Five patients had the history of drug use prior to admission. On their physical examination, 4 (14.2%) had petechia, 3 (10.7%) hepatomegaly and 1 (3.5%) short stature; no lymphadenopathy was found in the patients.

As a result of laboratory analyses, 24 (85.7%) patients had neutropenia, 7 (30.7%) mild neutropenia, 4 (30.7%) moderate neutropenia and 2 (15.3%) severe neutropenia. 16 (57.1%) patients had anemia and 20 patients (71.4%) thrombocytopenia. In the evaluation of peripheral smear, 3 (10.7%) patients had blast (Table 2). Sedimentation rate on average was 12.5 ± 10.7 (2-41) mm/sa and it was high in 7 (25%) patients. C-reactive protein median was 9.5 (1st quarter: 0.3-3rd quarter: 0.65) and it was high 6 (21.4%) patients.

Results of bicytopenia etiology were (-) Salmonella, Brusella, TORCH, EBV and Hepatitis A, B, C, Mumps IgG. Parvo virus was found in 2 (11.1%) patients.

Among the etiologic factors in patients, 18 (64.2%) had an infection focus. The infections in question were respectively: 10 (55.5%) had upper respiratory infection (URTI), 3 (16.6%) pneumonia, 2 (11.1%) acute gastroenteritis, 2 (11.1%) Parvo virus and 1 (5.5%) urinary tract infection. It was observed that 2 patient had (7.1%) ITP, 2 (7.1%) drug use, 1 (3.5%) megaloblastic anemia, 1 (3.5%) chronic disease anemia and neutropenia. In the further examinations of this patient, coeliac disease emerged. The 7 patients (25%) with bicytopenia were given BM aspiration/biopsy and 4 (14.2%) patients were diagnosed with acute leukemia (Table 3).

Table 2. Results of the complete blood cell count of the patients

| | n | % |
|--|----|------|
| Leukocyte count (<4000/mm ³) | 24 | 85.7 |
| ANC | | |
| Mild (1001-1500) | 7 | 25 |
| Moderate (501-1000) | 4 | 14.2 |
| Severe (0-500) | 2 | 7.1 |
| Hb (<11 g/dL) | 16 | 57.1 |
| Thrombosis count (<150 000/mm ³) | 20 | 71.4 |
| ANC: Absolute neutrophil count | | |

Twenty-two (78.5%) patients were given antibiotic therapy. Recovery period of bicytopenia was on average 6.5±2.1 day (4-11).

Discussion

Bicytopenia can be a life threatening or temporary condition. Especially viral infections, malignity, drugs, chemotherapy, radiotherapy administrations may cause bicytopenia (2).

When the relevant English literature regarding bicytopenia is reviewed, it is clearly seen that there is no any pediatric study (2). In their study where 347 children with bicytopenia were included, Naseem et al. (2) found that while the most common complaint on admission was fever, fever and hepatomegaly were the most frequent in the physical examination. While other complaint on admission were weakness, rashes on the body, bleeding and bone pain, splenomegaly, petechial rashes and lymphadenopathy were the common complaint in the physical examination. In our study, fever was on top of the list of complaints (67.8%) as well. Among the examination findings, fever and petechial rashes were the most common ones and this result is in line with the relevant literature.

It was stated in Naseem et al.'s (2) study that in patients with bicytopenia, benign causes were detected in their etiology and ITP, megaloblastic anemia and aplastic anemia were the most common causes of bicytopenia (2). In a study done in Pakistan, on the other hand, megaloblastic anemia was the most common causes in the patients with bicytopenia and pancytopenia (11). In our study, on the other hand, while the most common benign causes were found in the etiology, infections were on top of the list.

