Journal of Pediatric Academy

Case Report

Year: 2023 Volume: 4 Issue: 4
Doi: 10.4274/jpea.2023.226
J Pediatr Acad 2023; 4: 146-148

Evaluation of Lupus Cases Related to TNF Inhibitors in Children

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Article Information

Article Type: Case Report
Article Group: Pediatric Rheumatology

Received: 02.04.2023
Accepted: 14.06.2023
Epub: 20.07.2023
Available Online: 28.12.2023

Cite this article as: *Türkmen Ş, Gerenli N, Sözeri B. Evaluation of Lupus Cases Related to TNF Inhibitors in Children. J Pediatr Acad 2023; 4: 146-148*

Abstract

Systemic lupus erythematosus (SLE) due to anti-tumor necrosis factor (TNF) agents is a rare entity. We reported three cases who developed lupus-like syndrome while receiving infliximab therapy for various reasons. All cases demonstrated clinical and laboratory findings of SLE. And all of them needed treatment. We would like to emphasize that the risk of anti-TNF-alpha-induced lupus should be kept in mind in patients receiving anti-TNF therapy for any reason.

Keywords: Child, infliximab, systemic lupus erythematosus

Introduction

Drug-induced lupus (DIL) usually presents with a clinical pattern similar to systemic lupus erythematosus (SLE); however, typical SLE complications are not observed. Classical DIL is characterized by anti-nuclear antibody (ANA) and anti-histone antibody positivity, accompanied by symptoms such as fever, arthralgia, myalgia, and atypical skin rashes. It is believed that drug metabolites can induce T-cell response and autoantibody production, leading to this clinical presentation.[1]

The most implicated agents are procainamide and hydralazine, but various antibiotics, antiarrhythmics, antihypertensives, antiepileptics, and biological treatments, such as anti-tumor necrosis factor alpha (anti-TNF-α) agents, can also trigger lupus.[2]

The mechanism by which biologic treatments cause lupus differs from other drugs, as they directly affect the immune response and resemble idiopathic SLE rather than DIL. This may result in clinical findings characterized by hypocomplementemia, low anti-histone antibodies, high anti-double stranded DNA (anti-dsDNA) antibodies, and a typical SLE eruption. Since low TNF levels play a role in the pathogenesis of SLE, the reduction of TNF levels, apoptosis of cytotoxic T-cells, and induction of B-cell activation with anti-TNF-α treatments are possible mechanisms that increase the susceptibility to SLE.[3] However, anti-

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TNF-α-induced lupus (ATIL) is rare.[4] Here, we report three cases that developed lupus-like syndrome while receiving infliximab therapy for various reasons.

Case Reports

Case-1

A 16-year-old girl, who had been receiving infliximab treatment for ulcerative colitis for eight months, was referred to us because of joint pain, morning stiffness lasting half an hour, hair loss, malar rash, recurrent oral aphthae, and Raynaud's phenomenon. In laboratory examination, ANA was positive (1/160 titer in nucleolar pattern), both complement 3 (C3) and complement 4 (C4) were lower [0.85 g/L (0.9-1.8) and 0.06 g/L (0.1-0.4), respectively], though anti-dsDNA and anti-histone antibody were negative. The patient was evaluated as ATIL because of new onset clinical findings under infliximab treatment and at least one laboratory finding. Infliximab treatment was discontinued. In the follow-up, low-dose corticosteroid and hydroxychloroquine treatment was started. Clinical and laboratory findings were recovered in the second month of follow-up.

Case-2

A 16-year-old girl with a diagnosis of juvenile idiopathic arthritis was diagnosed with ATIL at the tenth month of treatment after receiving infliximab for nine months for uveitis. The patient had a malar rash, anemia, and persistent hypocomplementemia. ANA, anti-dsDNA, and anti-histone antibody were found positive. Infliximab was discontinued. Therefore, the patient had refractory uveitis, adalimumab treatment was started. Low-dose corticosteroid and hydroxychloroquine were added to her treatment. During the follow-up, mycophenolate mofetil (MMF) treatment was started as a steroid-sparing treatment. Her clinical findings regressed in the sixth month of her follow-up.

Case-3

A 14-year-old male patient had been receiving infliximab treatment for 20 months for uveitis and was diagnosed with ATIL in the 21st month of treatment. In the examinations of the patient due to weight loss and recurrent oral aphthae, ANA was found 2 positive (a granular pattern at a titer of 1/320), and anti-dsDNA: 177.96 IU/mL (+). The complement levels of the patient were normal, anti-histone antibody was negative. Infliximab treatment was discontinued in the patient whose uveitis was under control. Hydroxychloroquine was added to the treatment of the patient whose symptoms continued. While the patient was being followed up in remission, in the examinations performed due to recurrence of oral aphthae six months later, ANA was found to be (+) in a homogeneous pattern at a titer of 1/160. Since there was no response to the hydroxychloroquine treatment, it was discontinued and MMF was started as a steroid-sparing treatment. At the follow-up one month later, the patient's ANA positivity continued, but his symptoms regressed. Adalimumab treatment was started in the patient who had an attack of uveitis in the follow-up. However, the patient's SLE findings did not recur. The clinical features of three patients diagnosed with ATIL are summarized in **Table 1**.

