# AMEGAKARYOCYTIC THROMBOCYTOPENIC PURPURA: A FIFTEEN YEAR EXPERIENCE

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**Abstract-** Amegakaryocytic thrombocytopenia, a rare variation of bone marrow aplasia, has been described in association with viral infection, vaccination, alcoholism and drug-toxicity. In the present study, we presented 20 cases of amegakaryocytic thrombocytopenic purpura in a cohort of Iranian patients presented to hematology clinics of two university hospitals with mucocutaneous bleeding. Complete blood counts, reticulocyte counts and repeated bone marrow aspiration/biopsy were carried out. Repeated bone marrow examinations revealed markedly decreased megakaryocytes but minimal or no decrease in myeloid and erythroid cell lines. Progression to aplastic anemia in 3 and progression to myelodysplasia/acute non lymphoblastic leukemia were observed in ۲ patients. Two patients died from intracranial hemorrhage. In two patients splenectomy resulted in significant improvement in platelet counts and transfusion needs. Other patients had a fluctuating variable course with supportive care. It is suggested that splenectomy can be effective in reducing transfusion requirement in selected alloimmunized patients with acquired amegakaryocytic thrombocytopenia.

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**Key words:** Amegakaryocytic thrombocytopenia, splenectomy

## INTRODUCTION

Amegakaryocytic thrombocytopenia, a rare variation of bone marrow aplasia, has been described in association with viral infection, vaccination, alcoholism and drug-toxicity (1-11). Immune mediated inhibition of megakaryocytopoiesis has been postulated as a pathogenetic mechanism and has been documented in some cases (12, 13). Acquired idiopathic amegakaryocytic thrombocytopenia presents with spontaneous mucocutaneous bleeding and moderate to severe decrease in platelet counts. Repeated transfusions of platelet concentrates are often necessary to minimize the risk of intracranial hemorrhage. Many patients with this life-threatening disorder may become alloimmunized and refractory to the subsequent platelet transfusions.

In the present study, 20 cases with amegakaryocytic thrombocytopenia have been followed during a 15 year period in two university hospitals.

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## MATERIALS AND METHODS

All patients with easy bruising and decline in platelet counts were admitted for bone marrow aspiration and biopsies. A detailed history and clinical observation for detection of any unusual exposure and symptom or sign were taken and record. Reticulocyte counts and Coombs' test were carried out. Serologic tests for systemic lupus erythematosus were done in 16 patients. Repeated bone marrow aspiration/biopsy was performed at intervals of two to four months for most of the patients. Severity of hemorrhagic tendency was recorded.

All patients received 400-600 mg/day danazol, short courses of steroids and supportive care. Platelet concentrate transfusions were carried out at intervals of 4 to 8 weeks. Eight patients received cyclosporin 200-400 mg daily for at least two months and then according to the renal function tests further administration of the drug was re-evaluated.

In 5 patients cytogenetic analysis were carried out and did not reveal any constant chromosomal abnormality.

## RESULTS

A total of 20 patients were included in the study. The patients' characteristics are summarized in table 1. A careful history failed to identify any inciting agent or exposure in these patients and physical examination was unremarkable except for purpuric and ecchymotic lesions of the skin. Reticulocyte counts, Coombs' test and serologic tests for SLE did not show any specific abnormality and there was no evidence of hemolytic process at the time of initial diagnosis.

Seventeen patients were followed up for five years. Two patients died of cerebral hemorrhage early in the course of their illness and one patient was lost during follow-up.

