CASE BASED REVIEWS

Secukinumab-induced systemic lupus erythematosus in psoriatic arthritis

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ABSTRACT

Case report: A 68-year-old male treated with secukinumab for psoriatic arthritis suspended treatment for three months due to COVID pandemic. Upon secukinumab reintroduction, anorexia and weight loss ensued and four months later he had an abrupt onset of low-grade fever, fatigue, flu-like symptoms, dyspnoea and widespread inflammatory arthralgias. Laboratory investigations showed de novo anaemia, leukopenia, lymphopenia, cytocholestasis, elevated acute phase reactants, C3 complement consumption, proteinuria (1630mg/24h), active urine sediment, positive antinuclear (1:1280) and anti-double-stranded DNA (212.3 IU/mL) antibodies. Chest imaging showed peripheral pulmonary embolism, lobar pneumonia, and a small bilateral pleural effusion. Drug-induced lupus erythematosus (DILE) was suspected, and the patient was hospitalised. Secukinumab was discontinued and treatment with enoxaparin, antibiotics, enalapril, hydroxychloroquine and prednisolone 0.5mg/kgqd was started. Clinical and laboratorial remission ensued after one month except for proteinuria (decreased to 653mg/24h). Proliferative lupus nephritis was assumed and mycophenolate mofetil was introduced, with sustained complete remission over a 33-month follow-up.

Discussion: This is the second reported case of systemic secukinumab-associated DILE, and the first with renal involvement. Clinical and laboratory features of DILE are reviewed and compared with previously described cases.

Keywords: Systemic lupus erythematosus and autoimmunity; Spondyloarthopathies (including psoriatic arthritis); Renal; Drug-induced rheumatic disease; Biological therapies.

INTRODUCTION

Drug-induced lupus erythematosus (DILE) manifests as cutaneous or systemic features of lupus erythematosus following treatment with a wide range of drugs. DILE is characterized by typical clinical and laboratory features, and it is usually self-limited after withdrawal of the culprit drug. Here, we discuss the first case of systemic DILE with renal involvement that presumably occurred due to treatment with secukinumab.

CASE REPORT

We present a 68-year-old male patient followed at our spondyloarthritis clinic for the past 15 years due to psoriatic arthritis with axial and peripheral involvement. He had a history of psoriasis vulgaris since his 30’s and later developed musculoskeletal manifestations, characterized by inflammatory low back pain and peripheral asymmetrical oligoarthritis, along with elevated inflammatory markers, negative HLA-B27, bilateral radiographic sacroiliitis (grade III-IV) and asymmetric cervical spine ankylosis. There was no prior history of lupus or other rheumatic diseases. His past medical history included mild haemophilia A (Factor VIII mutation c.5813A>G, minimal recorded factor VIII activity of 43%, previous bleeding dyscrasia during an orthopaedic surgery) and hyperuricaemia. He did not take any regular medication for associated conditions.

The patient was initially treated with nonsteroidal anti-inflammatory drugs and methotrexate 15 mg/week, which provided relief for the musculoskeletal pain but yielded an inadequate cutaneous response. Methotrexate was stopped due to dyspepsia. Subsequent treatment with etanercept 50 mg/week, adalimumab 40 mg every

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other week and ustekinumab 45 mg every 12 weeks were attempted, but they proved to be ineffective due to loss of efficacy on psoriasis, despite stable arthritis remission. In June 2018, the patient's treatment was switched to subcutaneous secukinumab at a monthly dose of 300 mg resulting in a rapid improvement of the cutaneous psoriasis lesions.

In February 2020, due to the COVID-19 pandemic, the patient stopped secukinumab resulting in worsening polyarthralgia, which motivated re-introduction in May 2020. When assessed one month later he had four swollen joints (metacarpophalangeals) and reported partial improvement. In September 2020, four months after the re-introduction of secukinumab, the patient referred anorexia and significant weight loss (8 kilograms) over a span of three months and a sudden onset of general malaise, low-grade fever, night sweats, mild flu-like symptoms, dyspnoea and worsening of widespread inflammatory arthralgias. On physical examination, he showed arterial hypertension (156/96 mmHg), tachycardia (120 bpm) with normal respiratory rate, mild pallor, apyrexic, peripheral oxygen saturation of 96-98% in room air, fine crackles on both lung bases, four swollen joints (metacarpophalangeals) and 6 tender joints (metacarpophalangeals, proximal interphalangeal and elbows). Skin lesions were absent.

