AETIOLOGICAL CONSIDERATIONS OF ACQUIRED APLASTIC ANAEMIA

Saqib Malik, Iram Sarwar*, Tariq Mehmood, Farhat Naz**

Department of Medicine, *Obstetric & Gynaecology, **Department of Physiology, Ayub Medical College, Abbottabad, Pakistan

Background: Acquired aplastic anaemia is one of the important causes of pancytopenia. This study was conducted to observe the mode of presentation of acquired aplastic anaemia and to find out its possible etiological factors. **Methods:** It is a hospital based descriptive study of 100 patients of acquired aplastic anaemia. **Results:** Out of 100 patients 60 were male and 40 female. Majority (44%) of the patients were between 12–20 years of age. Patient presented with variable symptoms majority (40%) with fever. Most of the patients had haemoglobin levels between 4–6 gm/dl. (53%). Seventy percent of the cases had no obvious cause, while in 30% some known causative factors were found. Chloramphenicol was found to be the most common causative drug. Mortality was 35%. Thirty patients were partially treated and 15 were lost to follow up. Twenty patients showed improvement with treatment. **Conclusions:** Acquired aplastic anaemia is common among males and more prevalent in younger age group. It is idiopathic in 70% cases while 30% had some cause. It has very high mortality. Doctors need to keep in mind this fatal condition in patients presenting with anaemia and should properly investigate before prescribing antibiotics and haematinics.

Keywords: Aplstic anaemia pancytopenia, bone marrow suppression

INTRODUCTION

Aplastic anaemia is defined as pancytopenia with hypocellularity (aplasia) of the bone marrow. It is a serious condition that may be inherited but commonly acquired. It is due to reduction in the number of pluripotential stem cells together with a fault in those remaining or an immune reaction against them, so that they are unable to repopulate the bone marrow.[1]

Aplastic anaemia may be congenital as Fanconi's anaemia but mostly it is acquired. Acquired Aplastic anaemia may occur spontaneously or appear due to some secondary causes like drugs, viruses, radiations or during pregnancy.[2]

Idiopathic acquired aplastic anaemia accounts for most of the cases of acquired aplastic anaemia. Activated cytotoxic-T-cells in blood and bone marrow are responsible for the marrow failure.[2]

The incidence in US is 0.6–6.1 cases for million population & almost similar in Europe with 2 cases per million population. It is more common in Asia & is as high as 14 cases per million population in Japan. The increased incidence may be related to environmental rather then genetic factors because this increase is not observed in Asian people living in West.[3]

Clinical features of aplastic anaemia occur due to pancytopenia, and are due to deficiencies of the cellular elements of the blood, i.e., white cells, platelets and red blood cells. Bleeding manifestations are often the first that take the patient to seek help from the doctor. Initially minor signs of the bleeding tendency present, like excessive bruising or a petechial rash may be noticed. Commonly patient presents with bleeding from gums or nose (epistaxis). Haemorrhages in the buccal mucosa are not uncommon and retinal haemorrhages occur when platelet count is very low.[4] Then anaemia develops with passage of time and patients complain of mild fatigue or shortness of breath on exertion.

Infections may be the presenting feature. Infections exacerbate the effect of thrombocytopenia particularly mouth ulcera.[5,6] The treatment of acquired aplastic anaemia has two main components. The first is to protect and support the patients from consequences of pancytopenia and to keep them alive so that there may be chance of spontaneous recovery. The second is to try to accelerate the recovery of the bone marrow by different means, without eradicating the chances of spontaneous recovery.[7] Bone marrow transplantation or peripheral blood stem cell transfusion in the treatment of choice for young patients with sever aplastic anaemia who have an HLA identical sibling donor.[3]

This study was conducted to observe the mode of presentation of acquired aplastic anaemia and to find out its possible etiological factors.