Ten patients had platelet counts between $30 \times 10^9$/L and $60 \times 10^9$/L and variable bleeding from nasal and buccal mucosae. This group of patients had neither complete recovery nor clinically downhill course and needed few if any platelet transfusion. Two patients showed gradual decrease in white cell counts with absolute neutrophil counts below 1500/ml. Subsequent bone marrow aspiration and biopsy revealed moderate to severe myeloid hypoplasia. In two cases, progressive increase in white cell counts and leftward shift in myeloid cell line was noted and bone marrow examination showed remarkable increase in immature myeloid cells from 10% to 25%. The mean interval between initial diagnosis and development of myelodysplasia was nine months. Two patients with platelet counts below 20×l0/L and repeated platelet transfusions were found to have allo-reactive antiplatelet antibodies. For these two alloimmunized patients,

**Table 1.** Patients age, Hb, WBC and PLT counts and bleeding tendency

| Patient | Age | Sex | Hb g/dl | Hct % | WBC × $10^7$/L | PLT ×$10^9$/L | Bleeding tendency |
|---|---|---|---|---|---|---|---|
| 1 | 23 | M | 10.2 | 32.0 | 6.8 | 12 | Moderate/ severe |
| 2* | 25 | M | 9.1 | 28.0 | 3.8 | 10 | Severe |
| 3 | 31 | M | 10.4 | 32.0 | 4.2 | 25 | Moderate |
| 4 | 26 | F | 11.1 | 34.0 | 6.3 | 36 | Moderate |
| 5 | 33 | M | 9.7 | 29.0 | 8.5 | 55 | Mild |
| 6 | 16 | F | 10.5 | 32.0 | 3.8 | 32 | Moderate |
| 7 | 24 | M | 10.1 | 31.0 | 4.3 | 45 | Moderate |
| 8 | 29 | M | 11.1 | 33.0 | 6.8 | 26 | Moderate/severe |
| 9† | 55 | F | 8.5 | 25.0 | 12.9 | 15 | Severe |
| 10 | 28 | M | 10.2 | 32.0 | 10.2 | 32 | Moderate |
| 11† | 62 | M | 8.1 | 2.0 | 14.2 | 10 | Severe |
| 12 | 26 | M | 8.6 | 26.0 | 5.4 | 22 | Moderate/severe |
| 13 | 22 | F | 10.3 | 32.0 | 6.3 | 45 | Mild |
| 14‡ | 31 | M | 10.1 | 31.0 | 3.4 | 50 | Mild |
| 15 | 35 | M | 9.6 | 29.0 | 4.5 | 35 | Moderate |
| 16 | 28 | F | 9.2 | 28.0 | 8.3 | 42 | Moderate |
| 17* | 23 | M | 8.6 | 26.0 | 5.4 | 10 | Severe |
| 18 | 25 | M | 9.1 | 28.0 | 6.2 | 42 | Mild |
| 19 | 33 | F | 10.2 | 32.0 | 7.5 | 15 | Severe |
| 20 | 27 | M | 9.1 | 28.0 | 8.2 | 25 | Moderate |

Abbriviations: Hb, hemoglobolin; M, male; F, female; ICH, intracranial hemorrhage.
* Died of ICH.
† Developed MDS/ AML.
‡Progressed to aplastic anemia.

splenectomies were carried out with leukodepleted platelet concentrates and steroids. These two splenectomized patients had ten-year event free survival with clinically significant rise in platelet counts more than 60000/ml.

Two patients aged 23 and 25 had progressive increase in muco-cutaneous bleeding and died of intracranial hemorrhage (ICH). These two cases had persistently low platelet counts below 20 × 10/L and received platelet transfusions and intravenous infusion of tranexamic acid.

Most of the patients had normocytic, normochromic anemia as the result of repeated bleeding. Three patients had microcytic hypochromic anemia due to recurrent hemorrhage and iron deficiency. Serum ferritin levels were reduced in these three patients, indicative of iron deficiency anemia. None of the patients required packed red cell transfusion.

Pharmacologic intervention with danazol and cyclosporine did not result in any remarkable rise in platelet counts in patients with severe thrombocytopenia (Table 2).

