Case report

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Methotrexate-induced manic episode in a patient with seropositive rheumatoid arthritis: A case report

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Introduction

Substance/Medication induced bipolar disorder is characterized by (A) presence of symptoms of mania; (B) symptoms develop after exposure to a medication and it is known that the medication is capable of producing manic symptoms; (C) there is no evidence of bipolar disorder that precede the medication use; (D) symptoms do not occur exclusively during an episode of delirium; and (E) the symptoms cause clinically significant distress or impairment (1).

Methotrexate (MTX) is a first-line disease-modifying medication for rheumatoid arthritis. There are case reports of MTX causing manic episodes in patients with and without bipolar disorder (2,3). We report a case of new onset manic episode triggered by MTX, in a patient with rheumatoid arthritis.

Case presentation

A 59-year-old female, presented to a medical unit with fever, fatiguability, and severe pain and swelling of bilateral small joints of the hand, wrists, and the right knee, associated with morning stiffness. She had a history of occasional joint pain, but no history of autoimmune diseases. She had a family history of rheumatoid arthritis. She had been using local applications and over the counter medications sporadically for pain relief. On examination, there was evidence of synovitis in multiple joints. There were no signs of deformity, muscle weakness or extra-articular manifestations.

Her investigations revealed an elevated rheumatoid factor (80 IU/mL) and erythrocyte sedimentation rate (ESR) (85 mm/hr). Her CRP (16 mg/L) and white cell count (13,500 cells/µL) were slightly elevated. She had normal liver functions. The patient was diagnosed as having seropositive rheumatoid arthritis. She was commenced on oral methotrexate (MTX) 7.5 mg and folic acid 5 mg weekly by the rheumatologist. The dose of methotrexate was titrated to 15 mg in two weeks and reviewed fortnightly. She responded well to methotrexate.

During the fifth week after commencement of MTX, family noticed the patient to be overtalkative and overconfident. She had developed poor sleep and had become overactive. She had become irritable, and aggressive towards family members. She had started believing that she had the powers of God Patthini. The family had to physically restrain her to bring her to hospital. On the way to the hospital, she jumped out of the moving vehicle and sustained minor abrasions. The patient did not have a history or family history of mental illness. She had not experienced any major stressors prior to the onset of these symptoms. She had not been on any other medications apart from metformin 500mg bd (her routine diabetic medication), MTX and folic acid.

At presentation to the psychiatry unit, the patient was overfamiliar, restless, easily distractible and pacing up and down in the interview room. She was overtalkative and had flight of ideas. Her mood was elevated. She had grandiose delusions, where she believed that she had powers from God Paththini. She had no perceptual disturbances. She was oriented in time, place and person. She had poor insight. On physical examination, she was afebrile and had mild swelling and tenderness of small joints in both her hands. Neurological and other system examinations were unremarkable.

Her white cell counts (13500/mm) and ESR (22mm/hr) were marginally elevated, and the rheumatoid factor was high (15 IU/mL). Her liver functions, serum electrolytes, serum creatinine and thyroid function tests were normal. Magnetic resonance imaging (MRI) of the brain was normal.

She was managed as an inpatient in the psychiatry unit. Her manic episode was suspected to have been triggered by MTX, and MTX was withheld. She was started on haloperidol 1.5 mg twice daily (bd), sodium valproate 200 mg bd, and clonazepam 0.5 mg bd. Over the course of three days, her medications were gradually increased to haloperidol 3 mg bd, sodium valproate 600 mg bd, and clonazepam 2 mg at night. There was partial improvement of her symptoms by the end of one week.

Her joint symptoms worsened after ceasing MTX and rheumatologists' input was taken. IP had diabetes mellitus which made unsuitable for steroids. Given her previous good response to MTX, MTX was recommenced at 7.5mg, in combination with her anti psychotics and mood stabilizer. However, her mood symptoms reappeared when the MTX dose was titrated to 15mg, and the dose of MTX had to be kept at 7.5mg weekly.

The patient was diagnosed with methotrexate-induced mania and discharged after two weeks. She was discharged on the same doses of haloperidol, sodium valproate, clonazepam, and methotrexate 7.5 mg.

The patient was subsequently followed up at outpatient psychiatry and rheumatology clinics, where she remained in remission to date (6 months since discharge).

Discussion

Our patient had onset of manic symptoms after commencing MTX and had no history of mental illness in the past. Her symptoms improved once MTX was withdrawn, and reappeared when the dose of MTX was increased. All the above features confirm a diagnosis of mania secondary to MTX.

Mood swings, depression, anxiety and suicidality are all reported as side effects of MTX (4). However, reports of mania occurring as a result of MTX are sparse. There are few case reports of MTX inducing mania in patients with and without bipolar disorder (2,3). These suggests that withdrawal of MTX leads to improvement of manic symptoms, with reappearance of manic symptoms with rechallenge, which is consistent with our patient. According to post-marketing surveillance data, 0.02% of people on MTX developed mania, especially females, those between 50-59 years of age, who have been on MTX for 1-6 months and those with bipolar disorder (5). The exact mechanism of methotrexate causing manic symptoms is unknown but is thought to be related to its effect on dihydrofolate reductase inhibition, which leads to a decrease in nucleic acid synthesis and cellular replication. It is hypothesized that interference with folate metabolism, glutaminergic neurotransmission, and neurotoxicity may also be responsible for the occurrence of manic symptoms in patients taking MTXb (6). MTX induced changes in brain glucose metabolism is also thought to contribute to psychiatric symptoms.

This case report highlights the need to consider medication-induced manic episodes in patients with new onset mania associated with commencing a new medication. It also emphasizes the importance of close monitoring of patients on MTX for emergence of psychiatric symptoms.

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