Severe Dermatomyositis Triggered by Interferon Beta-1a Therapy and Associated With Enhanced Type I Interferon Signaling

Ally-Khan Somani, MD, PhD; Alan R. Swick, BSc; Kevin D. Cooper, MD; Thomas S. McCormick, PhD

Background: Type I interferons (IFNs) are common therapeutics for several diseases, including viral infections and multiple sclerosis (MS). Although numerous studies have implicated type I IFNs with the production of autoantibodies and the development of certain autoimmune disorders, interferon beta has not previously been described in association with dermatomyositis, to our knowledge. Previous microarray studies of muscle biopsy specimens from patients with dermatomyositis disclosed a type I IFN–induced gene expression profile. The central role of plasmacytoid dendritic cell precursors, together with increased type I IFN production, suggests a pivotal role for type I IFNs in dermatomyositis. We report a case of dermatomyositis exacerbated or induced by interferon beta therapy for MS and provide evidence that demonstrates enhanced type I IFN signaling in this patient.

Observations: We observed new-onset dermatomyositis in a 57-year-old patient treated with interferon beta for MS. His symptoms were exacerbated temporally by interferon beta injections. Immunohistochemical staining of skin biopsy specimens for myxovirus-resistance protein A (a surrogate marker for cutaneous type I IFN signaling) showed increased staining that correlated temporally with interferon beta treatment and subsequent disease activity. In vitro treatment with interferon beta of peripheral blood mononuclear cells isolated from our patient revealed enhanced type I IFN signaling assessed by interferon-induced gene expression profiles.

Conclusions: To our knowledge, this is the first description of dermatomyositis exacerbated or induced by interferon beta treatment. Our results demonstrate enhanced type I IFN signaling following interferon beta treatment in our patient with dermatomyositis.

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Dermatomyositis is an inflammatory autoimmune myopathy characterized by proximal muscle weakness, muscle inflammation, and characteristic cutaneous manifestations (including V sign, shawl sign, mechanic hand, Gottron sign, Gottron papule, periungual telangiectasias, and heliotrope rash with periorbital edema). The pathogenesis is poorly understood, and the disease represents a complex disorder that may result in significant morbidity and mortality. Recent gene microarray investigations on muscle biopsy specimens from patients with dermatomyositis reveal a characteristic signature of type I interferon α (IFN-α) or IFN-β–inducible genes associated with this disease. Systemic lupus erythematosus (SLE) shares common histologic features with dermatomyositis and a similar gene expression signature, including overexpression of type I IFN–inducible genes. Although the exact mechanistic pathways are unclear, genes induced by type I IFN are highly expressed and likely contribute to cutaneous and systemic findings in these diseases.

The involvement of type I IFNs in the pathogenesis of autoimmunity has long been suspected primarily on the basis of early articles documenting enhanced type I IFN serum levels in patients with lupus that cycled with disease activity. Further evidence for IFN-α– or IFN-β–associated induction of autoimmune disease has emerged from studies demonstrating induction of autoimmune following interferon alfa or interferon beta therapy. Interferon alfa- and beta–induced SLE has been reported, along with case reports of interferon alfa- or inter-
faron beta–induced subacute cutaneous lupus erythematosus.\textsuperscript{12,15,16} However, to date (to our knowledge) there have been no published reports of interferon beta inducing or exacerbating dermatomyositis, and only a single article\textsuperscript{13} describes dermatomyositis developing following high-dose interferon alfa therapy for melanoma.

Herein, we report a case of severe dermatomyositis exacerbated or induced by interferon beta therapy. We provide in vitro evidence in a patient with dermatomyositis for enhanced type I IFN signaling in nonadherent (lymphoid) cells in response to interferon beta.

**REPORT OF A CASE**

A 57-year-old man was diagnosed as having multiple sclerosis (MS) almost 30 years previously. During this period, he experienced approximately 4 to 5 flares consisting mainly of loss of balance. These were readily treated with intravenous methylprednisolone sodium succinate. Approximately 5 years earlier, treatment with interferon beta-1a (30 µg [6M IU] intramuscularly) once a week was started as specific treatment for MS. He had remained well until his presentation following a 3-week history of a violaceous skin eruption involving his face, chest, back, upper extremities, and knees. There was associated periorbital edema, dysphagia, and proximal muscle weakness. On physical examination, he was noted to have classic cutaneous stigmata of dermatomyositis (heliotrope rash, shawl sign, and Gottron papules) (Figure 1A and B). Skin biopsy specimens and blood samples were obtained.

