Tumor Necrosis Factor Inhibitor–Associated Dermatomyositis

Rachel Klein, BA; Misha Rosenbach, MD; Ellen J. Kim, MD; Brian Kim, MD; Victoria P. Werth, MD; Jonathan Dunham, MD

Background: Dermatomyositis is an autoimmune disease of unknown etiology characterized by inflammation of the skin and muscles. Several medications have been implicated in the development of dermatomyositis; however, the disease has rarely been linked to the use of tumor necrosis factor (TNF) inhibitors. We report 4 cases of dermatomyositis that developed or were exacerbated by exposure to the TNF inhibitors etanercept and adalimumab.

Observation: Four patients with symptoms of inflammatory arthritis were treated with TNF inhibitors for a duration ranging from 2 months to 2 years. All 4 patients developed symptoms consistent with dermatomyositis, including inflammatory rash and muscle weakness. Their symptoms persisted after discontinuation of the treatment with the TNF inhibitors but responded to treatment with corticosteroids and immunosuppressive medications.

Conclusions: Tumor necrosis factor inhibitors have been associated with the onset of a number of autoimmune disorders, most commonly vasculitis and a lupuslike syndrome. Rarely have they been associated with dermatomyositis. The 4 cases reported herein indicate that TNF inhibitor use can be associated with either induction or exacerbation of dermatomyositis.

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Dermatomyositis, which is an autoimmune inflammatory condition of unknown etiology, is characterized by classic cutaneous findings and proximal muscle weakness. It can also be associated with interstitial lung disease and underlying malignancy. The primary rash is often pruritic and appears as confluent, violaceous, photodistributed erythema on the face, V-neck area of the chest, posterior aspect of the neck and shoulders, and extensor surfaces of the arms. Other hallmark cutaneous manifestations include heliotrope periorcular erythema, malar rash involving the nasolabial folds, Gottron papules, periungual telangiectasias, mechanic's hands, poikiloderma, and flagellate erythema. Although the pathogenesis of dermatomyositis is unknown, there have been reports of cases of dermatomyositis that appear to be drug induced. Nineteen different medications have been implicated, the most common being hydroxyurea (36 cases), penicillamine (10 cases), and HMG-CoA reductase inhibitors (6 cases). To our knowledge, only 2 cases have been described in association with tumor necrosis factor (TNF) inhibitors, ie, lenenercept and etanercept. We herein report 4 additional cases of dermatomyositis associated with TNF inhibitors.

REPORT OF CASES

CASE 1

A 33-year-old woman with arthralgias and low-titer rheumatoid factor (RF) positivity was diagnosed as having rheumatoid arthritis (RA) and treated sequentially with etanercept followed by adalimumab for 5 months. When her symptoms did not improve, she saw a different rheumatologist, who diagnosed her as having fibromyalgia and stopped the adalimumab therapy. Over the course of the next year, her arthralgias persisted and she developed mild proximal muscle weakness and pain as well as faint periorcular erythema and swelling.

She also developed an exacerbation of symptoms, including arthralgias and mild malar and heliotrope erythema, after sun exposure. Her original rheumatologist treated her with a single in-office injec-
tion of etanercept. Within days, she developed very severe myalgias, arthralgias, exacerbation of her rash, shortness of breath, and temperatures as high as 40°C. She was admitted to the intensive care unit at an outside hospital and treated with antibiotics for possible sepsis, although the results of her infectious workup were negative. Soon thereafter, she developed a generalized pruritic morbilliform rash and was placed on a regimen of oral prednisone for a possible drug reaction.

