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CASE REPORT

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Adalimumab-induced manic episode in an adolescent with juvenile idiopathic arthritis

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Abstract

Background Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in children, and adalimumab is one of the primary treatment options. Although it is widely used for inflammatory diseases, there is limited research on its safety and efficacy in patients with psychiatric disorders or in those with inflammatory diseases who also have comorbid psychiatric conditions.

Case report We report a 12-year-old adolescent boy who presented with emotional instability for 1 year, exacerbated leading to hospital admission in the past month. Upon detailed evaluation after admission, it was found that the patient's emotional fluctuations may be related to the use of Adalimumab. Follow-up after psychiatric inpatient treatment revealed that the patient did not experience emotional excitement again after discontinuing Adalimumab.

Conclusions Although tumor necrosis factor-α inhibitors have positive effects on the emotional, cognitive, and physical functions of patients with inflammatory diseases, their use may induce mood swings in patients with comorbid mood disorders. This is particularly important for adolescents with rapid mood changes, where greater caution is required. Further research is necessary to clarify the correlation between the adverse effects of these drugs and their impact on patients with bipolar disorder.

Keywords Juvenile idiopathic arthritis, Bipolar disorder, Manic, Adalimumab, Tumor necrosis factor inhibitors

Background

Juvenile idiopathic arthritis (JIA) is a term that encompasses chronic arthritis of unknown etiology and is the most common chronic inflammatory rheumatic disease in children. It is characterized primarily by a disease course lasting over six months and an onset age of less than 16 years [1]. Currently, there are various treatment strategies, including Nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biologic disease-modifying antirheumatic drugs (bDMARDs), among others [2]. Adalimumab, as a novel Tumor necrosis factor inhibitor, acts through its mechanism as a human monoclonal antibody against circulating and membrane-bound TNF-α [3]. Studies have shown that it can improve the quality of life in various autoimmune diseases such as Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis. It significantly reduces the number of active joints, enthesitis sites, and pain in specific arthritis patients [2, 4].

Bipolar disorder (BD) is a mood disorder characterized by episodes of mania/hypomania and depression [5]. The

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pathogenesis of BD remains incompletely understood, but research indicates that some BD patients exhibit elevated central and peripheral pro-inflammatory cytokines, increased expression of inflammatory genes, and abnormalities in cell and complement activation [6]. The mechanism of action of adalimumab may result in alterations in the levels of certain inflammatory cytokines, potentially affecting the mood states of BD patients and increasing the risk of manic episodes. Previous reports have documented cases where the use of immunosuppressants led to manic switching, although the precise mechanisms underlying these mood changes have not been identified [7, 8].

In this report, we present a case of a patient with mood disorder and juvenile idiopathic arthritis who experienced a manic switch following adalimumab therapy. This case aims to investigate the potential adverse effects of adalimumab treatment in patients with BD.

Case presentation

A 12-year-old Chinese male, currently in the sixth grade of elementary school, presented to the hospital with a history of emotional instability for one year, which had worsened over the past month. In May 2023, during his sixth-grade studies, the patient experienced significant academic pressure, high parental expectations, a lack of understanding from his parents, and poor relationships with classmates. This led to progressively worsening symptoms, including low mood, inability to feel happiness, difficulty concentrating in class, feelings of life being meaningless, palpitations, shortness of breath, fatigue, and poor sleep. During this period, he occasionally reported auditory hallucinations, such as hearing classmates speaking ill of him, but denied visual hallucinations, paranoid delusions, or elevated mood.

Additionally, over the past year, the patient frequently complained of pain in the lumbosacral region and lower legs, which was initially neglected and untreated. In February 2024, he was hospitalized in the rheumatology and immunology department of a children's hospital. Upon admission, investigations revealed a positive FABER test, elevated IL-17 A levels, and MRI findings indicating mild synovial thickening and enhancement in both hip joints with a small amount of joint effusion. Other findings included elevated intraocular pressure (23 mmHg), mildly elevated liver enzymes, and bone marrow cytology suggesting a reactive bone marrow pattern. Routine blood tests, coagulation profile, autoantibody panel, rheumatoid factor, tuberculosis interferon assay, X-rays of long bones, fundoscopy, bilateral sacroiliac joint MRI with contrast, hepatitis virus markers, TBNK, HLA-B27, and tumor markers showed no significant abnormalities.

