



CASE REPORT

Psychotic Depression Induced by Adalimumab in a Patient with Ankylosing Spondylitis: A Case Report

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ABSTRACT

Tumor Necrosis Factor Alpha antagonists, which are used for the treatment of inflammatory diseases, are considered to be associated with psychiatric diseases. Herein we have reported an adult ankylosing spondylitis case with psychotic depression induced by adalimumab therapy and improved after treatment. We aimed both to discuss the relationship between psychiatric disease and inflammatory factor over this case and to make contribution to the literature. A 57-year-old male patient. He had experienced depressive symptoms nearly 5 months ago after 15 days of adalimumab therapy started for ankylosing spondylitis. Meanwhile, the symptoms of the patient, who continued adalimumab therapy once every two weeks, progressed and accompanied by psychotic symptoms such as disorganized speaking and behavior. The patient was admitted to the psychiatry clinic; however, his complaints did not significantly improve with treatment but rapidly regressed after discontinuation of adalimumab therapy. To our knowledge, there is limited data on the mood episodes triggered by adalimumab. In the present case, presence of a connection between symptom onset and the date of starting the medication, as well as rapid symptom regression with discontinuation of the medication, was considered as "potential adverse drug effect" according to the Naranjo Algorithm. This suggests that alteration in proinflammatory processes such as Tumor Necrosis Factor (TNF) might be associated with the onset of mood episodes. Further studies would be important in understanding the role of immune system in the pathophysiology of depression, particularly the sub-types such as psychotic depression.

Keywords: Adalimumab, psychotic depression, TNF-Alpha antagonists

INTRODUCTION

Studies focusing on the pathophysiology of mood disorders prove evidences about inflammatory, immune, and neuroendocrine dysregulation (1). Earlier studies have tried to examine particularly the interaction between immune system and depression. The relationship with central neurotransmitters has made the role of cytokines in major psychiatric disorders an issue of concern. These studies report increased levels of acute phase reactants, which are the indicators of the efficacy of proinflammatory cytokines

(IL-1, IL-6 and TNF- α) and immune cells, with alterations also in other functions of the immune system (2, 3, 4).

Adalimumab is completely a human monoclonal IgG1 antibody against TNF (5). TNF antagonists such as adalimumab, infliximab, and etanercept have been shown to have beneficial effects on emotional, cognitive, and somatic healing. Adalimumab in particular, improves the quality of life in the patients with Crohn disease, rheumatic arthritis, and ankylosing spondylitis (1). Although adalimumab was reported to improve depressive symptoms in psoriatic patients, this has been attributed to improved psoriatic symptoms (6). However, contrary to this, it was suggested that adalimumab therapy may have been associated with depression and suicidal attempt (7). The literature focusing on the relationship between monoclonal antibody therapy and mood episodes is

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limited to case reports. It has been reported that manic episodes are induced by infliximab (8), rituximab (9), and etanercept (10) in the patients treated for autoimmune disorders. Here, we present a patient with psychotic depression thought to be induced by adalimumab therapy comorbid with ankylosing spondylitis. We think that this case reported in the literature would contribute to the clarification of the potential relationship between inflammatory-immune system and psychiatric disorders.

CASE PRESENTATION

A 57-year-old, married, retired male patient with 4 children. He was brought to our outpatient clinic by his relatives for demoralization, anxiety, sleeplessness, loss of appetite-weight loss, and disorganized behavior and speaking. The history obtained from the patient and his relatives revealed that these complaints have started nearly 4.5 months ago. They had taken the patient to the psychiatry outpatient clinic 1.5 months ago as he was saying "I am finished, I will fall short of money, I will be unable to make ends meet" although he does not have financial problems, and accordingly, he began receiving escitalopram daily 15 mg. However, they have discontinued treatment as his complaints did not relieve. In the last week, he has begun to exhibit disorganized behaviors such as rolling on the ground and biting his hand, and he has referred to our clinic by an external center diagnosing with psychotic disorder and commencing daily 3 mg risperidone therapy.

His medical history revealed a depressive episode 15 years ago, which has completely improved with treatment. He had documented uveitis and ankylosing spondylitis for 10 years. Reviewing the hospital database, we found out that he has recently received at least three non-steroid anti-inflammatory drugs at maximum dose but switched to TNF alpha inhibitor adalimumab because of unsatisfactory response nearly 15 days before the onset of his complaints. The patient has been receiving adalimumab at a dose of 140 mg via subcutaneous route once every two weeks.

On his presenting mental examination, he was conscious, cooperated and oriented with poor self-care and eye-contact. His affect was depressed. Content of

thought revealed perseverative speech with extreme pitifulness and guilt. Inquiry about his suicidal thought indicated suicidal risk and impaired reality testing based on his statements such as "it is the best for me to die but I am not even deserving death", "even the soil would not welcome me and I would live forever". He had poor insight. His psychomotor skills have been slowed down.

