REVIEW ARTICLE

Pancytopenia in Indian Children: A Clinico-hematological Analysis

DEVENDRA MISHRA*, ASHOK KOHLI†, RAJ BALA YADAV‡, SUBHASH CHANDRA*

ABSTRACT

Objective: To determine the etiological profile of pancytopenia in pediatric patients in India. **Material and methods:** Medical records review of a 5-year period between 1st September 1997 and 31st August 2002. Clinical and hematological data of all patients with pancytopenia (hemoglobin [Hb] ≤10 g/dL, TLC ≤4 × 109/L, platelet count ≤150 × 10^9/L) at presentation were analyzed. Patients on cytotoxic chemotherapy, those developing pancytopenia during hospital stay, patients referred from other centers with hematological malignancies and neonates were excluded. **Results:** Forty-two children (mean age 8.26 years, range 8.5 months to 13 years, M:F : 1:0.8) were included. Megaloblastic anemia, aplastic anemia and infections were commonest causes, being responsible for 25%, 19.6% and 32.1% of the cases, respectively. Bone-marrow aspiration (BMA) was helpful in reaching a definitive diagnosis in 92.8% of those in whom sufficient marrow tissue was retrieved for analysis. Aplastic anemia was the commonest reason for failure of BMA in providing a diagnosis. **Conclusions:** Majority (almost 60%) of the causes of pancytopenia among pediatric patients in this region are easily treatable. There is a need to be aware of such conditions and appropriate investigative modalities should be undertaken for the same.

Keywords: Megaloblastic anemia, aplastic anemia, bone-marrow aspiration

Pancytopenia is the simultaneous presence of anemia (hemoglobin [Hb] less than the normal for age), leukopenia (total leukocyte count [TLC] <4 × 10^9/L) and thrombocytopenia (platelet count <150 × 10^9/L). It is a common clinical problem with an extensive differential diagnosis, but there is relatively little discussion of this abnormality in major pediatric and hematology textbooks.[1,2] Although a few authors have discussed it as a separate entity,[3] most of the discussion is centered on aplastic anemia, which is a relatively uncommon cause of pancytopenia in children. The lack of an optimal investigative approach to pancytopenia (especially the role of bone-marrow examination) has also been previously highlighted.[1] A wide variety of disorders can lead to pancytopenia but their relative frequency differs considerably between different age groups and different geographical areas.[1] Also, there have been very few systematic studies of pancytopenia.[1,4] Quite a few studies from India have been published on this topic, but none has addressed this issue in the pediatric age group.[5-8] We, therefore, retrospectively reviewed the medical records of 42 pediatric patients presenting with pancytopenia over a 5-year period, to determine the clinico-hematological characteristics of pancytopenia among pediatric patients in India.

MATERIAL AND METHODS

Pancytopenia was defined as Hb ≤10 g/dL, TLC ≤4 × 10^9/L and platelet count ≤150 × 10^9/L. The case-records of all the patients admitted in the Dept. of Pediatrics with an admitting diagnosis of pancytopenia over a 5-year period between 1st September 1997 and 31st August 2002 were reviewed. The records of the Hematology Division, Dept. of Pathology for the same period were also reviewed to identify all cases in which a diagnosis of pancytopenia was made at the time of admission. The details of clinical profile, hematological parameters (Hb, TLC and differential leukocyte count [DLC], platelet count, reticulocyte count, peripheral smear), and BMA and/or biopsy examination results were recorded in a structured proforma. In the Hematology Division, blood counts are performed on

*Senior Resident
†Senior Pediatrician
‡Consultant Pathologist
Dept. of Pediatrics and Dept. of Pathology
Ram Manohar Lohia Hospital, New Delhi
Address for correspondence
Dr Ashok Kohli
Senior Pediatrician
Ram Manohar Lohia Hospital, New Delhi - 110 001
E-mail: drdmishra@gmail.com

an automated counter and abnormal findings confirmed by a hematopathologist. All peripheral blood films, bone marrow aspirates (BMA) and/or trephine biopsies were processed as per standard techniques. Other investigations done (cultures of blood, body fluids and bone marrow; splenic aspiration, radiological examination, Mantoux testing, serological tests, etc.) were also recorded.

