Dermatomyositis–lupuslike syndrome overlap under treatment with etanercept for rheumatoid arthritis

Anna Lyakhovitsky, MD,[a,c] Karin Warshavsky, MD,[a,c] Lihi Rozner, MD,[a,c] Theodoulos Drousiotis, MD,[a,c] Sharon Baum, MD,[a,c] and Aviv Barzilai, MSc, MD[a,b,c]
Ramat-Gan and Tel Aviv, Israel

Key words: dermatomyositis; etanercept; lupuslike syndrome; overlap syndrome; rheumatoid arthritis; tumor necrosis factor α inhibitor.

INTRODUCTION

Tumor necrosis factor (TNF) α inhibitors are a group of medications used to treat different immunomediated inflammatory conditions, although they have been reported to cause a broadening spectrum of adverse autoimmune reactions.[1,2] We report a case of dermatomyositis-lupuslike overlap syndrome that appeared under treatment with etanercept for rheumatoid arthritis.

Abbreviation used:

TNF: tumor necrosis factor

CASE REPORT

A 68-year-old woman was referred for a pruritic eruption involving the face, back, and extremities. Her medical history included hypertension, hypothyroidism, and a 3-year history of rheumatoid arthritis. The patient's long-term medications comprised bisoprolol, levothyroxine, famotidine, and brotizolam. Her rheumatoid arthritis was initially treated with hydroxychloroquine, which was discontinued because of an urticarial eruption. Subsequent treatment with methotrexate and tofacitinib yielded no response. Approximately 6 weeks before admission, she started treatment with etanercept at 50 mg weekly. Approximately 3 weeks after treatment initiation, she developed a pruritic eruption on the face, trunk, and extremities. She also reported fever, muscle weakness, and dysphagia. Physical examination on admission revealed a papular erythematous eruption involving the face, trunk, and extremities. There was accompanying swelling of the eyelids (heliotrope) (Fig 1, *A*). Well-demarcated, dusky, erythematous plaques, with periungual swelling and telangiectasias resembling chilblains (lupus pernio), were observed over the distal aspects of the fingers and toes (Fig 1, *B*). The rash over the trunk was scaly and partly confluent, with particular involvement of the V-neck area of the chest, posterior aspect of the neck, and shoulders (shawl sign) (Fig 1, *C*). Several joints exhibited tenderness without movement restriction; muscle weakness was not apparent. Laboratory tests showed normal complete blood cell count, electrolytes, and liver function test results; elevated creatinine kinase level (323 IU/I); and normal aldolase levels. The serum level of C-reactive protein was 500 mg/L (reference $\leq$5 mg/L), ferritin 154 ng/mL (reference 10-120 ng/mL), and rheumatoid factor 19.95 IU/mL (reference <14 IU/mL); repeated C3 test results ranged between 73.1 and 86.9 mg/dL and repeated C4 test results ranged between 8.5 and 9.9 mg/dL (reference 85-180 and 10-40 mg/dL, respectively). Because clinical findings suggested collagen vascular disease, further serologic testing was performed and revealed positive antinuclear antibody result (1:2560), positive anti-double stranded DNA antibody result of 55 IU/mL (reference 0-4.9 IU/mL), anti-double stranded DNA titer 1:320, positive antihistone antibody result (10.5 units), and

From the Department of Dermatology, Sheba Medical Center, Tel-Hashomer, Ramat-Gan[a]; Institute of Pathology, Sheba Medical Center, Tel-Hashomer, Ramat-Gan[b]; and Sackler Faculty of Medicine, Tel Aviv University.[c]

Funding sources: None.
Conflicts of interest: None disclosed.

Correspondence to: Anna Lyakhovitsky, MD, Sheba Medical Center, Dermatology Department, Tel-Hashomer, Ramat-Gan, Israel. E-mail: anna.lyakhovitsky@sheba.health.gov.il.

JAAD Case Reports 2020;6:758-60.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.06.014