She then presented to our institution with continued fevers, weakness, and a generalized rash. She underwent an extensive autoimmune workup, which revealed the following negative laboratory results: antinuclear antibody (ANA), double-stranded DNA (dsDNA), Scl-70, Smith/ribonuclear protein, SSA, SSB, histone, antithrombophilip antibodies, RF, antineutrophil cytoplasmic antibody, HLA-B27, cryoglobulins, and the myositis panel (Mi-2, Jo-1, PM-Scl, PL-7, PL-12, EJ, OJ, KU, and SRP). The levels of C3, C4, creatine kinase, and antimitochondrial antibody were normal; however, the aldolase level was elevated (18.0 U/L; reference range, 1.2-7.6 U/L) (to convert to microkatal per liter, multiply by 0.0167). Ferritin levels were persistently markedly elevated (16 282 ng/mL; reference range, 9-120 ng/mL) (to convert to picomoles per liter, multiply by 2.247). The results of an infectious workup, including blood and urine cultures and serologic tests for Rocky Mountain spotted fever, Lyme disease, *Ehrlichia*, and parvovirus B19, were negative. A punch biopsy specimen from a sun-exposed area showed an interface dermatitis with a mixed inflammatory infiltrate.

Based on the results of the skin biopsy, elevated aldolase and ferritin levels, morbilliform rash, and fevers, an underlying dermatomyositis, a drug reaction, or Still’s disease was suspected. The patient was started on intravenous methylprednisolone (2 mg/kg) followed by oral methylprednisolone (1 mg/kg), resulting in prompt resolution of both the fevers and the rash. As her corticosteroid therapy was tapered (oral methylprednisolone (8 mg/d), however, she developed new skin findings consistent with dermatomyositis, including a heliotrope rash, Gottron papules on her elbows and interphalangeal joints, malar erythema involving the nasolabial folds, and mechanic’s hands. She also had fixed, violaceous patches on the V neck of her chest, the extensor surfaces of her arms and legs, her back, and her abdomen (Figure).

Magnetic resonance imaging of the patient’s thighs and electromyography while she was receiving steroids did not show evidence of active myositis or myopathy. Pulmonary function tests (PFTs) revealed mild restrictive lung disease with decreased diffusing capacity for carbon monoxide (DLCO), but a high-resolution computed tomographic (CT) scan of the chest showed no abnormalities. Given the results of the biopsy, the elevated aldolase level, the new rash, and the abnormal PFT results, a diagnosis of dermatomyositis was made.

The results of a malignancy screening, including a colonoscopy; Papanicolaou smear; mammography; positron emission tomography; bone scan; peripheral blood flow cytometry; CT scans of the chest, abdomen, and pelvis; and transvaginal and retroperitoneal ultrasonography, were unremarkable.

As an outpatient, the patient was treated with mycophenolate mofetil and later with hydroxychloroquine sulfate, which resulted in a marked clinical improvement. Six months later, she had stable proximal muscle weakness and shortness of breath with unchanged DLCO. Her rash remained in remission with a low-dose regimen of methylprednisolone, mycophenolate mofetil, hydroxy-
Chloroquine, topical corticosteroids (triamicinolone acetonide, 0.1%, ointment as needed), and broad-spectrum sun protection.

**CASE 2**

A 40-year-old woman with symptoms of inflammatory arthritis and low-titer RF positivity was diagnosed as having RA. She was started on etanercept therapy and 2 years later developed pruritus and erythema in a photodistributed pattern that was exacerbated by sun exposure. The etanercept therapy was discontinued, and she was treated with clobetasol cream (0.05%) twice daily, prednisone (maximum dose, 40 mg/d), and hydroxychloroquine sulfate. Eight months later, the rash continued to progress and she developed symmetrical proximal lower-extremity muscle weakness. She had no pulmonary symptoms. Physical examination revealed Gottron papules on the proximal aspect of the interphalangeal joints, periungual erythema with cuticular hypertrophy and telangiectatic vessels, facial erythema, and poikilodermatous patches on the neck, chest, upper back area, trunk, and thighs.

