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Systemic lupus erythematosus induced by anti-tumor necrosis factor α therapy in inflammatory rheumatic diseases: a case series

D. Oliveira[1,2*], A. Martins[1*], F. Martins[3], C. Gomes[1], S. Pimenta[1,4], C. Vaz[1,2,4], L. Costa[1], M. Bernardes[1,4]

[1]Rheumatology Department, Centro Hospitalar Universitário São João, Porto, Portugal;
[2]Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto, Portugal;
[3]Rheumatology Department, Centro Hospitalar Universitário do Algarve, Faro, Portugal;
[4]Medicine Department, Faculty of Medicine, University of Porto, Portugal
**These authors contributed equally*

SUMMARY

This case series aims to characterize the development of systemic lupus erythematosus (SLE) induced by anti-tumor necrosis factor α (anti-TNFα) therapy in patients with inflammatory rheumatic diseases, namely rheumatoid arthritis (RA), spondylarthritis (SpA), and psoriatic arthritis (PsA). Patients with a diagnosis of SLE induced by anti-TNFα therapy and registered on the Rheumatic Diseases Portuguese Register (Reuma.pt) who started their first anti-TNFα between 2001 and 2020 were included. Demographic, clinical, and laboratory data were obtained by consulting Reuma.pt. The diagnosis of SLE induced by anti-TNFα was considered if there was a temporal relationship between the onset of anti-TNFα therapy and manifestations (clinical and immunological) in accordance with the American College of Rheumatology/European League Against Rheumatism criteria (2019). A total of 607 patients with inflammatory rheumatic diseases and six cases of SLE induced by anti-TNF-α therapy were reviewed: two patients were affected by RA, three patients by SpA, and one by PsA. All these patients had articular and constitutional symptoms that improved after discontinuation of the anti-TNFα agent. After switching to a second anti-TNFα agent, there was no recurrence of SLE over time. The development of SLE secondary to anti-TNFα agents in inflammatory rheumatic patients is rare. In this case series, all patients had a mild disease that improved after therapy discontinuation without recurrence of the disease. SLE induced by anti-TNFα should be considered in the follow-up of RA, SpA, and PsA patients.

***Key words**: Systemic lupus erythematosus, anti-tumour necrosis factor α therapy, rheumatoid arthritis, spondylarthritis, psoriatic arthritis.*

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INTRODUCTION

Anti-tumor necrosis factor α (anti-TNFα) agents are commonly used to treat inflammatory conditions, such as rheumatoid arthritis (RA), spondylarthritis (SpA), and psoriatic arthritis (PsA). These treatments can induce autoantibodies production, in particular antinuclear antibodies (ANA). In addition, systemic lupus erythematosus (SLE) induced by anti-TNFα therapy, although rare, is a cause of concern in clinical practice in these patients (1). The diagnosis of anti-TNFα-induced SLE in rheumatic patients can be difficult due to the similar symptoms of their underlying disease, such as arthralgia, myalgias, arthritis, rash, serositis, fever, cytopenia, among others. Furthermore, clinical and laboratory findings of SLE induced by anti-TNFα therapy differ in several ways from the clinical and laboratory findings typically associated with classic drug-induced lupus erythematosus (DILE).

Thus, this study aimed to describe cases of SLE induced by anti-TNF-α therapy in patients with inflammatory rheumatic diseases.

Corresponding author
Daniela Oliveira
Rheumatology Department,
Centro Hospitalar Universitário São João,
Alameda Prof. Hernâni Monteiro,
4200-319 Porto
E-mail: danielasoff@gmail.com

METHODS

In this case series, the authors report six cases of SLE induced by anti-TNFα therapy in patients with inflammatory rheumatic diseases, namely RA, SpA, and PsA. Patients with a diagnosis of SLE induced by anti-TNFα therapy and registered in the Rheumatic Diseases Portuguese Register (Reuma.pt) who started their first anti-TNFα between 2001 and 2020 were included. The diagnosis of SLE induced by anti-TNFα therapy was considered if there was a temporal relationship between the initiation of anti-TNFα therapy and manifestations, such as positive ANA (mandatory), clinical manifestations (mucocutaneous, articular, constitutional, hematologic, serosal, renal, neuropsychiatric) and immunological (antiphospholipid antibodies, hypocomplementemia, specific antibodies for SLE) according to the 2019 American College of

Table I - Clinical features and management of six patients with systemic lupus erythematosus induced by anti-tumor necrosis factor α therapy.

