A Case of Ethosuximide-Induced Aplastic Anemia Successfully Treated with Methylprednisolone Pulse Therapy

Hyun Sik Kang, M.D.¹ and Sun Hyung Kim, M.D.²

Departments of ¹Pediatrics and ²Laboratory Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea

Aplastic anemia may develop secondary to environmental exposure to entities such as chemicals, medical drugs, and infectious agents. Fatal complications from antiepileptic medications may occur despite careful and appropriate use. We report the case of a 9-year-old girl with a presenting diagnosis of aplastic anemia following treatment with ethosuximide for absence seizures. Aplastic anemia can now be cured with stem cell transplantation or immunosuppressive therapy. In this case, however, because of the impossibility of bone marrow transplantation and the specific needs of the patient’s parents, three courses of methylprednisolone pulse therapy were administered. Following the therapy, there was improvement in pancytopenia and complete remission in the bone marrow. No adverse side effects of therapy were observed. The authors suggest that methylprednisolone pulse therapy may be a treatment for acquired aplastic anemia.

Key Words: Aplastic anemia, Ethosuximide, Methylprednisolone, Anticonvulsants

Introduction

Aplastic anemia (AA) is a rare bone marrow failure syndrome characterized by peripheral blood pancytopenia resulting from reduced or absent production of blood cells in the bone marrow [1]. AA can be classified as inherited or acquired. The diagnosis of acquired AA in children is based on the exclusion of a variety of inherited bone marrow failure disorders [2]. Acquired AA has been strongly associated with exposure to chemicals and drugs in the environment, ionizing radiation and infectious agents [1]. More than 80% of AA cases are idiopathic and 20% are drug-induced, while the post-infectious form constitutes fewer than 5% of cases [1,3]. There have been case reports of patients in whom particular chemicals or drugs were associated with the occurrence of AA [1,3,4]. A variety of drugs have been associated with AA.
Many of drugs felt to be related to aplasia are not used in childhood, with the exception of antiepileptic drugs [1,5]. In a recent study, 16 (9.2%) of 173 patients with aplastic anemia were found to be receiving antiepileptic drugs, whereas only 0.8% of patients in the control population received there drugs, which translates into a nine-fold increase in risk [5]. Among patients who have taken antiepileptic medications, a small number have experienced the complication of bone marrow failure [5]. Rare cases of AA have been associated with carbamazepine, phenytoin, ethosuximide, and valproic acid [5]. An inciting event, such as a medical drugs, provokes an aberrant immune response, triggering oligoclonal expansion of cytotoxic T-cells that destroy hematopoietic stem cells [3]. Regardless of the causes, allogeneic stem cell transplantation (SCT) from a human leukocyte antigen matched sibling donor and immunosuppressive therapy (IST) are the main treatment options for children with AA [2,6]. Allogeneic SCT is the only curative treatment [2,6]. Some patients will not receive up-front SCT because of patient choice, physician preference, or SCT access issues [6]. Other therapies for AA include androgens, hematopoietic growth factors, eltrombopag, cyclophosphamide, alemtuzumab, mycophenolate mofetil, recombinant humanized anti-interleukin-2 receptor antibody, and splenectomy [1,2,6]. Ethosuximide-induced AA has been reported, but it appears to be extremely rare [7]. Herein, we report the case of a 9-year-old girl diagnosed with ethosuximide-induced AA who underwent methylprednisolone pulse therapy without SCT.

### Case Report

A 9-year-old girl presented with bruises and petechiae, which had begun one week earlier. She had visited a local clinic two weeks previously for an upper respiratory infection, and had been taking medication, not including antibiotics, since that time. One day before admission, laboratory tests showed severe thrombocytopenia (5,000/µL), neutropenia (730/µL), normal hemoglobin (Hb, 11.3 g/dL), mean corpuscular volume (MCV, 89.6 fL), and normal white blood cell (WBC) count (5,400/µL). The peripheral blood smear revealed atypical lymphocytes, neutropenia, and thrombocytopenia. The patient had no significant family medical history. She was admitted for further examination and follow-up of thrombocytopenia of unknown origin. At the time of admission, the patient’s general condition was fine, and her vital signs were stable. Heart sounds were normal, with no murmur. No organomegaly was present.