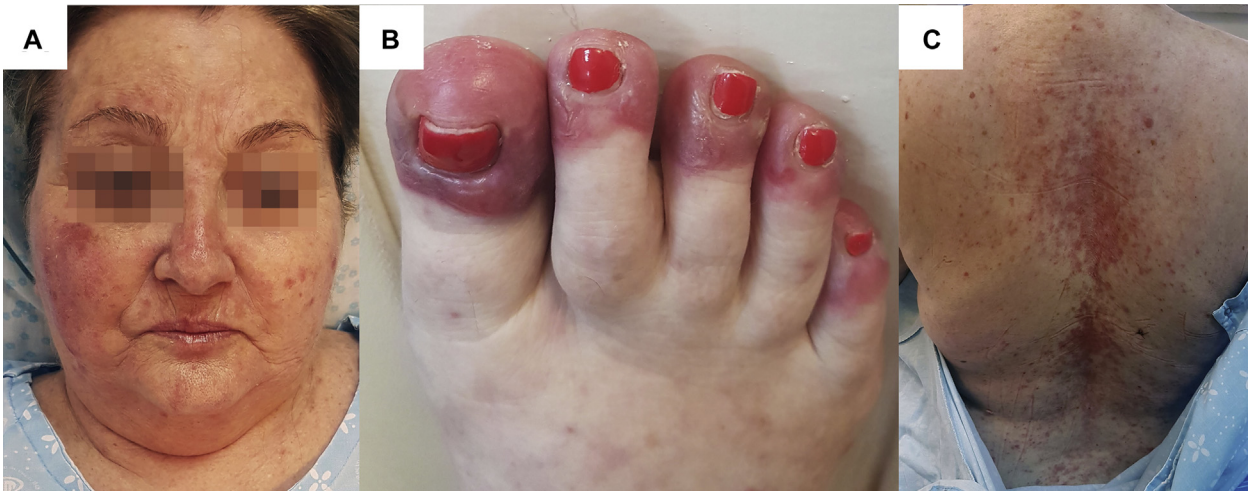

Fig 1. A, Facial erythematous papular eruption with swelling and erythema of the eyelids (heliotrope). **B**, Well-demarcated, dusky, erythematous plaques resembling chilblains over the distal aspects of the toes, with periungual swelling and telangiectasias (chilblain lupus, lupus pernio). **C**, Erythematous scaly papular eruption over the trunk, with particular involvement of the V-neck area of the chest, posterior aspect of the neck, and shoulders (shawl sign).

β2 microglobulin (3.77 μg/mL). Anti-Sm antibody result was negative. Assessment for dermatomyositis demonstrated positive results for anti-transcription intermediary factor 1-gamma, whereas anti-histidyl tRNA synthetase autoantibodies, anti Sjögren's syndrome related antigen A, anti glycyl-tRNA synthetase, anti melanoma differentiation-associated gene 5, anti cyclic citrullinated peptide, perinuclear anti-neutrophil cytoplasmic antibodies, and cytoplasmic antineutrophil cytoplasmic antibodies results were negative. A skin biopsy from the back showed partial epidermal necrosis, as well as superficial and middeep perivascular and periadnexal inflammation with vacuolar interface changes and many dyskeratotic cells (Fig 2). Electromyography revealed mild proximal myopathy of the upper extremities. A fiberoptic swallowing test result was normal. An extensive evaluation for neoplasia and infection was performed, with no abnormalities found. Based on clinical, laboratory, and histopathologic findings, a diagnosis of dermatomyositis—lupuslike overlap syndrome was favored. Given the timeline of its appearance, the causative role of etanercept was implied. Therefore, it was discontinued and intravenous hydrocortisone 300 mg/d was initiated, titrated gradually and switched to oral prednisone. Follow-up after 3 months showed continuing synovitis of several joints. Therefore, rituximab at 2000 mg was administered. Follow-up after 6 months revealed no symptoms under a maintenance dose of prednisone 5 mg/d.

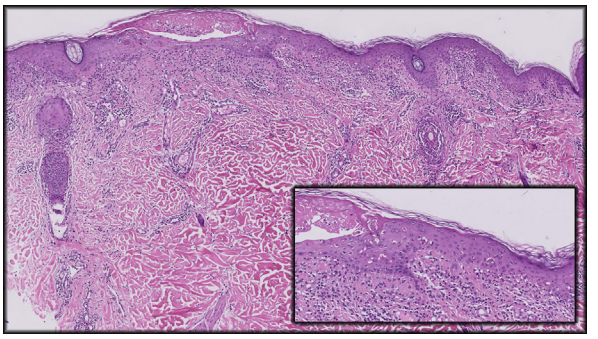

Fig 2. Skin biopsy from the back. Hematoxylin-eosin staining showing partial epidermal necrosis (on the left side of the figure [inset]), as well as superficial and middeep perivascular and periadnexal inflammation with vacuolar interface changes and dyskeratotic cells.

DISCUSSION

An overexpression of TNF-α and its receptors described in dermatomyositis has led to trials of TNF-α inhibitor use for its treatment. Although several authors showed an efficacy of TNF-α inhibitor, cases of exacerbation and even fatalities have also been described.[3-6] Moreover, induction of dermatomyositis by TNF-α inhibitor has been reported as well, with most inductions in rheumatoid arthritis patients.[7] The most common TNF-α inhibitor associated with dermatomyositis is etanercept, followed by adalimumab and infliximab. The interval between TNF-α inhibitor initiation and dermatomyositis onset ranged between 2 weeks and 3 years, with some cases of reactions appearing on recommencement of

the medication. The pathogenesis of this phenomenon is unclear. One hypothesis suggests that TNF-α inhibitors promote humoral autoimmunity, changing the balance between T helper cell type 1 and 2 cytokine production and the expression of interferon type 1, which has been implicated as a key element in dermatomyositis pathogenesis. Additionally, TNF-α inhibitors hinder cytotoxic T lymphocytes, causing reduced elimination of autoantibody productive B lymphocytes. Another hypothesis suggests apoptosis disruption, resulting in decreased clearance of nuclear debris with increased autoantibody formation. The role of infections after TNF-α inhibitor—induced immunosuppression, leading to polyclonal B lymphocyte activation and autoantibody formation, was also implied.[6]

