J Korean Med Sci 1998; 13: 541-4
ISSN 1011-8934

Severe Aplastic Anemia Induced by Ticlopidine
: Report of Two Cases

Aplastic anemia is a rare side-effect associated with ticlopidine therapy. We report two cases of severe aplastic anemia developed after the use of ticlopidine. A 51-year-old woman took ticlopidine at 500 mg/day for 49 days to prevent a secondary stroke. She developed fever and dizziness within 49 days of initiating ticlopidine therapy. A 70-year-old woman was started on ticlopidine after coronary stent insertion. Fifty days after starting ticlopidine, she developed fever and dizziness. Both patients showed pancytopenia and were diagnosed as aplastic anemia which were confirmed by bone marrow examination. Both patients were hospitalized and received antibiotics, blood products and hematopoietic growth factors. Four and seven weeks after the withdrawal of ticlopidine, the hematologic parameters of each patient improved. A complete blood count should be monitored during ticlopidine therapy to check for cytopenia.

Key Words : *Anemia, aplastic; Ticlopidine*

Hyeseung Bahng, Je-Hwan Lee, Cheolwon Suh, Jin Hee Ahn, Sung-Bae Kim, Sang-We Kim, Kyoo-Hyung Lee, Jung-Shin Lee, Woo-Kun Kim, Chan Jung Park,* Hyun Sook Chi,* Sang-Hee Kim

Departments of Medicine and Clinical Pathology*, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received : January 22, 1998
Accepted : April 1, 1998

Address for correspondence
Je-Hwan Lee, M.D.
Department of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-040, Korea
Tel : +82.2-224-3210, Fax : +82.2-224-6961
E-mail : jhlee@amc.seoul.kr

INTRODUCTION

Ticlopidine hydrochloride is a new potent antiplatelet drug which inhibits platelet aggregation by adenosine diphosphate (ADP). It has been used in the treatment of a variety of disease in which platelets play a predominant role (1, 2). The frequent adverse effects of ticlopidine are rash and gastrointestinal complaints. Neither of these necessarily require discontinuation of therapy in most patients. Hematologic complications have been reported, including agranulocytosis (1), thrombocytopenia (3), and rarely aplastic anemia. We report two patients who developed severe aplastic anemia after ticlopidine therapy.

CASE REPORT

Case 1

A 51-year-old woman was admitted with a two-week history of fever, rigor and sore throat. Forty-nine days before admission, she had suffered sudden paresthesia of right upper extremity. A CT scan of the brain revealed a small infarction in the left thalamus. Blood count was normal at that time. She had been taking ticlopidine (500 mg/day), aspirin (200 mg/day) for 49 days.

On admission, the spleen and liver were not palpable. Hemoglobin was 6.8 g/dL with 0.22% reticulocyte; the white cell count was 1,300/mm^3 with 1% neutrophil, 89% lymphocyte, 10% monocyte, and 1% atypical lymphocyte; the platelet count was 56,000/mm^3. Bone marrow examination showed that the marrow was nearly devoid of hemopoietic cells and mainly composed of lymphocytes and plasma cells (Fig. 1). Blood and throat swab culture were positive each for *Bacillus* species and non-beta streptococci. Biochemical parameters including immunoglobulins were normal. Screening was negative for Hepatitis B and C and parvovirus. She was diagnosed as aplastic anemia induced by ticlopidine. She received antibiotics, blood transfusions and hemopoietic growth factors (GM-CSF 400 μg/day for 7 days and G-CSF 300 μg/day for 5 days). Four weeks after ticlopidine was stopped, the hemoglobin was 6.2 g/dL with 2.58% reticulocytes; the white-cell count was 2,000/mm^3 with 49% neutrophil, 34% lymphocyte, and 15% monocytes; the platelet count was 56,900/mm^3 (Fig. 2). Repeated bone marrow examintion showed normal cellularity with trilineage regeneration.