Skin biopsy specimens were consistent with dermatomyositis, demonstrating prominent interface dermatitis with vacuolar changes and the presence of dermal mucin (Figure 1C). The mucin was further highlighted by a colloidal iron stain (Figure 1D). The patient’s time line for his clinical course, interferon beta injections, timing of laboratory tests, and creatine kinase, aspartate aminotransferase, and alanine aminotransferase values is shown in Figure 2. Laboratory results showed mild lymphocytosis, positive results for antinuclear antibody (1:320 titer, speckled staining pattern), and negative results for anti–double-stranded DNA, anti-Sm, anti-Scl 70, anti-Jo, anti-Ro, anti-La, and antihistone antibodies. The C3 and C4 levels were normal. The erythrocyte sedimentation rate (53 mm/h) and the creatine kinase (4065 U/L), aspartate aminotransferase (377 U/L), and alanine ami-
notransferase (195 U/L) levels were markedly elevated (Figure 2B) (to convert creatine kinase, aspartate aminotransferase, and alanine aminotransferase levels to microkatal per liter, multiply by 0.0167).

At the patient’s initial presentation, he had received his interferon beta injection less than 48 hours earlier (Figure 2B). Because of worsening disease, the patient was admitted to our service and a 5-day course of intravenous corticosteroid therapy was started. Results of a full workup for occult malignancy were normal, and magnetic resonance imaging of his quadriceps showed significant muscle edema and inflammation consistent with dermatomyositis.

Because of the proximity of interferon beta treatment with disease onset, we speculated that interferon beta might be contributing to the severity of the patient’s disease. However, because the patient’s MS had been well controlled for many years with interferon beta and given the lack of a published association between interferon beta and dermatomyositis, therapy was continued. The patient was discharged home on a regimen of oral corticosteroids after clinical improvement.

Subsequently, the patient experienced a severe clinical flare 9 days following discharge within 24 hours after reinitiation of his interferon beta therapy (Figure 2). He was readmitted for severe worsening of his myopathy, including dysphagia. His creatine kinase (4458 U/L), aspartate aminotransferase (457 U/L), and alanine aminotransferase (210 U/L) levels were elevated, reflecting his clinical exacerbation. Interferon beta therapy was dis-
and the patient was treated with intravenous immunoglobulin, intravenous corticosteroids, and methotrexate. He slowly began to improve during his 33-day hospitalization (Figure 2).

The flare had been temporally related to restarting interferon beta therapy. Therefore, we decided to investigate whether interferon beta had a role in inducing or exacerbating his dermatomyositis.

Institutional review board–approved consent was obtained from our patient and from healthy volunteers before their participation, and the study was performed with strict adherence to the principles of the Declaration of Helsinki. Authorization from our patient and from healthy volunteers before their participation was also obtained.

IMMUNOHISTOCHEMICAL ANALYSIS

Formalin-fixed paraffin-embedded skin specimens were available from our patient with dermatomyositis (2 and 19 days after interferon beta treatment), from a patient with discoid lupus erythematosus (DLE) (positive control for myxovirus-resistance protein A [MxA]), and from a healthy control subject (negative control for MxA). Sections were deparaffinized and stained with standard hematoxylin-eosin for routine histologic examination. Cutaneous type 1 IFN signaling was evaluated by immunostaining for MxA antigen as an indicator for IFN signaling. Antigen retrieval was performed using target retrieval solution (DAKO, Carpinteria, California) consisting of a citrate buffer (pH 6.0) in a heated water bath according to the manufacturer's instructions. Tissue sections were incubated for 1 hour with mouse monoclonal antibody to human MxA (IgG 2a, clone M143, 1.5 µg/mL), followed by Cy2-labeled donkey antimouse IgG (8.4 µg/mL) (Jackson ImmunoResearch Laboratories, West Grove, Pennsylvania) for 1 hour at room temperature. Using DLE sections, negative controls were obtained by omission of the primary MxA mouse monoclonal antibody and by incubation with isotype control mouse monoclonal antibody (IgG 2a, 2.5 µg/mL) (BD Biosciences, San Jose, California). Before mounting, all sections were stained with the nuclear stain DRAQ5 (20 µM) (Invitrogen, Carlsbad, California). After mounting, the sections were examined using an inverted confocal laser scanning microscope (Carl Zeiss, Jena, Germany) with excitation wavelengths of 488 nm for Cy2, and 633 nm for DRAQ5. Confocal images were stored as digital files and were analyzed using the laser scanning microscope (Image Browser Rel 4.2; Carl Zeiss).