Based on his mental examination and psychometric measurements, he was admitted to our clinic prediagnosing with psychotic depression according to DSM-5 diagnostic criteria. Laboratory analysis at admission was within the normal range and blood analysis was regularly repeated over the period of hospital stay. P-A lung radiography, routine EEG and cranial MRI were reported as normal. Neuropsychological tests such as MMPI and Bender-Gestalt test could not be performed as he was non-compliant. The Hamilton Depression Rating Scale (HDRS) score was 40.

Venlafaxine was initiated at a dose of 37.5 mg/day and potentiated to 150 mg/day under blood pressure control. As his psychotic symptoms and behavioral disorder persisted, olanzapine was added at a dose of 5 mg/day. Electroconvulsive therapy was started because of uncontrolled self-destructive behaviors and performed for seven sessions.

Evaluation by Naranjo algorithm (11) yielded a score of 6 (probable adverse drug reaction), thus the patient's psychotic depression was considered to be induced by adalimumab therapy. Consultation was requested from rheumatology department and his treatment was discontinued. After the discontinuation of adalimumab therapy, his depressive complaints and psychotic symptoms have rapidly and remarkably improved. The patient was discharged from the hospital to be monitored at routine follow-up visits as his thoughts of guilt and depressive symptoms have completely improved. The Hamilton Depression Rating Scale (HDRS score at his discharge was 10.

DISCUSSION

In this case report, an ankylosing spondylitis patient with psychotic depression, which was considered to be

associated with adalimumab therapy, has been presented. To our knowledge, the literature includes no reported case of adalimumab-induced psychotic depression. The facts that onset of the symptoms coincides with the date of starting the drug and that the symptoms improved rapidly and remarkably by skipping the second dose were considered as "probable adverse drug effect" according to the Naranjo's algorithm (11).

The pathophysiology of mood disorders is quite complex. Studies suggest that it results from the interaction between various neurotrophic, immune, cellular, and epigenetic factors (12). Besides, depression is a complex disorder with heterogeneous nature, of which the neurobiological aspects remain unclear. Although the drugs are suggested as the probable causes of depression, data about many drugs are conflicting. Cytokines are one of the factors with potential role in the pathogenesis of depression. They modulate the human neuroendocrine system passing through the blood-brain barrier via various mechanisms and play a role in mood regulation (13). For a long time, it has been considered that only the immune system is impaired in major depressive disorder; however, more recently, it has been understood that stress and depression not only suppress the immunity but also lead to inflammatory activation. In a population study conducted in a large sample-size of major depressive disorder, positive correlation was reported between depressive symptoms and IL-6 and TNF- α . A relationship was reported between the somatic symptoms of both depression and anxiety and IL-6 and TNF- α levels (14). However, it is debatable whether the changes in TNF- α and other proinflammatory cytokines are the causes of depressive symptoms or they are elevated as a compensatory mechanism. In addition, there are studies reporting no relationship between depression and cytokines (15,16). Despite the contradictory outcomes in the literature, current data suggest that neuroinflammation might be playing a role in the etiopathogenesis of MDD.

Adalimumab is a TNF-specific recombinant human monoclonal antibody IgG1 used for the treatment of ankylosing spondylitis and rheumatic arthritis. Information on its relationship with psychiatric disorders is limited to a

several case reports. Contrary to the present case, there are authors reporting that it improves depressive symptoms when used for the treatment of psoriasis (6). Nevertheless, it is difficult to say whether this results from TNF- α antagonist effect or this is secondary to the improvement of psoriatic symptoms. One of the several studies in the literature focusing on the relationship between adalimumab and psychiatric disorders is a case with mania occurred during treatment (17). It gains priority that these conflicting results about the role of cytokines in mood disorders may be associated with the changes in the severity of depressive symptoms and/or presence of anxiety and psychotic symptoms with depression.

Consistent with the present case, a case report focusing on the relationship between adalimumab and depression reported suicide in the case diagnosed with psoriasis. In this paper, it was reported that TNF- α inhibitors cause suicidal thoughts very rarely; however, comparing within themselves, it was reported that adalimumab and infliximab are more frequently associated with completed suicide, attempted suicide and thought suicide (7).

Although depression and suicidal thought are not common adverse effects of adalimumab, it is important to know there is a relationship between adalimumab and mood swing. To our knowledge, the present case is the first case with depression with psychotic features reported under adalimumab therapy. This case report will not give information about the exact role of adalimumab in induced psychotic depression. However, it is important in terms of paying attention to the individuals prone to depression while prescribing the drug and gaining awareness for potential psychiatric symptoms in the patients using the drugs.

Further studies are required to clarify the overall role of adalimumab and immune modulation in mood disorders.

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