MATERIAL AND METHODS

This descriptive hospital based study of 100 patients of acquired aplastic anaemia was conducted in The Department of Medicine, Ayub Teaching Hospital, Abbottabad, over a one year period, from 1st April 2007 to 31st March 2008. All patients above 12 years of age and of either sex with acquired aplastic anaemia admitted in Medical Units of Ayub Teaching Hospital, Abbottabad were included in this study. Patients below the age of 12 years and those with congenital aplastic anaemia, i.e., Fanconi's Anaemia were not included in the study. Upper age limit was not fixed. Informed consent was taken either from the

patient or their guardians. Detailed history was taken including history of present illness, history of any past illness particularly viral hepatitis, joint pains, myelgias, butterfly rash or fever, history of any drug intake (including any medication for fever, aches and pains, or any medicine prescribed by quacks and history of blood transfusion. Socioeconomic history was taken in detail to know whether patient would be able to afford treatment or not. Each patient was examined in detail including general physical examination and complete systemic examination. During examination signs of pancytopenia were searched like signs of neutropenia (fever, mouth ulcers, candidiasis, respiratory tract infections and infections of other sites), signs of thrombocytopenia (petechiae, echymosis and epistaxis) and signs of anaemia (pallor, trachycardia and a functional murmur). All patients underwent investigations from the same laboratory. These included complete blood count including platelets, peripheral smear, bone marrow aspiration/trephine, blood urea, glucose, electrolytes and serum creatinine, X-ray chest, liver function tests, HbsAg and anti HCV antibodies, Anti DNA antibodies and ANF.

RESULTS

Results are given in tabulated form. Out of total 100 patients 60 were male and 40 female.

According to our study 44% patients were less than 20 year of age (Table-1). Most of the patients had haemoglobin level 4–6 gm/dl (Table-2). Eighty percent (80%) patients had mild to moderate changes on peripheral smear (Table-3). Bone marrow trephine biopsy showed marked hypocellularity in 20% (Table-4).

We found that 70% of the cases had no obvious cause and hence were labelled as idiopathic. While in the rest 30% some known causative factors were found. Out of these 30%, 25% were drug induced and 5% were viral. The most common drug was chloramphenicol found in 12 patients followed by NSAIDS in 8 patients, while 5 patients were using some traditional medicine.

Most of the patients presented with fever and other features of pancytopenia (Table-5).

In our study 35 patients expired, 30 patients were partially treated, 15 were lost to follow-up and 20 patients improved with treatment.

Table-1: Age distribution of patients

Age in years	Male	Female	Total
<20	26	18	44
21–40	16	10	26
41–60	10	8	18
>60	8	4	12
Total	60	40	100

Table-2: Distribution according to haemoglobin level

Hb (gm/dl)	Male	Female	Total
<4	9	6	15
4–6	33	20	53
>6<8	18	14	32
Total	60	40	100

Table-3: Distribution according to severity of aplastic anaemia based on peripheral smear

Patients	WBC count /L	Platelets /L	Retic count %	Severity
20	$<0.5\times10^9$	$<20\times10^9$	<1	Severe
80	$>5\times10^9$	$>20\times10^9$	>1	Mild to moderate

Table-4: Severity of aplastic anaemia based on bone marrow trephine biopsy (n=100)

Cellularity		Severity	
<25% normal	25–50% normal	Markedly hyopcellular	Moderately hypocellular
20	80	20	80

Table-5: Clinical presentations of acquired aplastic anaemia and their frequencies

Symptoms and signs	Percentage
Fever	40%
Pallor	32%
Epistaxis	30%
Palpitations	30%
Dyspnoea	28%
Easy fatigability	25%
Menorrhagia	22%
Haematemesis	10%
Melaena	10%

DISCUSSION

Acquired aplastic anaemia is one of the important causes of pancytopenia. This was evident from our hospital based descriptive study of 100 patients. Similar observation was made by earlier studies.[9–13]

Out of 100 patients of acquired aplastic anaemia, 60 were male and 40 were female. A similar study was conducted by Adil *et al*.[5] which also showed male predominance. This male predominance shown by our study may be due to the fact that males consult doctors earlier as compared to females, as females are the neglected sex in our society.