The most common cause for infection in patients in their etiology was viral URTI and neutropenia was also found in these patients. The reasons for temporary neutropenia/leukopenia in childhood are infections and the drugs. On the top of the list of infections are especially

Table 3. Etiologic reasons in patients with bicytopenia (n=28)

| | n | % |
|---|----|------|
| Infection | 18 | 64.2 |
| URTI | 10 | 35.7 |
| Pneumonia | 3 | 10.7 |
| Acute gastroenteritis | 2 | 7.1 |
| Parvo virus | 2 | 7.1 |
| Urinary Tract Infection | 1 | 3.5 |
| ALL | 4 | 14.2 |
| ITP | 2 | 7.1 |
| Drug use | 2 | 7.1 |
| Megaloblastic anemia | 1 | 3.5 |
| Coeliac disease | 1 | 3.5 |
| ITP: idiopathic thrombocytopenic purpura; URTI; upper respiratory infection | | |

viral infections; RSV, CMV, EBV, Parvo virus and Influenza viruses (3, 6-8).

Viruses generally cause neutropenia attacks in the first 24-48 hours (viremia) lasting for 3 to 6 days (5, 12). While Tantawy et al. (8) reported in their study that recovery period from neutropenia was 7 days, it was reported in many other studies that temporary neutropenias might last as far as 16 days to 2 months (6-8, 13, 14). The period of recovery in our study was in line with the period as stated in Tantawy et al.'s study. Mild and moderate neutropenia is encountered in temporary neutropenia (8, 12, 14). Mild and moderate neutropenia emerged in our study as well in line with the literature.

Alexandropoulou et al. (7) reported that in 32 (19.9%) of the 161 patients in whom infection-caused neutropenia developed had anemia at the same time and 29 (18%) had bicytopenia accompanied by thrombocytopenia. Accompanying anemia was found in 8 (44.4%) infection-driven bicytopenia patients and accompanying thrombocytopenia in 6 (33.3%) patients in our study.

Neutropenia/bicytopenia caused by drug use may develop due to causes such as idiosyncratic suppression caused by drugs (antibiotics, sulfonamides, antihistaminics) and destruction due to dose-dependence in cytotoxic drugs and drug-heptane relationship (5, 13). In 2 patients in our study, bicytopenia developed due to the use of analgesic-antipyretic (ibuprofen) and antibiotic (ampicillin-sulbactam).

While ITP, chronic disease anemia (Coeliac disease) and megaloblastic anemia were among the causes of bicytopenia, ALL was found in 4 (14.2%) patients. It was thought that erythroid and myeloid suppression developed as a result of the infiltration of leukemic cells into the bone

marrows and accompanying anemia or thrombocytopenia developed as result of leukemic cells suppressing megakaryocytic series.

Early diagnosis of malignancy is crucial in the prevention of mortality and morbidity likely to develop in pediatric patients. Naseem et al. (2) reported that the rate of acute leukemia in children with bicytopenias was 69.5% and 26.6% in pancytopenia patients. They also reported that blast rate of peripheral smear, splenomegaly and lymphadenopathy in bicytopenias patients with leukemia was more prevalent than pancytopenia patients. In their study, where 230 children with pancytopenia, Memon et al. (15) found that the most common causes of pancytopenia were; aplastic anemia (23.9%), megaloblastic anemia (13.04%), leukemia (13.05%) and infection (10.8%). On the other hand, in their study where 205 children with pancytopenia, Jan et al. (16) revealed the as the most common in their etiologies; aplastic anemia 28.3%, leukemia, megaloblastic anemia 19.5% and ITP 7.8%. In our study, the rate of acute leukemia in bicytopenia patients was found as 14.2%. Of these patients, 3 had hepatomegaly, 1 splenomegaly and 3 patients had blast in peripheral smear. Since there was no pancytopenic patients in our study and the number of patients were low, it is possible to conclude that our rates were low as well.

It should be noted that bicytopenia might be seen in patients with any kind of respiratory tract infection or diarrhea admitted due to fever, with a history of drug use and those diagnosed with hepatomegaly, splenomegaly, lymphadenopathy and short stature.

We wished to emphasize in our study that the routine hematologic parameters in the evaluation of bicytopenic patients are non-specific; and all the viral causes regarding the etiology should be further researched, the peripheral smear should be considered; in case of suspicion, BM aspiration/biopsy should be performed.

Conclusion

In conclusion, even though benign causes are the most prevalent ones in the etiology of bicytopenia, malignancy should also be remembered.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Research and Training Hospital/February 2012/454.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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