An autoimmune workup showed elevated titers of ANA (255 AU [arbitrary units]/mL; reference range, 0-99 AU/mL) and RF (14.8 IU/mL; reference range, 0-13.9 IU/mL). The results of laboratory tests, including mitochondrial antibody, histone antibody, Jo-1, SSA, SSB, dsDNA, C3, C4, Smith, ribonucleoprotein, and erythrocyte sedimentation rate, were normal. The level of C-reactive protein was mildly elevated (6.9 mg/L; reference range, 0.0-4.9 mg/L) (to convert to nanomoles per liter, multiply by 9.524). A urinalysis revealed no abnormalities. The levels of creatine kinase (1245 U/L; reference range, 24-173 U/L) and aldolase were elevated (20.4 U/L; reference range, 1.2-7.6 U/L). A punch biopsy specimen from a poikilodermatous patch on the patient’s abdomen showed a focal interface dermatitis, a focal vacuolar alteration, and a superficial perivascular infiltrate. The results of PFTs and radiography of the chest were normal. A malignancy screen, including mammography, Papanicolaou smear, complete blood cell count, and CT scans of the chest, abdomen, and pelvis, was in progress. The patient was treated with prednisone (60 mg/d) and rituximab, and her rash and muscle weakness improved.

**CASE 3**

A 29-year-old woman with a history of a seronegative inflammatory arthritis and a family history of psoriasis was treated with adalimumab and methotrexate. She previously had malar erythema but no additional skin findings, muscle weakness, or shortness of breath. Three months after starting the adalimumab therapy, she developed photosensitivity and proximal muscle weakness in the lower extremities bilaterally. Physical examination revealed diffuse V-neck erythema, Gottron papules over the interphalangeal joints, periungual erythema, and pitting of the nails.

An autoimmune workup demonstrated a positive ANA titer (1:640) and normal levels of dsDNA, Jo-1, SSA, SSB, Smith, ribonucleoprotein, C3, C4, and C-reactive protein as well as a normal erythrocyte sedimentation rate.

The levels of creatine kinase (95 U/L; reference range, 20-150 U/L) and aldolase (3.7 U/L; reference range, 1.5-8.1 U/L) were within normal limits. Lyme antibody titers were negative. A biopsy specimen showed an interface dermatitis with increased mucin deposition and a lymphocytic perivascular infiltrate. Magnetic resonance imaging of the thighs demonstrated muscle edema. Electromyography showed evidence of myopathy in the proximal muscles of the upper extremities. The results of the PFTs were normal. The results of a malignancy workup, including a Papanicolaou smear, transvaginal pelvic ultrasonography, radiography of the chest, and CT scans of the chest, abdomen, and pelvis, were normal.

The adalimumab therapy was discontinued, and the patient was treated with successive additions of prednisone (maximum dose, 30 mg/d), methotrexate, hydroxychloroquine, azathioprine, and quinacrine. Her muscle weakness improved with therapy. She had a slight improvement of her rash initially, but it ultimately remained active despite treatment.

**CASE 4**

A 51-year-old man with a history of a dermatomyositis and RA overlap syndrome (positive for RF and anticyclic citrullinated peptide antibody) that was refractory to methotrexate and azathioprine therapy presented with worsening pulmonary symptoms after treatment with adalimumab. When he was initially diagnosed as having dermatomyositis overlap, he had myalgias in the proximal muscles, mechanic’s hands, a heliotrope rash, Gottron sign on the interphalangeal joints, and palmar erythema. The findings of a malignancy workup, including endoscopy, colonoscopy, prostate-specific antigen, and CTs of the chest, abdomen, and pelvis, were unremarkable. A high-resolution CT scan showed mild interstitial fibrosis at the bases, but the results of the PFTs were normal. Two months after starting adalimumab therapy, the patient noted an increased dry cough, and his DLCO decreased from 98% to 58% of the predicted normal value. The adalimumab therapy was stopped, and treatment with prednisone, hydroxychloroquine, and cyclophosphamide was initiated. One year later, his DLCO had increased to 68% of the predicted normal value, and his exercise tolerance had improved.

**COMMENT**

Tumor necrosis factor inhibitors have been associated with the development of a wide array of autoimmune diseases, including lupuslike syndromes, vasculitis, interstitial lung disease, sarcoidosis, autoimmune hepatitis, and uveitis, and antiphospholipid syndrome. Of these, lupus and vasculitis are the most common, together representing 60% of documented cases of TNF-induced autoimmune disease. Moreover, the incidence of ANA positivity increases 3-fold with anti-TNF therapy, even in the absence of a lupuslike syndrome. Tumor necrosis factor–induced dermatomyositis, however, is rare, representing fewer than 1% of reported cases of TNF-induced autoimmunity. Previous case se-
tients with RA are treated with TNF inhibitors, they de-