Children receiving cytotoxic chemotherapy and those developing pancytopenia during the hospital stay were not included. If a patient was admitted more than once, only the first admission record was included for analysis, although the final etiological diagnosis made was recorded. Records of the Neonatal Unit were not included. A total of 47 cases of pancytopenia were thus identified. Full blood counts at admission were available for all of them but counts at discharge and BMA/biopsy results were available for 45 and 42 cases, respectively (as they obtained discharge against advice or absconded prior to BMA).

RESULTS

Complete records of 42 children were analyzed. The mean age of the children was 8.26 years (range, 8.5 months to 13 years; median age, 9 years; mode, 7 years; M:F : 1:0.8). The underlying causes for pancytopenia in these children are tabulated in Table 1.

On statistical analysis, no significant difference was found between the major diagnostic categories (megaloblastic anemia, aplastic anemia and acute lymphoblastic leukemia [ALL]) with regards to sex, age at presentation, presenting complaints and initial hematological values. Megaloblastic anemia was the commonest cause of pancytopenia and responsible for one-fourth of the cases. It was due to folate deficiency in two cases, and vitamin B_{12} deficiency in one case. One patient with megaloblastic anemia passed Ascaris worms in stool during hospital stay. All patients with disseminated tuberculosis were over 8 years of age and all patients of kala-azar were residents of endemic areas.

Table 1. Underlying Causes in 42 Children Presenting with Pancytopenia

Diagnosis	Number of patients (%)
Megaloblastic anemia	10 (23.8)
Aplastic anemia	8 (19)
Acute lymphoblastic leukemia	6 (14.3)
Enteric fever	7 (16.6)
Kala-azar	4 (9.5)
Disseminated tuberculosis	4 (9.5)
Others	3*

*One case of non-Hodgkin's lymphoma, one cases of disseminated tuberculosis with associated enteric fever. One case was not diagnosed.

Aplastic anemia was responsible for 20% of the cases but no etiologic factors could be implicated in any of these children except three with probable heavy metal poisoning. Two of these were distant cousins working in a battery-manufacturing unit although they presented to the hospital 8-month apart. Another had received indigenous medicines (Unani medicine) for atopic dermatitis with sudden appearance of pallor and petechiae within a month of these medications. No other clinical evidence of heavy metal poisoning was noted in these three children.

BMA had been done in all 42 patients and was inconclusive in 6 patients only. Three of these had aplastic anemia (proved on bone-marrow biopsy) and one had kala-azar (proved on splenic puncture and serology, and responded to sodium antimony gluconate). The remaining two had evidence of disseminated tuberculosis elsewhere in the body but no supportive bone marrow findings; although, one had associated enteric fever. One responded to antitubercular therapy alone, and the other to antitubercular therapy in combination with antibiotics, respectively. Bone marrow biopsy was helpful in making the diagnosis in only 3 patients out of the 6 in whom it was conducted. However, it ruled out underlying aplastic anemia/aleukemic leukemia in the other 3 patients.

Six patients with aplastic anemia and 5 patients with ALL were referred to higher centers for management and 3 patients were lost to follow-up.

DISCUSSION

The results of this study show that pancytopenia can be the presenting feature of a wide variety of illnesses in the pediatric population of our country. Similar to the studies of pancytopenia in adults from India, majority of the patients had megaloblastic anemia, aplastic anemia and hematological malignancies. Although, kala-azar has previously also been reported to present with pancytopenia, disseminated tuberculosis and enteric fever were found to be responsible for a significant number of case (9.5% and 16.6%, respectively).

