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A case of levetiracetam-induced thrombocytopenia

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ABSTRACT – Rare cases of levetiracetam-induced thrombocytopenia have been reported in the literature. We report a case of glioblastoma multiforme and partial epilepsy treated with levetiracetam with subsequent development of thrombocytopenia. After ruling out all other possible causes of a decreased platelet count, we conclude that levetiracetam was the cause of this adverse event.

Key words: glioblastoma multiforme, seizures, levetiracetam, thrombocytopenia

Levetiracetam is a widely used antiepileptic drug for the treatment of partial-onset, myoclonic, and primary generalised tonic-clonic seizures. Although one of the best tolerated antiepileptic medications, levetiracetam is known to induce a wide array of adverse effects, ranging from headache, somnolence, dizziness and imbalance to more severe reactions such as psychosis (Kossoff *et al.*, 2001). Rare reports, with varying degrees of evidence, have also associated thrombocytopenia with the use of levetiracetam (Hartmann *et al.*, 2002; Kimland *et al.*, 2004; Meschede *et al.*, 2008).

We report a 50-year-old woman with a diagnosis of left frontal glioblastoma multiforme (GBM) complicated with epilepsy. The diagnosis of GBM was made in early November 2007 after the patient presented with a two-week history of headache, confusion and speech disturbance. Prior to these events, her medical history included asthma and generalised anxiety disorder and her only home medications were escitalopram, advair and multivitamins. The patient was a non-smoker, reported rare alcohol intake and did not follow any specific dietary regimen. Her weight on initial presentation was 79 kg and did not change significantly throughout her treatment. She underwent total resection of the tumour on the 14th of November 2007, with concurrent temozolomide and radiation therapies that were completed on the 4th of February 2008. She continued to receive monthly maintenance temozolomide treatment for six months, ending in August 2008. Her tumour recurred in November 2008, at which time monthly maintenance treatment with temozolomide was reinitiated, but was only implemented for one month and stopped in December 2008. Dexamethasone was concomitantly started and continued throughout the period of subsequent treatment without any changes in dosage. She continued to receive her home medications at the same doses and she had been prescribed a steady dose of ranitidine since the initiation of dexamethasone. The patient underwent a second resection on January 2nd, 2009. The patient had her first seizure in November 2008 which consisted of aphasia, behavioural arrest, and

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unilateral clonic movements with preservation of consciousness. Levetiracetam was started at a dose of 500 mg twice a day, followed shortly thereafter by the addition of phenytoin 100 mg three times a day to improve seizure control. At that time, her platelet count was at 147 x 10^9/L. Her serial complete blood counts showed a drop in platelet count starting in December 2008 *(figure 1)*. The decreased platelet counts prompted discontinuation of phenytoin in January 2009, with concomitant increase of the levetiracetam dosage to 1000 mg twice a day, and later to 750 mg three times a day in February 2009 *(figure 1)*. Despite discontinuation of phenytoin, the patient's platelet counts continued to drop to as low as 27 x 10^9/L on the 10th of April 2009, requiring multiple platelet transfusions during that period *(figure 1)*. At that time, phenytoin had been stopped for four months and temozolomide had been discontinued since December 2008. Steroid therapy had been continued throughout her illness and had not been changed around that period.

The patient was extensively evaluated by the haematology service and underwent two bone marrow biopsies in February and April 2009. The first biopsy showed markedly hypocellular bone marrow with mildly decreased megakaryocytes, while the second showed hypocellular bone marrow with granulocytic hypoplasia, but with adequate megakaryocytes. Platelet antibodies and antibody factor 4 were both negative. Heparin-induced thrombocytopenia and idiopathic thrombocytopenic purpura were both ruled out by history, physical examination and laboratory investigation. Other possible causes were also investigated such as autoimmune diseases, infections, and post-transfusion purpura, and were ruled out by appropriate testing. The decision was eventually made to stop levetiracetam and initiate topiramate treatment. The last dose of levetiracetam was received on the 11th of April 2009, beyond which the patient's thrombocytopenia gradually improved and platelet count returned to a baseline level comparable to her baseline prior to the initiation of the drug. The platelet counts obtained after levetiracetam discontinuation were 101 x 10^9/L on May 2nd 2009, 140 x 10^9/L on July 16th 2009 and 191 x 10^9/L on August 14th 2009.

