Valproic acid is a mood stabilizer used in bipolar disorder (1). As a result of its use, nausea, vomiting, diarrhea, constipation, and elevated liver enzymes can be seen (2). Development of thrombocytopenia is more probable than leukopenia, anemia, and pancytopenia, which are rare hematological side effects (3). Hematological side effects like thrombocytopenia, anemia, leucopenia, and pancytopenia are thought to be the result of bone marrow suppression by VPA. In our case, a 58-year-old male patient had thrombocytopenia and anemia due to the use of valproic acid. In the literature, among hematological side effects, thrombocytopenia is frequently reported due to the use of VPA but there is insufficient knowledge about thrombocytopenia with anemia. In the current case, the hematological side effects of VPA were evaluated.

A 58-year-old male patient feeling stronger had increased spend of money, paranoia and persecutive delusions, decreased sleep, increased psychomotor activity and aggressiveness for one month. He had a cerebrovascular accident 8 years previously and showed aggression and quietness. His blood tests, cranial CT and MR were normal and he was hospitalized as having mania.

He was given valproic acid 1000 mg and risperidone 2 mg per day. As his motility, increased speech and agitation continued, the risperidone dose was increased to 4 mg/day. In the first week of hospitalization, blood VPA was 60 so VPA was increased to 1500 mg/day. Due to development of Parkinsonism and audio-visual delusions, risperidone was discontinued and olanzapine 5 mg/day was initiated. A repeat of his cranial MR was again normal. As his aggressiveness increased, the olanzapine dose was increased to 20 mg gradually. In the second week of treatment, thrombocytopenia (platelets: 68000) was seen and acetylsalicylic acid and VPA were discontinued, while treatment with 20 mg per day olanzapine was continued. VPA level with its use of 1500 mg/day was 104.2. In the third week, together with thrombocytopenia, the hemoglobin level decreased to 13.2 g/dl. In the 4th and 5th weeks of treatment, motility, speech and agitation decreased and the thrombocyte level increased, but the tendency of decrease in hemoglobin level (12 g/dl) continued. There were no other reasons for the etiology of anemia. In the 7th week, hematological levels and clinical signs and symptoms were normal so the patient was discharged. There was no hematological pathology during 3 months of follow-up period with 20 mg olanzapine outside the hospital. This indicated to us that the hematological side effects were the result of VPA.

Valproic acid is widely used in epilepsy and bipolar disorder. Hematological side effects have been frequently reported, such as thrombocytopenia and thrombocyte function disorders. Rare side effects due to bone marrow depression or toxic effects include anemia and pancytopenia. It was reported that the underlying mechanism could be a toxic effect on progenitor cells in the bone marrow (4). There are a few studies concerning the hematological side effects. There was a reported negative correlation between the age of the patient and dose of valproic acid, but there was no relationship between the duration of treatment and thrombocyte levels (2,5). Especially for patients over 60 years old, the hematological side effects increased 2-3 fold (5). In psychiatric patients, hematological side effects due to valproic acid use were evaluated in some studies. A VPA level over 80 microgram/ml or use of 1000 mg/day was shown to be an important risk factor (6,7). In our case, an age of 58 years old and use of VPA at 1500 mg/day were important in the development of thrombocytopenia, which is mostly reported as temporary. Thrombocytopenia returned to normal levels during clinical follow-up after discontinuation of VPA. At the same time, in the 3rd week of treatment the hemoglobin
level decreased to 13.2 g/dl. In the 4th and 5th weeks of clinical follow-up, the hemoglobin level decreased to 12.0 g/dl, which later returned to normal levels. Although thrombocytopenia due to use of VPA is frequently observed, in the literature anemia is reported rarely (8,9). In one study, use of valproic acid led to a 9-fold increase in the development of aplastic anemia (10). Moreover, thrombocytopenia and neutropenia due to use of olanzapine was also previously reported. Especially a combination of olanzapine and VPA increases the side effects of olanzapine, with both p-glycoprotein inductions in the gut, UGT1A4 inhibition and CYP3A4 up regulation in the liver (11). In our case, side effects related to anemia disappeared after discontinuation of valproic acid.

Valproic acid is used in many psychiatric diseases, especially in bipolar disorder. In this case we try to emphasize the importance of follow-up of hematological parameters in the use of valproic acid in middle-aged or elderly patients. Lack of a bone marrow aspiration biopsy in our case is a deficiency in the definition of the etiology.

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