Patient	Rheumatic disease	Anti-TNFα agent	Disease duration (y)	Anti-TNFα therapy duration (months)	Clinical manifestations	Laboratory and immunologic manifestations	Specific treatment	Time to complete resolution (months)
1 Female, 66y	RA	IFX	17	16	Fatigue and polyarthritis (abrupt worsening)	ANA titer 1/320 diffuse pattern; positive anti-dsDNA antibodies (248 UI/mL)	–	17
2 Female, 43y	RA	ADA	11	41	Malar rash	ANA titer 1/320 diffuse pattern; positive anti-dsDNA antibodies (285 UI/mL); positive anti-histone antibodies; hypocomplementemia	–	18
3 Male, 53y	SpA	IFX	24	20	Fatigue, arthritis and serositis (bilateral pleural effusion)	High ESR; ANA titer 1/640 diffuse pattern; positive Anti-dsDNA antibodies (280 UI/mL); hypocomplementemia	Prednisolone 20 mg daily	11
4 Male, 69y	SpA	ETN	25	54	Polyarthritis (new onset) and subnephrotic proteinuria (~1.5 g/24h)	High ESR, ANA titer 1/100 speckled pattern; positive anti-dsDNA antibodies (105 UI/mL); positive anti-histone antibodies	Prednisolone 10 mg daily	8
5 Female, 42y	SpA	ADA	16	13	Polyarthritis (abrupt worsening), pustulosis of the fingers and Raynaud's phenomenon	High ESR; anemia and lymphopenia; ANA titer 1/1000 diffuse pattern; positive Anti-dsDNA antibodies (130 UI/mL)	Prednisolone 10 mg daily	4
6 Male, 43y	PsA	ETN	13	51	Fever, fatigue and weight loss	Anemia and leukopenia with lymphopenia; ANA 1/320 diffuse pattern; positive anti-dsDNA antibodies (252 UI/mL); positive anti-histone antibodies; positive lupus anticoagulant; positive Coombs test	Prednisolone 15 mg daily	Clinical resolution after 4 months. ANA and anti-dsDNA antibodies remain positive (ANA 1/640 homogeneous pattern and anti-dsDNA 121 UI/mL)

Anti-TNFα, anti-tumor necrosis factor α; y, years of age; RA, rheumatoid arthritis; SpA, spondylarthritis; PsA, psoriatic arthritis; IFX: infliximab; ADA, adalimumab; ETN: etanercept; ANA, antinuclear antibodies; anti-dsDNA, anti-double stranded DNA antibodies; ESR, erythrocyte sedimentation rate.

Rheumatology/European League Against Rheumatism criteria (2).
Arthritis was considered a manifestation of anti-TNFα-induced SLE only if it was a new manifestation or if an abrupt worsening was observed in patients with previous articular involvement due to their rheumatic condition. Patients with positive ANA (titre≥100), positive anti double-stranded DNA (dsDNA) antibodies, or a diagnosis of SLE at their first visit before the prescription of the first anti-TNFα agent were excluded. The ethical principles of the Declaration of Helsinki were followed. All patients signed informed consent and data were anonymized.

CASE SERIES

A total of 607 patients with rheumatic diseases were analyzed: 201 patients with RA, 290 patients with SpA, and 116 patients with PsA. SLE induced by anti-TNFα occurred in six patients (1%), 50% female, mean disease duration of 17.7±5.7 years and anti-TNFα therapy duration of 32.5±18.4 months. Table I summarizes the clinical, laboratory, and treatment features for each rheumatic disease.

Rheumatoid arthritis
SLE induced by anti-TNFα therapy occurred in two patients (2/201, 1%) with erosive and seropositive RA (positivity for rheumatoid factor and anti-citrullinated protein antibodies) treated simultaneously with a conventional synthetic disease-modifying antirheumatic drug.

Case Reports 1 and 2
The first patient is a 66-year-old woman who has been diagnosed with RA since 17 years and developed SLE after 16 months of infliximab. The clinical and laboratory manifestations were constitutional symptoms, abrupt worsening of polyarthritis, positive ANA, and positive anti dsDNA antibodies.
The second patient is a 43-year-old woman who has been diagnosed with RA since 11 years and developed SLE after 41 months of adalimumab. The clinical and laboratory manifestations were malar rash, hypocomplementemia, positive ANA, positive anti-dsDNA and anti-histone antibodies.
In these two cases, the anti-TNFα agent was stopped, and clinical and laboratory recovery occurred spontaneously without treatment. The first patient switched to adalimumab after 3 months, and the second switched to golimumab after 5 months, with no recurrence of SLE after 5 years of follow-up.

Axial spondylarthritis
SLE induced by anti-TNFα therapy occurred in three patients with radiographic axial SpA (3/290, 1%).