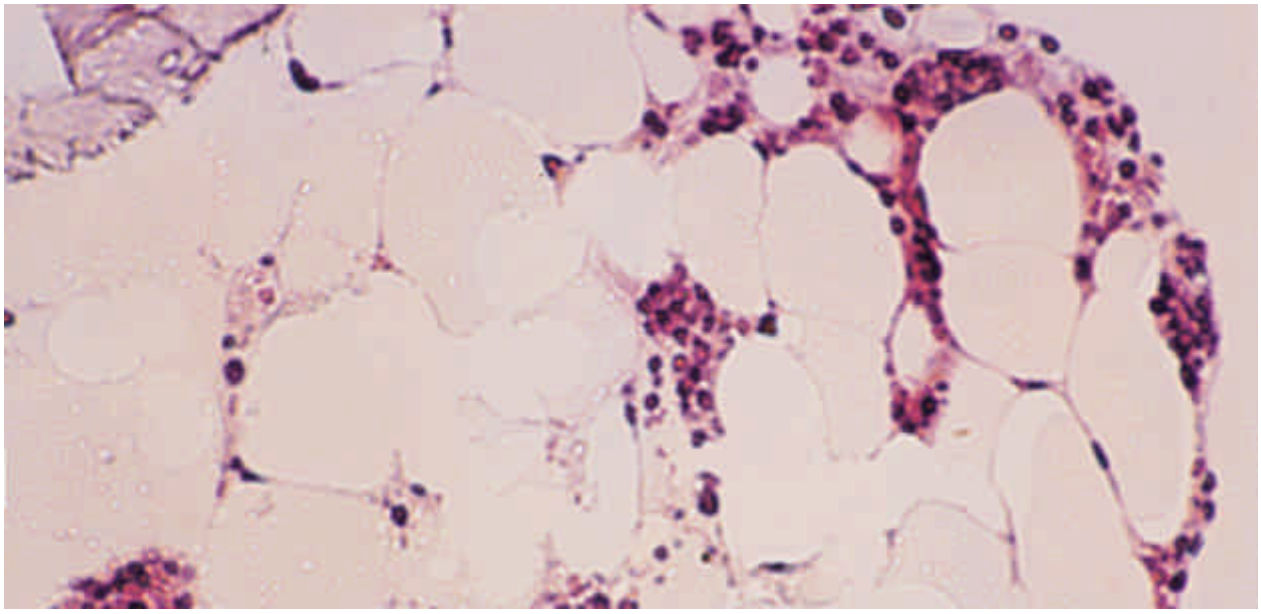

Fig. 1. Case 1, Bone marrow biopsy (×200): Bone marrow examination showed that the marrow was nearly devoid of hemopoietic cells and mainly composed lymphocytes and plasma cells.

Case 2

A 70-year-old woman was admitted due to fever, sore throat, and dizziness. Six weeks prior to admission, she had undergone the insertion of a coronary stent due to a subtotal obstruction of the left anterior descending artery. Thereafter she took ticlopidine (500 mg/day), aspirin, and diltiazem.

On admission, no lymphadenopathy or hepatosplenomegaly was found. The hemogram indicated pancytopenia; hemoglobin of 10.1 g/dL with 0.05% reticulocytes, the white blood cell count of 500/mm^3 with 15% neutrophils, 78% lymphocyte and 7% monocyte, and the platete count of 13,000/mm^3. Non-beta streptococci was identified in throat swab culture. A bone marrow examination revealed hypocellular marrow that was mainly composed of lymphocytes and plasma cells (Fig. 3). Biochemical parameters including immunoglobulins were normal. Screening was negative for Hepatitis B and C and parvovirus. She was diagnosed as aplastic anemia induced by ticlopidine. Treatment included broad-spectrum antibiotics, red cell and platelet support, GM-CSF 250 μg/day for 5 days and G-CSF 300 μg/day for 16 days. After ticlopidine was discontinued, the blood count improved. On 49th day following the discontinuation of the drug, the Hb was 7.8 g/dL with 2.44% reticulocyte; the white-cell count was 4,900/mm^3 with 42% neutrophil, 51% lymphocyte, 5% monocytes, 1% eosinophil, and 1% basophil; the platelet count was 107,000/mm^3 (Fig. 4).