Megaloblastic anemia was the commonest cause of pancytopenia (23.8%) in this study similar to African reports and adults studies in our country.[1,5,6] The

proportion reported from the West has been much lower (7.5% in adults).[4] Savage et al[1] have reported megaloblastic anemia to be responsible for 35.8% of their 134 hospitalized African pancytopenic patients (age range, 1-73 years; median, 40 years). Among studies in adults in India also megaloblastic anemia is responsible for a significant proportion of pancytopenic patients that varies from 22.3% to 39%.[5-10] Tilak and Jain have however reported a very high proportion of 68% in adult pancytopenic patients.[8]

The cause of megaloblastic anemia could only be determined in 3 of our patients due to the nonavailability of facilities for estimating folic acid and B_{12} at our center. Most studies from India have suffered from this drawback.[5-9] Folic acid and B_{12} are reported to be responsible for similar proportion of pediatric patients with megaloblastic anemia in this region and treatment with a combined preparation of B_{12} and folic acid is an acceptable option.[9]

Although megaloblastic anemia was found to be the commonest cause of pancytopenia among children, a diagnosis of megaloblastic anemia should not be based on the presence of macrocytes on the peripheral smear alone, as this finding is not infrequently found in those with aplastic anemia and also acute leukemia. Similarly, Kumar et al found megaloblastic marrow in 5 patients with falciparum malaria and in 1 patient with enteric fever, who presented with pancytopenia.[5]

Aplastic anemia was the next most common cause (19%) of pancytopenia in this study. Savage et al also reported it to be the second most common cause (26.1%) of pancytopenia in their study. It was responsible for pancytopenica in 62.9% of patients aged below 21 years.[1] Kumar et al; however, found it to be the commonest cause (29.5%) of pancytopenia among adults at a hematology center, which may have been due to high proportion of referred cases at their center.[5] No etiologic factor could be implicated in majority of our cases with aplastic anemia.

Acute leukemia was seen in 6 cases, all of which had ALL. One patient had non-Hodgkin's lymphoma. During the period under review, 4 other patients with pancytopenia and leukemia were seen by us (3 ALL, 1 acute myeloid leukemia [AML]) but were not included for analysis. Eight percent of patients in a Zimbabwean study of adults and children had acute leukemia and these cases were often children.[1]

Hematological findings in kala-azar can include any or all of the findings of anemia, thrombocytopenia, neutropenia and pancytopenia.[10,11] Pancytopenia is caused by hypersplenism, hemolysis, plasma volume expansion, ineffective erythropoiesis and reticuloendothelial hyperplasia. Hemophagocytic syndrome and trilineage myelodysplasia have also been reported as a complication of this illness.[10,12] All the patients with kala-azar in this study came from endemic areas, had history of prolonged fever with a massive splenomegaly, and the diagnosis was clinically suspected prior to bone marrow examination. One patient did not demonstrate Leishman-Donovan (LD) bodies on BMA and had to undergo splenic puncture. Kumar et al reported kala-azar in 4% of their patients; this low frequency could again have been due to the referral nature of their patients.[5]

The two unusual findings observed in this study were the previously unreported high proportion of pancytopenia due to enteric fever and tuberculosis (16.6% and 9.5% of the cases). In patients with tuberculosis, various hematological abnormalities including anemia, lymphocytopenia, thrombocytopenia, leukopenia, pancytopenia, etc. have been described. The commonest of these among Indian patients with disseminated tuberculosis has been reported to be anemia (present in 84%).[13]

In the same study, pancytopenia was found in 19% of the patients with disseminated or miliary tuberculosis. The various postulated mechanisms for pancytopenia include splenic sequestration, immune-mediated bone marrow depression and malnutrition.[13] The presence of a granuloma on bone marrow had no relationship with the occurrence of pancytopenia in previous studies.[13,14] Contrary to these reports; we found granulomas in 3 of the 4 patients with disseminated tuberculosis and pancytopenia. One other case of disseminated tuberculosis had associated enteric fever, thus pancytopenia could not be ascribed to any single condition. There was no granuloma on BMA but the child improved with antitubercular therapy in combination with specific therapy. The suggested conclusive proof of tuberculosis-induced pancytopenia is the resolution of both tuberculosis and pancytopenia with antitubercular therapy.[14]