Age of the patients in our study ranged between 12 to 70 years. Out of 100 patients, 44 were between age 12–20 years, 26 were 21–40 years, while 18 patients were 41–60 years and only 12 were above 60 years. This shows that acquired aplastic anaemia is more prevalent among young people. Earlier studies also showed similar results, that 77.7% of the case of acquired aplastic anaemia were below the age of 30 years.[5]

Our study showed that most of the patients presented with fever, palpitations dyspnoea, easy fatigability and epistaxis. About 40 % of the patients got admitted for investigation of pyrexia of unknown origin (PUO), and when investigated showed pancytopenia and hypocellular marrow. It means that

aplastic anaemia can present as PUO. Anaemia was present in 32%, palpitations in 30%, dyspnoea 28% and easy fatigability in 25% of the cases. Epistaxis was the presenting feature in 30% of cases, and all these were first referred to ENT department by the casualty medical officer. But on further investigations they were found to have aplastic anaemia and then shifted to the medical unit. Menorrhagia was the presenting complaint in 22% of the female patients who initially consulted a gynaecologist, but on proper evaluation were found to have aplastic anaemia and were also shifted to the medical unit. Haematemesis and malena were present in 10% of the cases and most of these patients were so critical that they died earlier.

All these observations show that aplastic anaemia can present with either features of anaemia, neutropenia or thrombocytopenia. Similar observations were made by earlier researchers.[10–12]

Our study showed that most of the patients had haemoglobin levels of 4–5 gm/dl (53%). The reason might be that patients with lesser degree of haemoglobin had received blood transfusions or died even before reaching tertiary care hospital. Earlier studies showed similar results.[12]

We classified acquired aplastic anaemia as mild, moderate and severe. This classification was made on the bases of granulocyte count, platelet count, reticulocyte count and bone marrow cellularity. Our study showed that 80% of the cases had mild to moderate degree of aplastic anaemia, while 20% had severe aplastic anaemia. Earlier studies showed that severe aplastic anaemia was found in 51.4% of the cases.[5,10–13] This difference might to be due to the reason that patients in this area do not seek doctors advice earlier. So most of the severe cases could not reach the hospital in time and died prior to proper diagnosis.

We also concentrated to find out the cause of acquired aplastic anaemia. We found that 70% of the cases had no obvious cause, and hence were labelled as idiopathic. While in the rest 30% some known causative factors were found. A previous study showed that cause of aplastic anaemia was found in 74.3% of the cases.[5] Out of the known causes (30%), 5% were due to some drugs, most common being chloramphenicol (12%), NSAIDs (8%) and other drugs including those prescribed by quacks (5%). International studies conducted on aetiology of acquired aplastic anaemia also showed same figures.[15–17] The most common cause is idiopathic, and among drugs chloramphenicol is the commonest one. About 5% of the cases were found to be associated with viral infections and most of the cases were HBSAg and anti-HCV antibodies positive. This was also evident from international and national studies conducted earlier.[5] This may be a coincidental finding as patients with aplastic anaemia might have had many unscreened blood transfusions and were now.

During our study 35 patients died, 30 were partially treated and 15 were lost to follow up. Rest of the 20 patients showed improvement with treatment. Most of them were treated with anabolic steroids, cyclosporine or simply high doses of steroids, depending upon affordability and availability of the medicines. The large number of deaths may be due to the fact that most of the patients presented with severe aplastic anaemia or were unable to afford appropriate treatment.

CONCLUSION

Acquired aplastic anaemia is common among males as compared to females, which may be due to the fact that either females always hesitate to seek doctors advice or they are a neglected sex in our society. Aplastic anaemia is more prevalent among younger age groups. It is idiopathic in 70% of the cases and has some know cause in about 30% of the cases. From this study it was observed that chloramphenicol is the most important among the know causes, found to be the culprit in 12% of the cases. The effect of chloramphenicol was not dose dependant and the features of pancytopenia appeared after 2–3 weeks of starting the drug. Other medications causing aplastic anaemia found in this stud were NSAIDs in 80% of the cases which included pyrazalone derivatives as well as indole derivatives like indomethacin. Rest of the drugs included among the causes were some self medications and some prescribed by quakes. Viruses were found to be the cause in 5% cases. Patients gave history of viral illness and were found to be HbsAg or anti-HCV antibodies positive.