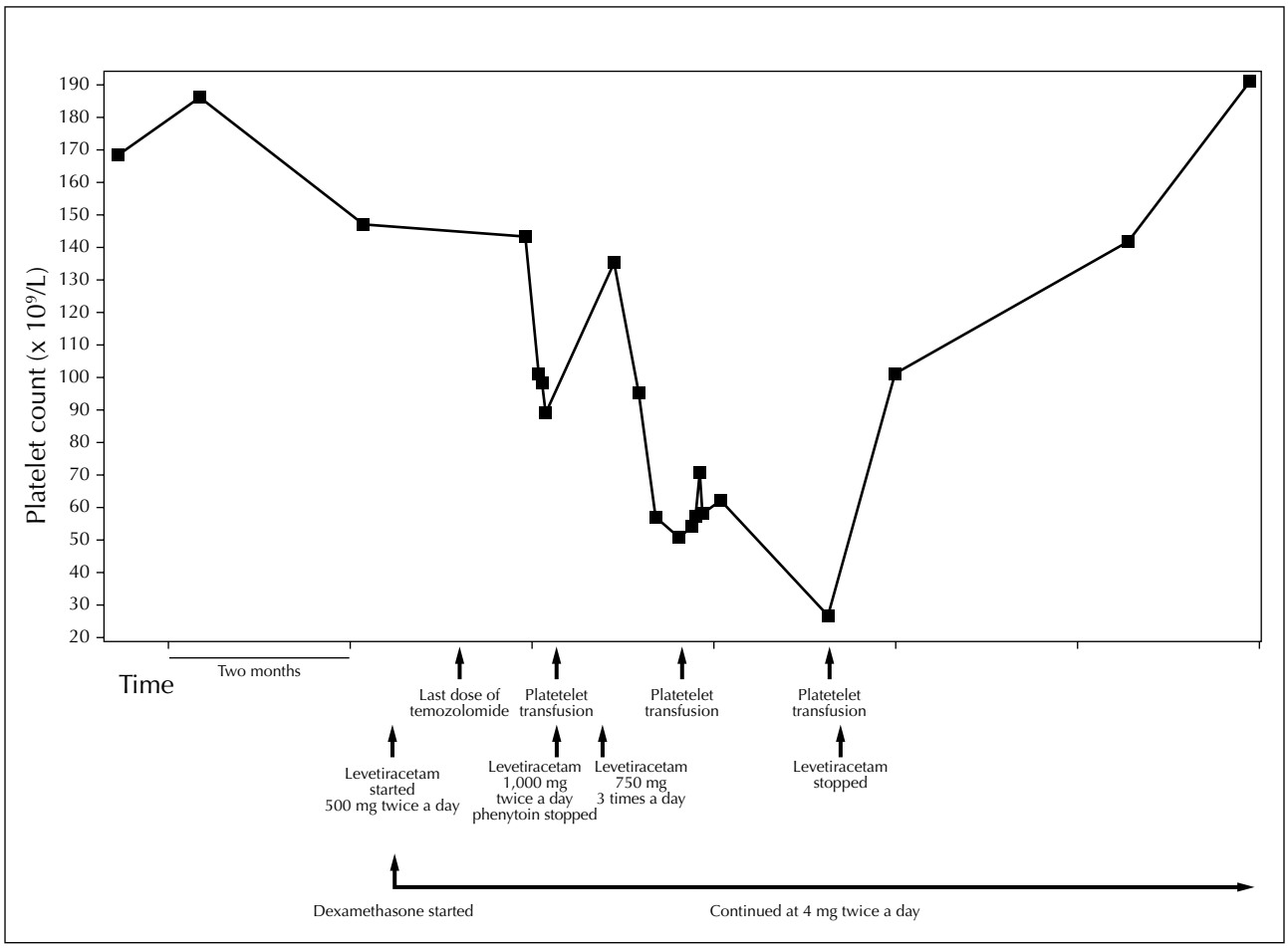

Figure 1. Serial platelet counts over time. Arrows indicate changes in medications and times of platelet transfusions.

For our patient, the timely drop in platelet count upon initiation of levetiracetam, and the abrupt resolution of thrombocytopenia upon discontinuation of the drug, suggest a strong causality in the absence of other confounding factors such as other medication changes or concomitant therapies. Although other antiepileptic medications such as valproic acid have been more convincingly shown to cause thrombocytopenia (Nasreddine and Beydoun, 2008), rare reports have discussed the correlation between levetiracetam therapy and thrombocytopenia (Hartmann *et al.*, 2002; Kimland *et al.*, 2004; Meschede *et al.*, 2008). Like our patient, another reported patient also received temozolomide therapy for oligoastrocytoma (Kimland *et al.*, 2004). In both cases, the long duration of effect on platelet count, after treatment had been discontinued, was unusual. Studies have shown that median nadirs for myelosuppression occurred at 28 days (range 1 to 44 days) for neutrophils and 26 days (range 22 to 40 days) for platelets. The average time for the absolute neutrophil and platelet counts to return to normal from the nadir was 14 days (Yung *et al.*, 1999). In our patient, the second bone marrow biopsy showed no evidence of decreased megakaryocytes which ruled out the possibility that the worsening thrombocytopenia, well beyond discontinuation of temozolomide, was secondary to bone marrow suppression. This evidence further indicates that the thrombocytopenia was caused by levetiracetam through a peripheral process. Steroid therapy was also ruled out as a cause since it was continued unchanged throughout the drop and recovery of the platelet counts. In view of all the above, it is highly likely that levetiracetam is implicated in causing thrombocytopenia. This adverse reaction should not be dismissed in the evaluation of patients with new onset, otherwise unexplained, thrombocytopenia. □

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