Based on relevant examinations and clinical manifestations, the patient was diagnosed with enthesitis-related arthritis, a subtype of juvenile idiopathic arthritis. He was prescribed naproxen 200 mg twice daily, sulfasalazine 1 g twice daily, and adalimumab 40 mg subcutaneous injection. The patient was discharged after receiving a subcutaneous injection of adalimumab 40 mg, with instructions to continue bi-weekly injections. Despite undergoing three adalimumab treatments, the patient reported no significant improvement in leg pain.

A detailed inquiry revealed that one month before hospitalization, the patient experienced increased emotional instability, reporting low mood, reduced activity, self-harm with sharp objects, suicidal ideation, and feelings of unreality. Approximately 80% of the time, he felt depressed, while 20% of the time, he felt happy, talkative, and engaged in increased activities such as meddling, impulsive shopping, and extravagant spending, with each episode lasting 1–3 h. During depressive episodes, he exhibited irritability, loud screaming, and avoidance of social interactions. He also reported auditory hallucinations (hearing classmates discussing him, calling his name, and urging him to die), visual hallucinations (occasional shadowy figures), and paranoid delusions (feeling monitored and discussed by others).During this period, the patient was treated with sertraline 25 mg daily, valproic acid 250 mg twice daily, aripiprazole 5 mg at night, or quetiapine 12.5 mg at night, and oxazepam 7.5 mg as needed, but the therapeutic effects were unsatisfactory.

Interestingly, upon detailed assessment of the patient's condition, we found that the episodes of excitement and agitation were temporally associated with the administration of adalimumab. The patient received adalimumab a total of three times, starting in March 2024, with injections administered bi-weekly. Adverse symptoms commonly appeared two days after each injection.

After the first injection, the patient experienced chest tightness, which the rheumatology specialist attributed to individual sensitivity or a common cold. Following the second injection, the patient began exhibiting confrontational behavior towards teachers, increased irritability, and reluctance to maintain personal hygiene, prompting a recommendation to reassess the medication regimen. Post the third injection, the patient displayed symptoms of agitation, argumentative behavior, a desire to go out frequently, and impulsive spending, leading him to independently request to see a psychologist. The patient's family history shows that there is no history of bipolar disorder among their immediate relatives.

The patient was hospitalized for one month at our facility, during which his medications were adjusted and he received electroconvulsive therapy (ECT), resulting in significant improvement and subsequent discharge. During hospitalization, we completed relevant examinations and found that the patient's alanine aminotransferase and γ-glutamyl transferase levels were mildly elevated, which

we considered to be drug-induced liver dysfunction. The discharge diagnoses were mood disorder, juvenile idiopathic arthritis (enthesitis-related), and liver dysfunction. Upon discharge, his prescribed medications included lurasidone, clonazepam, and polyene phosphatidylcholine capsules. Follow-up communication with the patient's mother revealed that after discharge, the patient did not continue adalimumab treatment. Although he occasionally reported physical discomfort such as joint pain and symptoms of cold and cough, his emotional state remained stable. He spent his days accompanying his mother at work or playing with friends, communicated well with his mother, and, to date, has not experienced a recurrence of manic symptoms.

Discussion and conclusion

Juvenile Idiopathic Arthritis (JIA) is the most common pediatric rheumatic disease, categorized into subtypes based on the criteria of the International League of Associations for Rheumatology (ILAR) [9]. However, reports of emotional issues and psychiatric symptoms in JIA patients are rare. Here, we present a case of an adolescent patient with JIA who exhibited worsening emotional symptoms and significant manic episodes following the administration of adalimumab. After undergoing systematic inpatient psychiatric treatment and outpatient follow-up, the patient's manic symptoms were alleviated. We hypothesize that the patient's mood changes were likely induced by the use of adalimumab, and this may be the first reported case of adalimumab use leading to manic episodes in an adolescent with mood disorders. Further clinical research is necessary to investigate the specific role of adalimumab in triggering mania.