Review of the patient’s medical history showed that she had been taking an antiepileptic medication for about a year and a half for absence seizures. She had initially taken valproate as an anticonvulsant. However, one month after the initiation of valproate, her medication was changed to ethosuximide owing to the side effect of enuresis. At the time of initiation of antiepileptic treatment, a complete blood count (CBC) showed Hb of 12.5 g/dL, WBC count of 4,300/µL, platelet count of 311,000/µL, and MCV of 82.5 fL. Thereafter, the patient did not experience any seizures and continued taking ethosuximide. Electroencephalograms were performed regularly, but no blood tests were performed.

On hospital day (HD) 1, the patient’s CBC showed Hb level of 9.6 g/dL, reticulocyte count of 0.46%, WBC count of 4,300/µL, absolute neutrophil count (ANC) of 460/µL, platelet count of 7,000/µL, and MCV of 89.7 fL. Her general condition was good, with the exception of bruises and petechiae. On HD 6, CBC revealed pancytopenia with a Hb level of 8.9 g/dL, a WBC count of 2,800/µL, an ANC of 310/µL, a platelet count of 6,000/µL, and a MCV of 88.3 fL. Serial CBC tests revealed progression to pancytopenia. However, the patient’s condition remained good, and there was no organomegaly. We recommended a bone marrow study on the basis of the pancytopenia, but the patient’s parents refused the study. On HD 6, intravenous immunoglobulin therapy (1 g/kg for 2 days) was then initiated owing to immune thrombocytopenia. On HD 10, laboratory findings revealed Hb level of 8.2 g/dL, WBC count of 3,000/µL, platelet count of 12,000/µL, and MCV of 88 fL. On HD 13, the patient’s Hb level was 7.9 g/dL, WBC count was 2,700/µL, and platelet count was 10,000/µL. The patient experienced no bleeding during the hospital stay. Ethosuximide was discontinued in response to the opinion of the neurologist.
On HD 15, a bone marrow study was performed following a platelet transfusion owing to persistent pancytopenia. The examination revealed markedly hypocellular marrow and acellular marrow with necrosis. The cellularity was significantly decreased less than 20% (Fig. 1). Erythroid elements were proportionally increased, while myeloid elements and megakaryocytes showed a proportionally marked decrease. The findings of this study were consistent with AA with no abnormal gene translocations and a normal 46,XX female karyotype on chromosomal testing. Results of a chromosomal breakage test were negative, and paroxysmal nocturnal hemoglobinuria test revealed no definitive paroxysmal nocturnal hemoglobinuria clones, Parvovirus B19, Epstein-Barr virus, and herpes simplex virus were not detected.

Due to legal problems, the patient’s parents unconditionally wanted treatment that we could do in our hospital. We had no bone marrow transplant unit and was unable to treat conventional IST because the anti-thymocyte globulin was not in the hospital. We had no choice but to treat the patient according to previous case reports. On HD 21, treatment with intravenous bolus methylprednisolone therapy (30 mg/kg) was initiated. Three courses of pulse methylprednisolone therapy were administered at intervals of one week. On HD 42, the patient’s CBC showed Hb level of 9.4 g/dL, WBC count of 5,200/μL, ANC of 430/μL, and platelet count of 32,000/μL. The patient was discharged at this time. Hematologic recovery was achieved 45 days after the last course of methylprednisolone pulse treatment. Laboratory tests at this time showed Hb level of 10.3 g/dL, WBC count of 3,200/μL, ANC of 1,230/μL, and platelet count of 126,000/μL.

A bone marrow study was performed six months after treatment. Bone marrow aspirates and biopsy revealed normocellular marrow for the patient’s age with trilineage regeneration (Fig. 2). At this time, CBC showed a Hb level of 10.3 g/dL, WBC count of 3,200/μL, ANC of 1,230/μL, and platelet count of 126,000/μL.