Laboratory tests revealed elevated erythrocyte sedimentation rate of 56 mm/h (normal <14 mm/h), C-reactive protein 2.73 mg/dL (normal <0.5 mg/dL), normochromic, normocytic anaemia (Hb 12.9 g/dL), leukopenia (3.92 x10^9/L) with lymphopenia (0.72 x10^9/L), cytocholastasis (gamma-glutamyl transferase 203 U/L, normal <60 U/L; total bilirubin 0.99 mg/dL, normal <1.2 mg/dL; direct bilirubin 0.47 mg/dL, normal <0.2 mg/dL; alanine transaminase 74 U/L, normal <41 U/L; and aspartate transaminase 73 U/L, normal <40 U/L) and low serum C3 complement levels (85 mg/dL, normal range 90-180 mg/dL). Renal abnormalities were characterized by the presence of haematuria (204.2 cells/µL, normal <5 cells/µL), leukocyturia (74.6 cells/µL, normal <10 cells/µL), proteinuria (150 mg/dL, 2+) and hyaline-granular casts in the urinary sediment, albeit renal function remained within the patient's usual range (creatinine 0.99 mg/dL). Serologic findings included strongly positive titres of antinuclear antibody (ANA 1:1280, AC-1 - nuclear homogeneous) and anti-double-stranded DNA antibody (anti-dsDNA 212.3 IU/mL, negative <27 IU/mL). Anti-histone, anti-extractable nuclear antigens as well as anti-phospholipid antibodies were negative. No prior ANA titre was available. The patient had a protein S deficiency of 26% (normal 64-129%; measured 3 days after admission) and normal levels of protein C.

The analysis of Factor V Leiden and prothrombin G20210A (factor II) mutation were negative. A high-resolution computed tomography (CT) with IV contrast revealed a multiple subsegmental pulmonary embolism (PE) and parenchymal densification with air bronchogram suggesting infection in the inferior left lobe, and a small bilateral pleural effusion.

Based on these findings, a diagnosis of a peripheral PE and pneumonia was established and DILE syndrome was suspected. The patient was admitted to our department, secukinumab therapy was discontinued and treatment with prednisolone (40 mg qd), hydroxychloroquine (400 mg qd), enalapril (5 mg qd), enoxaparin (160 mg qd), amoxicillin/clavulanic acid (875/125 mg bid) and azithromycin (500 mg qd) was initiated. Additional investigations included a 24h proteinuria of 1630 mg, negative blood and urine cultures, indeterminate IGRA test, negative SARS-Cov-2 Polymerase Chain Reaction (PCR) test, negative serum immunofixation, free light chains within normal range and negative cryoglobulinaemia. Renal ultrasound showed nonobstructive urolithiasis in the right kidney. Electrocardiogram revealed sinus tachycardia (108 bpm) and right bundle branch block, and transthoracic echocardiogram showed mild mitro-aortic valve thickening and no signs of right heart strain. The patient experienced a gradual improvement of clinical symptoms, decrease of anti-dsDNA antibody titres and normalization of serum complement levels and inflammatory markers, although anaemia, lymphocytopenia and proteinuria persisted.

One month after discharge, the patient was asymptomatic, with no swollen joints, and normal blood cell counts and decrease of proteinuria to 653 mg/24h was observed (on prednisolone 40-35 mg qd and hydroxychloroquine 400 mg qd alone). Due to concomitant haemophilia A, it was decided not to perform a kidney biopsy. Considering significant proteinuria and active urine sediment in a patient with clinical and laboratory markers of systemic lupus erythematosus (SLE), proliferative lupus nephritis class III-IV was assumed and mycophenolate mofetil (MMF) was started with a maximum induction dose of 1 g qd. MMF dose was not further increased because proteinuria decreased to 302 mg/24h two weeks after MMF was started, thereby achieving a complete renal response (proteinuria <500 mg/24h with no decrease of glomerular filtration rate). A positron emission tomography-CT scan did not find evidence of neoplastic tissue and the patient regained weight gradually. Anticoagulation was kept for 3 months, when a new contrast CT scan showed resolution of PE.