The etiology of Bipolar Disorder (BD) is complex, and there is no definitive explanation for its pathogenesis. However, multiple aspects can elucidate the relationship between BD and inflammatory cytokines. First, epidemiological studies have shown that BD patients have a higher likelihood of inflammation-mediated comorbidities compared to control groups [4]. Secondly, clinical research has indicated that, compared to healthy controls, BD patients exhibit elevated levels of inflammatory cytokines in serum and neuroinflammatory markers in cerebrospinal fluid [10]. Additionally, postmortem studies have revealed significantly higher protein and mRNA levels of interleukin (IL)-1β, the IL-1 receptor (IL-1R), and nuclear factor-kappa B subunits in the frontal cortex of BD patients compared to control subjects [11]. Moreover, studies have found that BD patients in different mood states have corresponding variations in inflammatory cytokine levels, and these changes correlate with the severity of symptoms [12, 13]. Furthermore, studies have found that postmortem analyses of frontal cortex samples from BD patients show elevated levels of caspase-1, IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and IL-10 [14]. These observed alterations in inflammatory markers suggest that immune dysfunction might be a critical mechanistic link between BD and concurrent inflammation.

The treatment options for Juvenile Idiopathic Arthritis (JIA) are diverse. Traditional synthetic disease-modifying antirheumatic drugs (csDMARDs) are a primary treatment modality, with methotrexate being the most commonly used in combination therapy. However, nearly one-third of patients experience severe gastrointestinal intolerance [15]. Currently, newer treatment approaches include Biologic disease-modifying antirheumatic drugs (bDMARDs), such as tumor necrosis factor-α inhibitors (e.g., infliximab, adalimumab, certolizumab, and etanercept). These have been found to positively impact the emotional, cognitive, and physical functioning of patients with inflammatory diseases [7]. Adalimumab functions as a human monoclonal antibody against circulating and membrane-bound TNF-α. TNF-α is a primary Th1-type pro-inflammatory cytokine that can bind to TNFR1 and/or TNFR2, subsequently activating downstream signaling pathways. These pathways facilitate a diverse range of biological responses, including apoptosis, cell differentiation, proliferation, survival, homeostatic synaptic plasticity, and inflammation [16].

TNF-α contributes to brain development, particularly by regulating the growth and function of the hippocampus [17]. However, during inflammatory responses, TNF-α secreted by microglia and other central nervous system sources plays a pivotal role in altering blood-brain barrier permeability and recruiting peripheral monocytes into the central nervous system [18]. Excessive elevation of cytokine levels can activate microglia, leading to sustained oxidative stress. Prolonged exposure to high levels of inflammatory cytokines and the resultant damage to central neurotransmitters can cause progressive declines in neurocognitive function and alterations in neural structures, contributing to disorders such as bipolar disorder and mood disorders [16, 19]. Although adalimumab is widely used in the treatment of inflammatory diseases, there is limited published research on its safety and efficacy in treating patients with psychiatric disorders or those with comorbid inflammatory and psychiatric conditions. To thoroughly explore this area, more systematic research and randomized controlled trials are needed to comprehensively assess the impact of adalimumab on patients with mood disorders and to develop more scientifically sound and appropriate clinical management strategies based on these findings.

This study has several limitations that must be acknowledged. Firstly, we cannot exclude the possibility that the patient's manic episodes coincided with the use of adalimumab, and we were unable to reassess whether

the patient had pre-existing BD before starting adalimumab treatment. Secondly, during the hospitalization, we did not measure relevant inflammatory markers, which might weaken the clinical symptomatology's support. Additionally, the patient, being an adolescent, may lack full awareness and control over his emotional state. During the follow-up process, our assessment of the absence of manic episodes relied primarily on the patient's subjective reports rather than using standardized scales, which may introduce bias into our conclusions.

In conclusion, although studies have found that tumor necrosis factor-α inhibitors have positive effects on the emotional, cognitive, and physical functioning of patients with inflammatory diseases, their use may trigger mood fluctuations in patients with comorbid mood disorders. This is particularly important in adolescent patients who exhibit rapid mood swings, necessitating a more cautious approach to their medication. Finally, further research is essential to elucidate the correlation between the adverse effects of tumor necrosis factor-α inhibitors and BD patients.

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Author contributions
Author YWG reviewed Literature search and wrote the first draft of the manuscript. Author JYL and RQH and ZZ revised the manuscript. HRL and JLT assisted in managing this patient during the hospitalization. Authors QHL and XTX guided the treatment, and all authors contributed to and have approved the final manuscript.

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Data availability
The data used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has been granted an exemption from requiring ethics approval. Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University grated the exemption.

Consent for publication
The written informed consent of the patient was obtained in this case report. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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