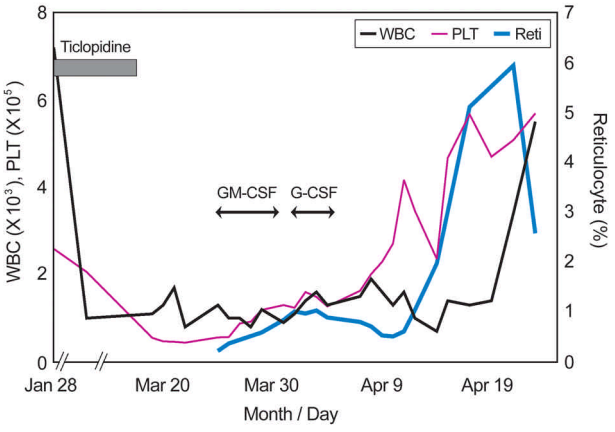

Fig. 2. Complete blood cell count profiles of the case 1.

DISCUSSION

Hematologic side effects such as neutropenia, thrombocytopenia, and rarely pancytopenia have been described after the use of ticlopidine. And the product label of ticlopidine as approved in 1991 included a boxed warning stating that neutropenia occurred in 2.4% and severe neutropenia and/or agranulocytosis occurred in 0.8% of stroke patients who received ticlopidine in premarketing clinical trials (4, 5, 6). In preliminary world-wide search of adverse hematologic events associated with ticlopidine through 1994, a total 645 cases of aplastic anemia, bone marrow suppression, pancytopenia, and agranulocytosis

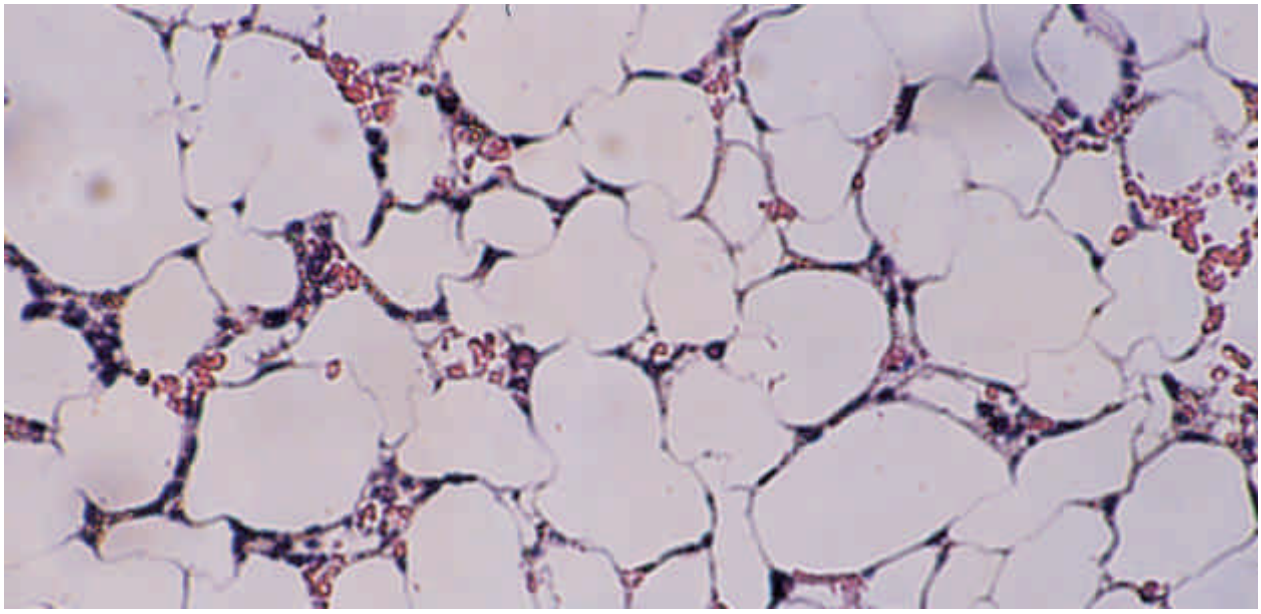

Fig. 3. Case 2, Bone marrow clot (×400): Bone marrow examination showed that the marrow was nearly devoid of hemopoietic cells and mainly composed lymphocytes and plasma cells.