esis is supported by the observation that when some pa-

proposed.13 The cytokine-shift hypothesis suggests that

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I interferon by altering the balance between TH1 and TH2

rations and open-label studies of TNF inhibitors that have

been used to treat dermatomyositis have suggested that

the use of these agents may exacerbate disease; in a case

eries of 5 patients who were treated with etanercept for
dermatomyositis, all 5 patients experienced worsening

of their muscle weakness and did not have any improve-

ment of their rash.8

In our case series, 3 of 4 patients did not have a diag-

nosis of dermatomyositis before exposure to the TNF in-
hibitors, although all 3 had a history of inflammatory ar-

thritis. For several years, their complaints of joint pain were
attributed to other disease processes, such as RA. Because
patients with dermatomyositis can develop arthritis, it is
difficult to ascertain whether the patients truly had an-
other disease or whether the arthritis was an early symp-
tom of dermatomyositis. If the latter were true, it would

see that the anti-TNF medications either uncovered or
accelerated the progression of underlying dermatomyosi-
tis in patients with otherwise limited symptoms.

Regardless, all patients in our series experienced wors-

ing of their symptoms after treatment with TNF in-
hibitors, and in 1 instance (case 1), the effects seemed
rapid and dramatic when the medication was reintro-
duced after a prolonged hiatus. Furthermore, all pa-
tients in our series showed some improvement in their
symptoms when both treatment with the TNF inhibitor
was stopped and appropriate therapy for dermato-
myositis was started. Therefore, while we cannot say with
certainty that the use of the TNF inhibitors induced der-

matomyositis in these cases, exposure seemed to coincide
with worsening and/or progression of symptoms that

might not be explained by the natural history of derma-

omyositis alone.

At first glance, the notion that TNF inhibition can ex-

acerbate dermatomyositis seems counterintuitive; TNF- 

α and its receptor are overexpressed in dermatomyositis,
suggesting a contribution to the pathogenesis of the dis-

ease.9-11 However, attempts at pharmacologically block-
ing TNF-α have led to disease flares in patients with in-

flammatory myopathies.8,12 It is not yet fully understood
why this occurs; however, several mechanisms have been
proposed.13 The cytokine-shift hypothesis suggests that

the inhibition of TNF-α promotes the expression of type
1 interferon by altering the balance between T₃₁ and T₃₂

cytokine production.12,14,15 This increase in type 1 inter-

feron, which has been shown to be important in the path-
ogenesis of dermatomyositis, may contribute to the exac-

erbation of symptoms.16,17 Another possibility is that

TNF-α blockade interferes with apoptosis, allowing the
increased formation of autoantibodies.18 This hypo-
thesis is supported by the observation that when some pa-
thents with RA are treated with TNF inhibitors, they
develop antibodies against ANA and dsDNA.7

Our cases differed significantly with respect to the tem-

aporal relationship between the initiation of anti-TNF
therapy and the worsening of dermatomyositis, ranging
from 2 months to approximately 2 years. This finding is
consistent with other reports in the literature of general
drug-induced dermatomyositis, which has been shown to
occur after a wide range of duration of therapy.1 Simi-
larly, exacerbation of inflammatory myopathies specif-
cally after treatment with a TNF inhibitor has also oc-
curred at varied times, ranging from 1 week to 10

months.8,12 The reasons for this heterogeneity are not clear
but may be related to unidentified host factors.

A recent review on drug-induced dermatomyositis
indicates that more than 90% of patients noted improve-
ment in their rash and myositis simply after discontinu-
ning the medication;2 however, the patients described
herein required additional therapy with corticosteroids and
immunosuppressive medications to control their symptoms.
This observation may reflect the previously described
notion that TNF inhibition may cause sustained alterations in the immune system that are not easily
overcome just by removing the offending agent.

In conclusion, TNF inhibitors are a valuable tool in
treating a number of inflammatory and autoimmune dis-
orders. While they can be an important asset to patient
care, their use has rarely been associated with serious ad-
verse events, including infections, certain cancers, dem-


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