**Table 2.** Changes in blood cell counts after six months

| Patient | Hb g/dl | Hct % | WBC×$10^9$/L | PLT×$10^9$/L |
|---|---|---|---|---|
| 1 | 9.3 | 28 | 7.2 | 15 |
| 2* | 9.5 | 29 | 4.3 | 10 |
| 3 | 10.1 | 31 | 6.5 | 28 |
| 4 | 10.2 | 31 | 8.6 | 35 |
| 5 | 10.7 | 33 | 9.2 | 46 |
| 6 | 11.1 | 34 | 3.5 | 32 |
| 7 | 11.2 | 34 | 2.2 | 42 |
| 8 | 9.8 | 29 | 6.5 | 20 |
| 9† | 7.6 | 22 | 56.2 | 20 |
| 10 | 9.8 | 29 | 10.8 | 35 |
| 11† | 7.6 | 22 | 85.5 | 12 |
| 12 | 11.1 | 33 | 5.8 | 25 |
| 13 | 11.6 | 35 | 5.5 | 36 |
| 14‡ | 10.7 | 32 | 1.8 | 45 |
| 15 | 9.8 | 29 | 5.2 | 32 |
| 16 | 10.1 | 31 | 7.8 | 36 |
| 17* | 7.4 | 22 | 6.2 | 10 |
| 18 | 9.3 | 28 | 5.4 | 40 |
| 19 | 8.6 | 25 | 6.4 | 15 |
| 20 ¶ | - | - | - | - |

* Died of ICH.
† Developed MDS/ AML.
‡ Progressed to aplastic anemia.
¶ Lost to follow up.

# DISCUSSION

Acquired amegakaryocytic thrombocytopenia -excluding those associated with infections, drug toxicity, alchohol abuse and myelophthisic infiltrative disorders of the bone marrow- is a rare variation of bone marrow hypoplasia (1-4, 7-10). Both humoral and cell mediated immune suppression of megakaryocytopoiesis have been linked to the pathogenesis of this unusual disorder. The initial defect seems to involve all lineages derived from the committed progenitor cells predominantly the megakaryocyte precursors (12,13). Serum thrombopoietin levels have been noted to be elevated in patients with amega-karyocytic thrombocytopenia. Antibody mediated suppression of thrombo-poietin activity has been documented in some patients with this disorder (14). A few patients with megakaryocytic aplasia have been reported with antibodies specific for platelet membrane glycoprotein complex GP IIb/IIIa, a surprising dysregulated immune reactivity against megakaryocyte membrane glycoproteins (15, 16).

A careful history failed to identify any inciting agent or exposure in our patients. Physical examination was unremarkable except for purpuric and ecchymotic lesions of the skin. In this study there were no prior infectious, inflammatory or toxic agents as the causal mechanism for bone marrow hypoplasia.

Course of the disease was variable. Patients with rapidly progressive downhill course were young (ages 20-30). Two patients aged 32 and 35 had a gradual decrease in other blood cell lines and panhypoplasia in the bone marrow. Progression to aplastic anemia has been described in some cases within months to a few years (17, 18). Two patients ageing 55 and 62 were noted to develop stepwise increase in white cell counts and increase in immature myeloid elements compatible with myelodysplastic syndrome, refractory anemia with excess blasts (RAEB) subtype. One of these patients developed acute myeloblastic leukemia (M2 subtype) later.

Splenectomy in two patients with allo-reactive antiplatelet antibodies resulted in significant improvement in platelet count and transfusion

requirements. Although invasive surgical intervention is not advised and can be associated with significant morbidity and mortality in cases of increased bleeding tendency, removal of the spleen as a major source of antibody production and phagocyte activity in selected alloimmunized patients with amegakaryocytic thrombocytopenia has been suggested by some investigators as a therapeutic adjunct in reducing transfusion requirement and would maintain a long-term stable clinical remission (19). Other anecdotal reports have indicated variable responses in platelet counts with above mentioned drugs and/ or anti-thymocyte globulin (20).

In conclusion, in most patients with platelet counts below $20 \times 10^9$/L, the outcome is unfavorable with ongoing life threatening hemorrhage. Progression to aplastic anemia or myelodysplasia/ acute myelogenous leukemia is suggestive of a defective common progenitor derived from pluripotent or early committed stem cell as a result of bone marrow microenvironment injury. In occasional patients with subsequent platelet alloimmunization, splenectomy can be effective in reducing transfusion requirement and will maintain long term clinical remission.

## Conflict of interests

We have no conflict of interests.

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