were found, of which 102 (16%) were fatal (4). Median duration of ticlopidine use to onset of symptoms or detection of abnormal laboratory results ranged from about 30 to 45 days (7). In our cases, the aplastic anemia occurred 4 and 8 weeks after initiation of ticlopidine treatment at usual dose. The pathogenesis of bone marrow toxicity by ticlopidine is unclear. Ono et al. (8) have recently demonstrated that this complication is due to a direct cytotoxic effect. Resegotti and associates have already shown that ticlopidine directly increases the synthesis of prostaglandin E1 (PGE1) (9). This prostaglandin may reduce the growth of the granulocyte-macrophage colony forming unit, as was shown by Ono et al. (8) In several reports in vitro bone marrow cultures from patients treated with ticlopidine showed that the granulocyte-macropharge colony forming unit (CSF-GM) growth was slightly reduced. This effect could be assigned to an increase in prostaglandin E1 (PGE1) synthesis directly produced by this drug. Perhaps the excellent response to corticosteroid treatment could be ascribed to a reverse in that inhibitory effect. This life-threatening complication could be especially serious in older patients who are the main population treated with ticlopidine (4). Physicians are reminded that complete blood cell count with differentials should be monitored during the ticlopidine therapy, and the drug should be promptly withdrawn when cytopenia develops.

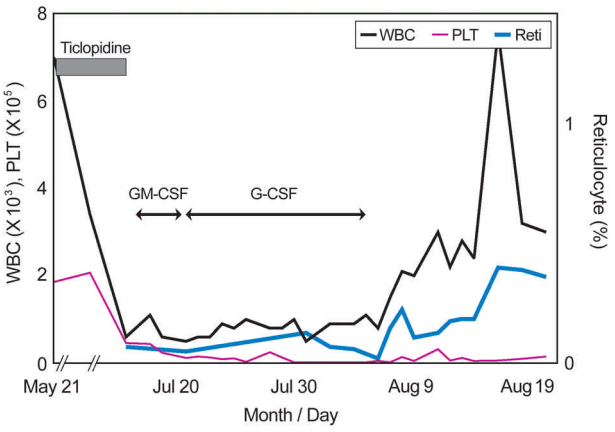

Fig. 4. Profiles of complete blood cell counts of the case 2.

REFERENCES

1. Haas WK, Easton JD, Adams HP. *Randomized trial comparing ticlopidine hydrochloride with aspirin for prevention of stroke in high-risk patients. N Engl J Med 1989; 321: 501-7.*
2. Gent M, Blakely JA, Easton JD. *The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989; 1: 1215-20.*
3. Class FHJ, de Fraiture WH, Meyboom RHB. *Thrombopenic causee par des anticorps induits par la ticlopidine. Nouv Rev Fr Hematol 1984; 26: 323-4.*
4. Barnett HJM, Eliasziw M, Meldrum HE. *Prevention of ischemic stroke. N Engl J Med 1995; 333: 460.*
5. Terrana R, Bertrand JC. *Thrombotic thrombocytopenic purpura*

related to ticlopidine. Lancet 1991; 337: 774-6.

6. Kovacs MJ, Soong PY, Chin-Yee IH. *Thrombotic thrombocytopenic purpura associated with ticlopidine. Ann Pharmacother 1993; 27: 1060-1.*
7. Wysowksi DK, Bacsanyi J. *Blood dyscrasias and hematologic reactions in ticlopidine users. JAMA 1996; 276: 952.*
8. Ono K, Kurohara K, Yoshihara M, Shimamoto Y, Yamaguchi M. *Agranulocytosis caused by ticlopidine and its mechanism. Am J Hematol 1991; 37: 239-42.*
9. Resegotti L, Pistone MA, Testa D. *Culture de moelle chez les sujets trites par la Ticlopidine. Nouv Rev Fr Hematol 1984; 27: 19-22.*