Acquired Amegkaryocytic Thrombocytopenic Purpura (AATP): A Hospital Based Study

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Abstract

Objective: To determine the frequency of Acquired Amegakaryocytic Thrombocytopenic Purpura (AATT), possible aetiolog, course and prognosis.
Design: Retrospectively diagnosed patients, treated and followed prospectively.
Setting: Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi.
Subjects: One hundred twenty patients with thrombocytopenic purpura.
Main Outcome Measures: Response to treatment and course of disease.
Results: Out of 22 patients 2 died of cerebra! haemorrhage, one transformed to Myelodysplastic Syndrome (MDS), one transformed to Acute Myeloid Levkaenia (AML). None is transfusion independent.
Conclusion: AATT is not an infrequent disorder. It shows poor response to all available therapeutic modalities and has a potential for transformation into Myelodysplasia and acute myeloid leukaemia (JPMA 49:114, 1999).

Introduction

Amegakaryocytic thrombocytopenia is a rare disorder as opposed to Idiopathic Thrombocytopenic Purpura (ITP) with normal or increased megakarycoytes[1] in the bone marrow. It is difficult to differentiate clinically and on peripheral blood finding from ITP. Bone marrow examination, particularly trephine biopsy, is essential for its diagnosis. It is characterised by severe thrombocytopenia due to selective reduction or total absence of megakaryocytes in an otherwise normal appearing bone marrow[2,3]. It may be congenital or acquired. In the congenital variety two groups are identified. In one group the amegakaryocytic thrombocytopenia is associated with absence of the radiai and the affected infants are said to have thrombocytopenia with absent radiai (TAR) syndrome[2]. While in the other group it is an isolated phenomenon. These children die of haemorrhage at birth or in the first year of life. The acquired variety may develop at any age and cause prolonged thrombocytopenia, which may remain stable for many years[4]. On the other hand it can progress to aplastic anaemia, myelodysplastic syndrome or acute myeloid leukaemia[3]. Majority of the cases are idiopathic. Few may be associated with collagen vascular diseases, lymphoid malignancies, infectious agents, drugs or toxins[2,5]. Major clinical manifestation is bleeding or symptoms related to anaemia in cases of significant bleeding.
ATP is a rare disorder, hence the literature on it consists of case reports and small studies. Clinical trials have not been reported making the establishment of treatment guidelines difficult. In general the approach is similar to that adopted for aplastic anaemia[2].
A study was carried out at Armed Forces Institute of Pathology, Rawalpindi to determine the frequency of ATTP, its possible aetiology, course and prognosis.

Patients and Methods

One hundred and twenty patients presenting with thrombocytopenic pupura between January, 1993 and December, 1996 were reviewed. Age, sex, history of drug intake, exposure to toxin and infections prior to bleeding symptoms, clinical features and peripheral blOod parameters were recorded from available documents. Bone marrow aspirates and trephine biopsies were evaluated for number of megakaryocytes and other findings. Where slides were not available, the report from other hospitals was taken as such. A diagnosis of AATP was made when there was a selective reduction or total absence of megakaryocytes in a normal appearing marrow. In two patients only the reports of bone marrow aspiration and trephine biopsy were considered. Slides were not available for review in these patients.
Patients with evidence of known causes of thrombocytopenic pupura (e.g. ITP, Myelodysplastic syndrome, Aplastic anaemia and systemic lupus erythematosis) were excluded by appropriate investigations (Bone marrow aspiration and trephine biopsy, autoimmune profile etc.).

Results

During the four-year period (Jan 1993 - Dec 1996) a total of 120 cases ofthrombocytopenic purpura presented at AFIP. Out of these 22 (18%) were diagnosed as having acquired amegakaryocytic thrombocytopen ic purpura.
The age of the patients ranged from 6-65 years (mean age 22 years and median age 16 years). There were 10 children (less than 15 years). Sixteen of the patients were male while 6 were female. There was no history of drug intake, exposure to toxins or infections before the development of bleeding.
Twenty out of 22 patients presented with mucocutaneous bleeding in the form of epistaxis (50%), ecchymosis (45%), bleeding gums (18%) and gastrointestinal bleeding (18%). Two females had menorrhagia and one patient complained of rectal bleeding. Eight patients had bleeding from more than one site. Two patients had no bleeding problems.
Platelet counts ranged from 4-58 x I 09/1 with a mean of 20 X lOu/I (CV 70%). EIeven (50%) of patients had platelet count of 10 x 109/1 or less. MCV of these patients ranged from 71 to 121 fI with a mean of 93.1 fl (CV15.57%). Twelve patients had red cell macrocytosis with mean corpuscular volume (MCV) ranging between 96-121 fl. Antinuclear antibodies were negative in all 4 cases tested.
Nine of these patients have been followed in the haematology clinic of AFIP. Details are shown in Table.