Discussion

DIL is an autoimmune condition in which certain drugs can induce clinical features resembling SLE. Typical complications of SLE are not observed in DIL.[2,5]

Anti-TNF treatments are among the causes of DIL. Most cases of ATIL occur due to infliximab therapy because infliximab is the most immunogenic anti-TNF agent due to its chimeric structure and ability to reach high tissue concentrations.[5]

ATIL findings were observed in these cases, and in two of them, adalimumab treatment was initiated following the development of uveitis after discontinuing infliximab, without recurrence of ATIL. Although all anti-TNF agents can lead to autoantibody production, the development of SLE is rare.[6] The precise incidence of ATIL is not well-known due to its relatively recent recognition, and few studies have been conducted on this topic.[7]

Some prospective studies have reported variable frequencies of ANA and anti-dsDNA positivity related to infliximab treatment.[8-10] The concomitant use of methotrexate with anti-TNF treatments may suppress autoantibody development and reduce the incidence of

Table 1. *Clinical characteristics of patients with anti-TNF-α therapy-induced lupus*

Parameters	Case-1	Case-2	Case-3
The age of diagnosis (years)	16	16	14
ATIL symptoms	- Malar rash, - Joint pain, - Morning stiffness - Hair loss, - Recurrent oral aphthae, - Raynaud's phenomenon	- Malar rash	- Weight loss, - Recurrent oral aphthae
Laboratory findings of ATIL			
ANA (titer and pattern)	1/160, nucleolar	1/1000, homogeneous	1/320, granular
Complement 3 (g/L)	0.85	0.75	1.22
Complement 4 (g/L)	0.06	0.05	0.15
Anti-dsDNA Ab (IU/mL)	<10	106.48	177.96
Anti-histon Ab	Negative	Positive	Negative

ATIL: Anti-TNF-α-induced lupus, ANA: Anti-nuclear antibody, Anti-dsDNA: anti-double stranded DNA, Ab: Antibody, TNF:Tumor necrosis factor

ATIL.[10,11] In our second and third cases, methotrexate was used for uveitis before biologic therapy. However, infliximab treatment was started in our cases because of severe methotrexate intolerance and refractory uveitis. MMF was added to adalimumab treatment after the development of ATIL due to methotrexate intolerance.

Although ATIL is considered one of the DIL forms; it differs in pathophysiology, clinical and laboratory findings. In 2018, Shovman et al.[4] have described ATIL cases with various clinical manifestations, such as thrombocytopenia, polyarthritis with lymphopenia, and severe serositis with pancytopenia, along with positive ANA and anti-dsDNA antibodies. The first of these was a patient with thrombocytopenia, which resolved after discontinuation of infliximab. The second patient had polyarthritis accompanied by lymphopenia after infliximab treatment. In the third case, severe serositis findings accompanied by ascites, pleural and pericardial effusion were present with pancytopenia. While ANA and anti-dsDNA positivity were detected in all three patients, anti-histone antibodies were positive only in the second case. Similarly, in 2022, Stranks and Chapman[6] described a case of infliximab-associated lupus in a patient receiving infliximab therapy for sarcoidosis. The patient had newly developed weakness, migratory joint pain, and positive serum autoantibodies. In 2008, Costa et al.[12] found that in a study, anti-dsDNA positivity, hypocomplementemia, rash and kidney disease more frequently in ATIL cases compared to DIL due to other drugs. While all of our cases had ANA positivity, two had anti-dsDNA positivity and two had low complement; anti-histone antibody positivity was detected in only one patient. All patients had at least one of the clinical findings of SLE. As seen in our patients, anti-TNF-associated DIL is reminiscent of idiopathic SLE; typical SLE rash, hypocomplementemia, low anti-histone and high anti-dsDNA antibodies may be found.[7]

There are no specific diagnostic criteria for the diagnosis of ATIL. However, a common approach used for diagnosis is to consider the presence of at least one clinical and serological criterion from the American College of Rheumatology criteria for SLE, along with the onset of symptoms after anti-TNF therapy and regression upon discontinuation of the treatment.[4] It should be noted that different criteria may be used in different studies.

The most important aspect of treatment is the withdrawal of the responsible agent. In general, clinical manifestations of ATIL tend to regress within the first six months, although autoantibodies may remain positive for an extended period.[5] Some patients may require corticosteroids and immunosuppressive agents.[4]

In mild cases, as observed in our patients, another anti-TNF agent may be considered. In a study by Ramos-Casals et al.[13] in 2007, most cases of ATIL showed regression of lupus-like symptoms after discontinuation of anti-TNF therapy. However, it should be noted that 40% of patients required corticosteroid treatment and 12% needed additional immunosuppressive therapy. Similarly, our cases required various immunosuppressive treatments in addition to discontinuation of infliximab therapy.

Conclusion

When patients receive anti-TNF therapy for any indication, the possibility of ATIL should be considered in the presence of a compatible medical history, clinical findings, and autoantibodies. Prompt recognition and appropriate management are crucial in optimizing patient outcomes.

Author Contributions: Türkmen Ş: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Gerenli N: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Sözeri B: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

Informed Consent: Written informed consent was obtained from the family for the publication of this case report.

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