Case Reports 3, 4 and 5
The third patient is a 53-year-old man who had been diagnosed with radiographic axial SpA 24 years before and developed SLE after 20 months of infliximab. The clinical manifestations were fatigue, oligoarthritis, and bilateral pleural effusion. Laboratory work-up revealed positive ANA, positive anti-dsDNA antibodies, and hypocomplementemia.
The fourth patient is a 69-year-old man with a diagnosis of radiographic axial SpA since 25 years and developed SLE after 54 months of etanercept. The clinical manifestations were new-onset polyarthritis and subnephrotic proteinuria (~1.5 g/24 h). Laboratory findings revealed positive ANA, positive anti-dsDNA, and anti-histone antibodies.
The fifth patient is a 42-year-old woman with radiographic axial SpA and peripheral involvement for 16 years, treated with leflunomide, who developed SLE after 13 months of adalimumab. This patient developed an abrupt worsening of polyarthritis, pustulosis of the fingers, and Raynaud phenomenon. Her laboratory work-up revealed a new onset of lymphopenia, anemia, positive ANA, and anti-dsDNA antibodies.
In these three cases, the anti-TNFα agent was stopped and oral corticosteroids were started with total recovery of clinical and laboratory features. The third patient switched to etanercept after 3 months, the fourth patient changed to certolizumab after

3 months, and the fifth patient switched to secukinumab after 22 months, without experiencing a recurrence of SLE during a 5-year follow-up period.

Psoriatic arthritis

SLE induced by anti-TNFα therapy occurred in one patient with PsA (1/116, 0.9%).

Case Report 6

The sixth patient is a 43-year-old man with PsA (polyarticular pattern) since 13 years who developed SLE after 51 months of etanercept. The clinical manifestations were fatigue, weight loss, and fever. His laboratory analysis revealed the new onset of anemia, leukopenia with lymphopenia, positive ANA and lupus anticoagulant, positive anti-dsDNA, and anti-histone antibodies. Etanercept was stopped, and oral corticosteroids were started with the resolution of constitutional symptoms and cytopenia. However, despite the decrease in autoantibodies concentrations, both ANA and anti-dsDNA remained positive at low titres. This patient switched to tofacitinib after 66 months of induced SLE. No recurrence of SLE was observed during the next 5 years of follow-up.

DISCUSSION

In this case series, six patients with rheumatic diseases developing SLE secondary to anti-TNFα agents are reported.

Induction of autoantibodies is frequently observed in patients treated with anti-TNFα agents and the possible development of induced SLE remains a matter of concern. However, similar to previous literature, in this case series only 1% of rheumatic patients developed SLE induced by anti-TNFα therapy (1).

The diagnosis of SLE induced by anti-TNFα therapy can be a challenge due to the heterogeneity of symptoms and similarity with symptoms of underlying diseases (1). In our case series, patients had mild disease, with the most common manifestations being articular (4 of 6 patients) and constitutional (3 of 6 patients) symptoms. Similar to previous literature, major organ involvement was uncommon and improvement occurred after therapy discontinuation with no subsequent recurrence of SLE (3). Furthermore, anti-TNFα-induced SLE shows some differences when compared to classic DILE. Cutaneous and renal involvement are more common in SLE induced by anti-TNFα therapy than in classic DILE (4). In our study, cutaneous involvement occurred in two patients and renal involvement in one.

Considering laboratory findings, all patients had positive anti-dsDNA antibodies, two (33.3%) patients had low serum complement levels, and one (16.7%) had positive lupus anticoagulant. Anti-histone antibodies were present in three out of six patients (50.0%). This is in line with previous studies, which have reported that patients with SLE induced by anti-TNFα therapy exhibit low serum complement concentrations, positive anti-extractable nuclear antigen antibodies, and anti-dsDNA antibodies in up to half of them; the same findings are rarely observed in classic DILE (3, 5, 6). In contrast, anti-histone antibodies are described in classic DILE more often than in SLE secondary to anti-TNFα agents (3, 5, 6).

In this case series, two patients developed SLE after infliximab, two after adalimumab, and two after etanercept. Most of the previous case reports of SLE induced by anti-TNFα therapy occurred in patients receiving etanercept or infliximab (3, 6, 7). An important question is whether patients with anti-TNFα-induced SLE can safely switch to another one. In agreement with previous cases, our findings demonstrated a low risk of SLE recurrence with an alternative anti-TNFα agent (3, 8). Thus, this condition seems to be drug-specific rather than class-related. Hence, according to our real-world data, the onset of SLE induced by an anti-TNFα agent is a rare adverse event. Switching to another anti-TNFα agent is well tolerated, suggesting that the occurrence of SLE should not discourage the switching from one anti-TNFα agent to another. However, since this evidence is limited, it is crucial to closely monitor these patients for any symptoms or signs of relapse.

CONCLUSIONS

In conclusion, we present six inflammatory rheumatic patients with a diagnosis of SLE induced by anti-TNFα therapy. Generally, patients improved after discontinuation of therapy and tolerated an alternative anti-TNFα agent without experiencing a recurrence of SLE over time. This study provides real-world insights into the prevalence, clinical manifestations, and treatment approaches for a relatively uncommon adverse event associated with anti-TNFα therapy in inflammatory rheumatic diseases. Further research with larger samples is needed to investigate the long-term impact of this adverse event on treatment outcomes and to clarifyif the switch to a second anti-TNF agent is indeed safe.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare no potential conflict of interest.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Written informed consent was obtained.

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Availability of data and materials
Data are available from the corresponding author upon request.

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