Prednisolone was slowly tapered, and six months after discharge the patient was in remission with a normal urinalysis (haematuria <5 cells/µL, leukocyturia...
<10 cells/µL, urine protein/creatinine ratio 80 mg/g) under prednisolone 5 mg qd, MMF 1 g qd and hydroxychloroquine 400 mg qd, sustained until present. Anti-dsDNA antibody persisted in low titres (64-90 IU/mL), without any other DILE manifestation. Prednisolone was completely withdrawn after one year in renal remission and MMF tapered to 500 mg qd in the last four months. Due to worsening of psoriasis, despite sustained musculoskeletal remission, guselkumab 100 mg/month was initiated in February 2023 with complete skin response and no recurrence of SLE manifestations. Total follow-up was thirty-three months since the beginning of the flu-like illness.

**DISCUSSION**

Five cases of secukinumab-induced DILE have been reported, four of them exclusively cutaneous (all in patients with chronic plaque psoriasis) and only one with systemic involvement (in a patient with ankylosing spondylitis). We report the second patient with systemic DILE presumably associated with secukinumab and the first with renal involvement.

Our patient had been successfully treated with secukinumab for 20 months. However, after a 3-month withdrawal, he developed polyarthritis, and upon reintroduction he did not regain his previous state of remission. This is suggestive of secondary failure due to an immune response to the secukinumab antibody after temporary withdrawal, as has been described for other biologics. Secukinumab reintroduction was immediately followed by anorexia, 10% weight loss, and four months later, by a constitutional syndrome and manifestations consistent with renal, haematological and serological lupus.

Several clinical features in this patient were typical of DILE, including the abrupt onset with myalgia, fever and serositis. Inaugural manifestations of idiopathic SLE in a 68-year-old male, with no previous symptoms consistent with this diagnosis, would also be unexpected. Positive ANA titres can be found in both DILE and SLE, even in high titres, as observed in the other report of secukinumab-induced systemic DILE. Lower ANA titres (1:160) were found in the cutaneous secukinumab-induced DILE reports. Renal involvement, however, is rare (<10%) in DILE and hypocomplementaemia or haematological abnormalities are unusual. In our case, anaemia, leukopenia and lymphopenia responded quickly to steroids alone, while partial renal response was observed at 1 month and complete response at 2 months after discharge, 2 weeks after MMF was started. A renal biopsy would be necessary to establish a definite diagnosis of lupus nephritis (LN). However, the clinical and laboratorial findings were strongly suggestive and ready response with no relapses was more in keeping with DILE than SLE.

Anti-dsDNA antibodies are seen in <5% of DILE but are well described in DILE associated with TNF inhibitors (TNFi) and were also reported in the previously described case of secukinumab-induced systemic DILE. As in this case, anti-histone antibodies, usually seen in DILE, were not found in ours. In contrast, low titre anti-dsDNA antibodies persisted in our patient after complete resolution of other clinical and laboratorial changes along a 33-month follow-up, but in lower levels that those seen at disease onset.

The pathogenesis of DILE is thought to involve genetic susceptibility and factors related to individual drugs, thus explaining different phenotypes. This patient had been previously exposed to two TNFi, which carry a higher risk of DILE. The scarcity of DILE reports with interleukin (IL)-17 inhibitors suggests that its mechanism is not directly related with IL-17 blockade. Indeed, production of IL-17 is increased in SLE patients, correlates with disease activity and is locally increased in class IV LN and secukinumab has anecdotally been used to treat LN. Treatment of psoriasis/psoriatic arthritis with secukinumab in patients with concomitant pre-existing SLE yielded mixed results. Of interest, access to a renal biopsy could have allowed to determine the degree of tissue infiltration by Th17 cells and local IL-17 production. Furthermore, the subsequent introduction of a monoclonal antibody blocking IL-23, an important upstream mediator of the IL-17 pathway, did not worsen lupus manifestations, suggesting that inhibition of this pathway was not responsible for the clinical picture.

Together with the persistence of anti-dsDNA antibodies, the presence of lupus nephritis is the most unusual feature of DILE, which could rise suspicion of intercurrent idiopathic SLE instead of secukinumab related DILE. Unfortunately, biopsy was not possible due to the high haemorrhagic risk. Still, considering the whole picture, the temporal association with secukinumab reintroduction, acute presentation in a 68-year-old male and rapid resolution after secukinumab discontinuation are strongly suggestive of DILE with secukinumab as a culprit.

We hope our report increases awareness for DILE as a rare complication of secukinumab treatment. Systemic treatment was needed, besides drug withdrawal, but a rapid and sustained response over 33 months was achieved.

**REFERENCES**

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