Another patient had pulmonary tuberculosis with absence of any diagnostic finding on BMA. He was discharged on request prior to bone marrow biopsy and was lost to follow-up. Merely the presence of pulmonary tuberculosis in this child did not justify labeling it as the cause of pancytopenia. In a previous series also, none of the patients with pulmonary tuberculosis had pancytopenia.[10]

As tuberculosis is quite common in our country, it may be coincidentally present in quite a few patients of pancytopenia. Presence of pancytopenia and disseminated tuberculosis in a pediatric patient does not therefore imply causation, and BMA or biopsy should demonstrate granuloma to definitively ascribe pancytopenia to be because of the tubercular infection. Kumar et al reported only 1 patient with disseminated tuberculosis out of 166 adult patients with pancytopenia and diagnosis was made only on a post-mortem liver biopsy.[5]

Isolated cytopenias, bicytopenias and pancytopenia in enteric fever are well-documented in literature.[15,16] Multidrug-resistant *Salmonella typhi* (MDRST) are reported to be more commonly associated with hematological findings. Around 84% of the pediatric patients with enteric fever at our center are found to be suffering from MDRST. Bone marrow histiocytic hemophagocytosis has been reported to be a cause for pancytopenia in enteric fever,[16] but was not found in any of our cases. Bone marrow hypocellularity was observed in 3 (43%) of the 7 patients with pancytopenia associated with enteric fever. In others, probably a peripheral mechanism for pancytopenia was operating. None of the children had been receiving chloramphenicol or any other bone marrow depressant. Studies in adults have also reported similar findings.[15]

BMA was extremely helpful in reaching a definitive diagnosis in a majority (92.3%) of those where sufficient marrow tissue was retrieved for analysis. It was inconclusive in only 6 (14.3%) cases; in 3 of which, sufficient marrow tissue was not available by aspiration (all aplastic anemia) and in three others, no diagnostic information could be provided after the examination.

In these 3 also, a primary marrow involvement was ruled out after the marrow examination. Bone marrow biopsy was most helpful in cases of aplastic anemia, where it was diagnostic in all the 4 cases in which it was done (after aspiration was inconclusive). Although BMA has been reported to be inconclusive in up to 38% of adult patients in one series, and simultaneous aspiration and biopsy have been recommended to overcome this problem,[5] we find ourselves unable to concur with this for pediatric patients. Bone marrow biopsy is definitely a more painful procedure than BMA, and subjecting every child with pancytopenia to it does not seem justified in the light of results from this study.

On the other hand, certain authors are of the opinion that BMA is not even needed in certain pancytopenic patients e.g., those with hypersegmented neutrophils on peripheral smear and, those with mild pancytopenia, splenomegaly, an unremarkable blood film and a known cause of portal hypertension.[1] In our opinion, the recommendations of Savage et al[1] seem more appropriate for pediatric patients in our country especially in the setting, where BMA is not feasible. However, at centers where facilities are available, BMA remains a simple test, which not only clears the diagnostic confusion but also rules out the more serious primary marrow involvement like malignancies and aplastic anemia.

This study shows that megaloblastic anemia and infections (kala-azar, enteric fever and tuberculosis), both of which are eminently treatable, cause nearly 60% of the pediatric cases presenting with pancytopenia in this region. This is contrary to the widespread perception of acute leukemia and aplastic anemia as the most common etiologic factors, with their associated poor prognostic implications. It is important to be aware of these conditions as a frequent cause of pancytopenia, so that prompt and appropriate investigative and therapeutic measures can be instituted and a uniformly poor prognosis is not communicated to the relatives.

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