Our study showed that aplastic anaemia has very high mortality, especially severe aplastic anaemia. This may be because of the fact that patients seek doctors advice when disease has already progressed into severe form or the doctors have missed early diagnosis because of vague symptoms.

RECOMMENDATIONS

As aplastic anaemia initially presents with very vague symptoms such as fever (pyrexia of unknown origin, PUO), pallor, shortness of breath, palpitations or epistaxis, patients receive antibiotics or haematinics without prior investigations. It is recommended that any patient presenting with fever, pallor, bruises or epistaxis should be properly investigated prior to prescribing medications.

There is a need of awareness among our general population that they should not take medications on their own and should avoid irrational use of drugs prescribed by quacks. Doctors should also avoid prescribing antibiotics and haematinics without appropriate investigations.

Treatment of aplastic anaemia is very expensive and the only hope for cure in most of the cases is a bone marrow transplant, every patient can not afford it, hence for the sake of survival of the poor patients the government should establish bone marrow transplant centers that can provide transplant facilities with minimal charges. Required free medication should be made available to poor patients.

REFERENCES

1. Young NS, Maciejewski J. The pathophysiology of acquired aplastic anaemia. N Eng J Med 1997;336:1365–72.
2. Aichison BP, Marsh JC, Hows JM, Russel NH, Gordon-Smith EC. Pregnancy associated aplastic anaemia-report of five cases and review of current management. Br J Haematol 1989;73:541–5.
3. Bakhshi S, Abella E. Aplastic anaemia. Available at: http://emedicine.medscape.com/article/198759-overview. Accessed on 7-6-2009.
4. Sleijfer S, Lugtenburg PJ. Aplastic anaemia: review. Neth J Med 2003;61(5):157–63.
5. Adil SN, Burney I A, Kakepoto G N, Khurshid M. Epidemiological features of aplastic anaemia in Pakistan. J Pak Med Assoc 2001;51:443–5.
6. Gordon Smith, E C and Issaragrisil, S Epidemiology of Aplastic anaemia. Clin Haematol 1992;5:475–91.
7. Marsh JC, Ball Se, Darbyshire P, Gordon EC, Keidan AJ, Martin A, *et al*. Guidelines for the diagnosis and management of acquired aplastic anaemia. Br J Haematol 2003;123:782–801.
8. Young NS, Barrett AJ. The treatment of severe acquired aplastic anaemia. Blood 1995;85:3367–77.
9. Naeem Khan M, Ayyub M, Nawaz KH, Naeem Naqi, HussainT, Shujaat H, *et al*. Pancytopenia: Clinicopathological study of 30 cases at Militiary Hospital Rawalpindi. Pak J Pathol 2001;12:37–41.
10. Maluf EM, Pasquini R, Eluf JN, Kelly J, Kaufman DW. Aplastic anaemia in Brazil- incidence and risk factors. Am J Haematol 2002;71:268–74.
11. Qazi RA, Masood A. Diagnostic evaluation of pancytopenia. J Rawal Med Coll 2002;6:30–3.
12. Iqbal W, Hassan K, Ikram N, Nur S. Aetiological breakup in 208 cases of pancytopenia. J Rawal Med Coll 2001;5:7–10.
13. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia–a six-year study. J Assoc Physicians India 2001;49:1078–81.
14. Isenberg SJ. The fall and rise of chloramphenicol. JAAPOS 2003;7:307–8.
15. Fox LE, Ford S, Alleman AR, Homer BL, Harvey J. Aplastic anaemia associated with prolonged high dose trimethoprim-Sulfadiazine administration in two dogs. Vet Clin Pathol 1993;22(3):89–92.
16. Muir KR, Chilvers Chief Executive,, Harriss C, Coulson L, Grainge M, Darbyshire P, Geary C, Hows, J, Marsh J, Rutherford T, Taylor M, Gordeon EC. The role of occupational and environmental exposures in the aetiology of acquired severe aplastic anaemia: a case control investigation. Br J Haematol 2003;123:904–14.

Address for Correspondence:

Dr. Saqib Malik, Department of Medicine, Ayub Teaching Hospital, Abbottabad, Pakistan. Tel: +92-300-9113433
Email: doctor_saqib@hotmail.com