Table. Age, Sex, Treatment and outcome in followed-up patients.

Case No.	Age (years)	Sex	Treatment	Out come	Follow up period (years)
8.	08	M	1. Steroids 2. Oxymethalone 3. Cyclosporin	1.Alive 2. Drop in Platelet count	3
11.	23	M	1. Steroids 2. Oxymethalone 3. Cyclosporin	1. Alive 2. No improvement in counts	3
16.	40	M	1. Steroids ALG* 2. Cyclosporin 3. Oxymethalone	1. Dead	2.5
17.	16	F	1. Steroids 2. Oxymethalone 3. Cyclosporin	1. Dead	2
18.	30	M	1. Cyclosporin	1. Alive 2. Low platelets	1.25
19.	23	M	1. Prednisolone 2. Oxymethalone 3. Cyclosporin	1. Alive 2. Drop in patelets	1
20.	06	M	1. Oxymethalone 2. Cyclosporin	1. Alive 2. No improvement	1
21.	06	F	1. Cyclosporin 2. Prednisolone	Progressed to erythroleukaemia	0.5
22.	28	M	1. Prednisolone	Progressed to myelodysplastic syndrome	1

* ALG: Anti lymphocyte globulin.

Seven patients were given steroids initially. This was followed by oxymethalone in 5 patients and cyclosporin-A (CSA) in 3 patients. One patient had a course of antilymphocyte globulin (ALG) prior to receiving CSA. One patient only had CSA and another had oxyrnethalone followed by CSA. All patients had supportive care in the form of red cell concentrates, platelet concentrates, antifibrinolytic agents (tranexamic acid) and primulut in females with excessive vaginal bleeding. None of the patients have shown any response to the various treatment modalities used. Two of the patients died of cerebral bleeding. One patient has progressed to myelodysplastic syndrome (MDS) and another to erythroleukaemia (AML M6). Three patients showed continued platelet count inspite of treatment.

Discussion

Acquired amegakaryocytic thrombocytopenic purpura (AATP) is a disorder of diverse etiologies. Factors leading to its production are defects in megakaryocytic maturation, intrinsic stem cell defects secondary to infections, drugs and toxins, cell and immunoglobulin mediated inhibition of megakaryocyte colony stimulating factor[1-9]. This disorder can occur at any age as seen in our cases. Patients usually present with thrombocytopenic bleeding such as ecchymosis, gum bleeding and epistaxis[2]. Twenty out of 22 of our patients also had similar complaints. Red cell macrocytosis is also seen and was present in 12 of our cases[2,12]. Platelet size is normal and platelet survival studies show longer survival time than in idiopathic thrombocytopenic purpura (ITP)[2,11]. This results in prolonged thrombocytopenia, which may remain stable, or progress to total aplasia, MDS or AML[13,10]. Three of our patients have shown deterioration in platelet counts. One patient has gone on to develop MDS and another one has progressed to AML. It is important to exclude ITP, Aplastic Anaemia, MDS and systemic lupus erythematosis at initial presentation mainly because of different management strategies and prognosis.

Treatment is usually supportive in the form of blood and platelet transfusion which should be given according to the physiological needs. Use of antifibrinolytic agents can reduce the need for transfusions. Other treatment strategies used are androgens, lithium carbonate, steroids, fresh frozen plasma, mercaptopurine, ALG, vincristine and CSA[3,9,12,13].

While the overall response to these agents is poor, as in our cases, there has been an occasional case report of response to oxymethalone and CSA[2,12,13]. Spontaneous remissions are also known to occur in this disease[5,14].

This hospital based study and its findings, although cannot be applied to general population, but suggest that the disease is not infrequent in Pakistan. It is important to evaluate all patients with thrombocytopenic purpura for the diagnosis AATP as the management and out come differs significantly from ITP.

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