Although TNF-α inhibitor—induced dermatomyositis is rare, TNF-α inhibitor—induced lupus erythematosus and lupuslike syndrome are commonly described with all TNF-α inhibitors. TNF-α inhibitor—induced lupuslike syndrome is defined as a post—TNF-α inhibitor exposure immunomediated disease presenting with at least 1 clinical manifestation and serologic test result compatible with lupus erythematosus, not fulfilling the diagnostic criteria for systemic lupus erythematosus. Diagnosis requires lack of lupus erythematosus background and resolution with TNF-α inhibitor discontinuation. Suggested pathogenic mechanisms include those raised for dermatomyositis.[8] Our rheumatoid arthritis patient developed features of both dermatomyositis and lupuslike syndrome shortly after initiation of etanercept. Several explanations for this overlap were suggested. First, given that rheumatoid arthritis preexisted for years, whereas dermatomyositis and lupuslike syndrome developed after recent commencement of TNF-α inhibitors, TNF-α inhibitor—induced dermatomyositis-lupuslike overlap syndrome is suggested. A further possibility is the unmasking of an existing overlap by TNF-α inhibitor. Additionally, dermatomyositis has been described in overlap with rheumatoid arthritis and lupus erythematosus. Rhupus, an overlap of rheumatoid arthritis and systemic lupus erythematosus, has also been reported, in which rheumatoid arthritis usually precedes lupus erythematosus by several years.[9] Furthermore, patients with dermatomyositis and lupus erythematosus can display arthritis as an early manifestation. A rheumatoid arthritis switch to lupus erythematosus has also been described.[10] Thus, we cannot be confident whether in our case the TNF-α inhibitor caused or unmasked an underlying primary overlap syndrome. However, considering that dermatomyositis and lupuslike syndrome appeared long after diagnosis of rheumatoid arthritis but shortly after TNF-α inhibitor initiation and improved promptly with its discontinuation, the diagnosis of dermatomyositis-lupuslike overlap syndrome induced by the TNF-α inhibitor is strongly suggested.

CONCLUSION

To our knowledge, this is the first case describing the overlap between dermatomyositis and lupuslike syndrome associated with TNF-α inhibitors. Awareness of an evolving adverse effect profile of biologic agents, including TNF-α inhibitors, is important. Therefore, it is imperative to gain knowledge and share experiences to improve patient care.

We thank Sara Bavli and Haim Baranes for technical help.

REFERENCES

1. Jani M, Dixon WG, Chinoy H. Drug safety and immunogenicity of tumour necrosis factor inhibitors: the story so far. *Rheumatology (Oxford)*. 2018;57(11):1896-1907.
2. Moustou AE, Matekovits A, Dessinioti C, Antoniou C, Sfikakis PP, Stratigos AJ. Cutaneous side effects of anti-tumor necrosis factor biologic therapy: a clinical review. *J Am Acad Dermatol*. 2009;61:486-504.
3. Iannone F, Scioscia C, Falappone PCF, Covelli M, Lapadula G. Use of etanercept in the treatment of dermatomyositis: a case series. *J Rheumatol*. 2006;33(9):1802-1804.
4. Zengin O, Onder ME, Alkan S, et al. Three cases of anti-TNF induced myositis and literature review. *Rev Bras Reumatol*. 2017;57(6):590-595.
5. Takata M, Yamasaki A, Yamada N, et al. A case of clinically amyopathic dermatomyositis that developed during anti-TNF-α therapy for rheumatoid arthritis. *Allergol Int*. 2018;67(2):286-288.
6. Brunasso AMG, Aberer W, Massone C. New onset of dermatomyositis/polymyositis during anti-TNF-α therapies: a systematic literature review. *ScientificWorldJournal*. 2014:179-180.
7. Dicaro D, Bowen C, Dalton SR. Dermatomyositis associated with anti-tumor necrosis factor therapy in a patient with psoriasis. *J Am Acad Dermatol*. 2014;70(3):64-65.
8. Macaluso FS, Sapienza C, Ventimiglia M, Renna S, Cottone M, Orlando A. Lupus-like reactions in patients with inflammatory bowel disease treated with anti-TNFs are insidious adverse events: data from a large single-center cohort. *Scand J Gastroenterol*. 2019;54(9):1102-1106.
9. Andrade-Ortega L, Irazoque-Palazuelos F, Muñóz-López S, Rosales-Don Pablo VM. Efficacy and tolerability of rituximab in patients with rhupus. *Reumatol Clin*. 2013;9(4):201-205.
10. Aguila LA, Lopes MRU, Pretti FZ, et al. Clinical and laboratory features of overlap syndromes of idiopathic inflammatory myopathies associated with systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis. *Clin Rheumatol*. 2014;33(8):1093-1098.