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CORRESPONDENCE

Antithymocyte Globulin Induced Recurrent Seizures in a Case of Severe Aplastic Anemia

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Abstract Antithymocyte globulin (ATG) has been the standard immuno suppressive therapy for aplastic anemia. ATG significantly improves survival and response rates vary between 40 and 70 %. Mild side effects are common but recurrent seizures have rarely been reported with ATG.

Keywords Aplastic anemia · Antithymocyte globulin · Seizures

Dear Editor,

Aplastic anemia is a serious life threatening disease characterised by pancytopenia and bone marrow hypocellularity with replacement of marrow by adipose tissue. Most patients do not have donors for stem cell transplantation and rely on immunosuppressive therapy (IST) as the first-line treatment. Antithymocyte globulin (ATG) has been the standard IST for aplastic anemia. ATG significantly improves survival compared with supportive care or androgen therapy and response rates vary between 40 and 70 % [1, 2]. Mild side effects are common with ATG but seizures have rarely been reported. We describe here a case of aplastic anemia who developed seizures following first dose of ATG and was given adequate anti-epileptic therapy followed by re-challenge with ATG but had recurrence of seizures.

A 48-years-old woman was admitted with weakness and bleeding from gums and nose for two months. Past medical, personal and family histories were non-contributory. Physical examination revealed pallor and petechial spots over limbs with no lymphadenopathy and hepatosplenomegaly. She was found to have pancytopenia with hemoglobin 7.6 g/dl, total leukocyte count 1.2×10^9/l and platelet count 10×10^9/l with peripheral smear showing neutrophils 16 %, lymphocytes 82 % and monocytes 2 %. Bone marrow aspiration showed hypocellular marrow with lymphocytic predominance and biopsy showed overall cellularity of 10 %. Flow cytometry was negative for paroxysmal nocturnal hemoglobinuria clone. Considering a diagnosis of very severe aplastic anemia she was planned for IST with horse-ATG (ATGAM 40 mg/kg/day for 4 days). Her baseline hepatic and renal parameters and electrolytes were normal. Prednisone 1 mg/kg orally daily was started to prevent serum sickness. A test dose of ATG (0.1 ml of 1:1,000 dilution) was given to rule out an allergic reaction before the full dose of ATG 40 mg/kg/day was administered i.v. over 6 h, which she tolerated well. She was transfused one unit single donor platelet one hour after completing ATG infusion. Six hours after completing the first dose of ATG patient developed generalized tonic–clonic seizures (GTCS) with loss of consciousness and tongue bite. She was given diazepam (5 mg i.v. bolus) and loading dose of phenytoin (15 mg/kg slow i.v. infusion). Seizures subsided and she regained consciousness after 10 min. She was hemodynamically stable during this course. Serum electrolytes including sodium, calcium and magnesium levels and random blood sugar were normal. Non-contrast computed tomograph (NCCT) of brain and magnetic resonance imaging did not reveal any intracranial bleed. Electroencephalography (EEG) revealed a normal wave pattern with no evidence of epileptic focus or encephalitis. CSF examination was not done because patient had severe thrombocytopenia refractory to single donor platelet transfusions, with increased risk of hemorrhage. She was started on

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clobazam (30 mg/day) and was given ATG on the second and third days, which she tolerated without any side effects. Four hours after completing third dose of ATG she again had GTCS. She was treated with intravenous diazepam and recovered completely within 15 min. Her serum electrolytes and NCCT head were repeated and were normal. She was not given further dose of ATG. Prednisone tapering was started from day 21 and cyclosporine (6 mg/kg/day) was added. She was continued on clobazam and did not have further recurrence of seizures.

Most patients experience fever and skin reactions with ATG. Other frequently reported adverse effects include chills, arthralgia, headache and vomitings. Less common side effects include periorbital edema, muscle ache, lightheadedness, myocarditis, hypotension, hypertension, respiratory distress and anaphylactic reaction. Seizures are very rare complications of ATG therapy [3, 4]. Our patient developed generalized seizures after ATG administration and there was recurrence of seizures after readministration of ATG. All biochemical parameters and CT scan and MRI brain were normal. This case highlights this rare side effect of ATG, which should be managed by withholding further treatment with ATG, as anti-epileptic drugs may not prevent the recurrence of seizures.

Though cyclosporine (CsA) [5–7] and rarely steroids [8] are known to cause seizures, this is a rare side effect of ATG. Ten to forty percent of patients who receive the CsA may experience some form of neurologic side effects. These are mild and include tremors, neuralgia and peripheral neuropathy. Severe neurological symptoms with CsA affect less than 5 % of patients and include psychoses, blindness, seizures or leukoencephalopathy [5, 6]. CsA may enhance seizure activity by metabolic, toxic or vascular effects or by direct neuronal excitability [9]. Steroids increase neuronal excitability and lower the seizure threshold particularly those with high mineralocorticoid and progesterone activity [10, 11]. Treatment includes withholding further therapy. Mechanism of ATG induced seizures is not known but ATG may have directly caused the seizures in our patient as there was recurrence following re-exposure to ATG. There was no seizure recurrence with continued prednisolone and cyclosporine therapy.

This case highlights the fact that seizures can develop following ATG therapy and are contraindication for further ATG treatment even in spite of adequate management of seizures by anti-epileptics drugs. Other causes of seizures such as viral encephalitis and bacterial meningitis are unlikely in this case since all the investigations which were done were negative for these conditions. CSF study could not be done due to the low platelet count. Recurrence of seizures on re administration of ATG strongly points towards a causal effect of the drug. Furthermore, the mechanism of ATG induced seizures may be different from those due to CsA as our patient did not develop seizures on continued CsA therapy which is a more common cause of seizures than ATG.

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