### Fig. 1. First bone marrow biopsy of the patient. Cellularity was significantly decreased less than 20%. Hematopoietic trilineage cells are markedly decreased and lymphocytes are relatively increased in proportion (H&E staining, ×100). (A) Left bone marrow biopsy; (B) Right bone marrow biopsy.

### Fig. 2. Second bone marrow biopsy after treatment. Cellularity was restored and seemed to be in normo-to slightly hypocellular range considering the patient’s age. Hematopoietic elements were being produced in a normal range, and the proportion of lymphocytes had also decreased compared to the first examination (H&E staining, ×100). (A) Left bone marrow biopsy; (B) Right bone marrow biopsy.
of 13.7 g/dL, WBC count of 6,700/μL, reticulocyte count of 0.91%, platelet count of 197,000/μL, and MCV of 84.3 fL. Trilineage hematologic recovery was observed.

Discussion

Ethosuximide was introduced in 1958 and has since become the drug of choice for control of absence seizures [7]. It is one of the oldest available antiepileptic medications [8]. Ethosuximide is a choice for initial empirical monotherapy in childhood absence epilepsy [8]. Ethosuximide monotherapy has been generally well tolerated, and serious adverse side effect of AA is rarely reported [5,7,8]. The patient described in this report received ethosuximide as monotherapy for absence seizures. Unfortunately, the reported patient was unable to undergo blood tests during treatment with the medication. However, routine monitoring cannot predict ethosuximide-related AA because early signs of bone marrow failure are not clear [7].

The gold standard therapy of AA in children remains allogeneic SCT from a human leukocyte antigen matched sibling donor. For children without a sibling donor, standard IST is indicated [2,6]. The choice of treatment is particularly influenced by the long-term sequelae of the disease and its therapy [9,10]. Lack of response, hematologic relapse, and secondary malignancy are problematic in IST, whereas graft failure, acute and chronic graft-versus-host disease, sources of graft, and infections limit the success of SCT [9,10]. In the case described here, the admitting hospital lacked a bone marrow transplant unit, so the patient was referred to a tertiary general hospital. As mentioned in the introduction, treatment decisions depend on circumstances including patient choice, bone marrow transplant access issues, and medicolegal concerns [6]. Owing to the topographical limitations of the island, the parents of the patient in this case wanted to treat her ethosuximide-induced AA at the authors’ hospital. The socioeconomic level of the patient must also be taken into account when considering compliance with therapy.

The pathophysiology of acquired AA results from T cell-mediated autoimmune destruction of hematopoietic stem cells, although the mechanism is not yet completely understood [3]. Increasing levels of interferon-γ and tumor necrosis factor-α reduce the levels of human hematopoietic progenitors [3,11]. Glucocorticoids can inhibit the production of both interferon-γ and tumor necrosis factor-α [3,12]. Anti-thymocyte globulin plays a role in depleting T cells through complement-dependent lysis and apoptosis, interference with functional properties of antigen-presenting cells [3,13]. Cyclosporine A inhibits IL-2 production of activated T cells and prevents expansion of cytotoxic T cells [3,13]. Decreasing levels of tumor necrosis-α and interferon-γ ultimately lead to reduced cell cycling and cell death by apoptosis [3,13]. Therefore, administration of glucocorticoids can have a similar mechanism to that of anti-thymocyte globulin and cyclosporine A [3,11-13]. The patient described in this report received methylprednisolone as therapy for ethosuximide-induced AA, as previously reported [7,14]. The treatment effect is slow, requiring about one and a half months from the final administration of methylprednisolone. No adverse side effects of the therapy were observed in the present case. We cannot comment on the occurrence of complications because of the short follow-up period.

In summary, we describe a rare case of ethosuximide-induced AA treated with methylprednisolone pulse therapy. This is one of the ways to treat AA caused by drugs. In case of patients that cannot be treated with SCT and conventional IST, methylprednisolone pulse therapy can be used as an alternative to IST [7,14,15].

References

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