IN VITRO TREATMENT OF PERIPHERAL BLOOD MONONUCLEAR CELLS WITH INTERFERON BETA

Peripheral blood mononuclear cells (PBMCs) from our patient with dermatomyositis and from 2 healthy donors were purified from freshly drawn human blood (in heparin tube) by density gradient centrifugation (Histopaque; Sigma Chemical Co, St Louis, Missouri) according to standard protocols. The PBMCs were resuspended at $2 \times 10^5$ cells/mL in RPMI medium plus 5% heat-inactivated fetal calf serum, 1-glutamine, sodium pyruvate, nonessential amino acids, and 10 mM HEPES buffer (Hyclone, Logan, Utah) and combined penicillin G (10 000 U/mL) and streptomycin sulfate (10 mg/mL). The PBMC samples were rested overnight at 37°C, then incubated for an additional 24 hours in the presence or absence of interferon beta (100 IU [0.5 ng/mL]) (Avonex; Biogen Idec, Cambridge, Massachusetts), and then separated into adherent and nonadherent cell populations for RNA extraction.

RNA EXTRACTION AND COMPLEMENTARY DNA SYNTHESIS

Total RNA was isolated from the adherent and nonadherent populations of PBMC specimens (RNeasy kit; Qiagen, Valencia, California) according to the manufacturer’s instructions. RNA was reverse transcribed using Moloney murine leukemia virus reverse transcriptase (Invitrogen) in a total reaction volume of 20 µL; this comprised 10 mM each of 1 µg of total RNA, 100 ng of random hexamer primers, $4 \mu$L of first-strand buffer, and 1 µL of deoxynucleotide triphosphate mix; 40 U of ribonuclease inhibitor (RNaseOut, Invitrogen); and 200 U of Moloney murine leukemia virus reverse transcriptase. The RNA concentration and purity were determined by spectrophotometric analysis (optical density, 260-nm to 280-nm ratio). RNA was stored at −80°C.

QUANTITATIVE REAL-TIME POLYMERASE CHAIN REACTION

Quantitative real-time polymerase chain reaction (PCR) primers and probes were obtained (TaqMan; Applied Biosystems; Foster City, California). For detection of MxA, ISG15, IFN-α, IFN-β, and IFNAR1, predeveloped TaqMan gene expression assay reagents were available. As the housekeeping endogenous control for sample normalization, 18S ribosomal RNA (rRNA) was used. The internal fluorescent TaqMan probe and 18S rRNA specific primers were designed as follows: 5’-CAT-TCT-TGG-CAA-ATG-CTT-TGG-3’, 5’-CGC-CGC-TAG-AGG-TGA-ACT-TC-3’ (Taqman probe, Applied Biosystems) and VIC-ACC-GGC-GCA-AGA-CGG-ACC-AGA-TAMRA (18S probe, Invitrogen). The messenger RNA (mRNA) levels of the genes MxA, ISG15, IFN-α, IFN-β, and IFNAR1 and of 18S rRNA were measured in adherent and nonadherent PBMC samples from our patient with dermatomyositis and from 2 controls (ABI Prism 7700 Sequence Detection System, Applied Biosystems). The PCR was performed (TaqMan Universal PCR MasterMix, Applied Biosystems) using the following conditions: 2 minutes at 50°C and 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Dilution experiments were performed to ensure similar efficiency of the PCR. The relative expression levels of MxA, ISG15, IFN-α, IFN-β, and IFNAR1 were calculated according to the 2−ΔΔCt method. Briefly, the cycle threshold (Ct) values of triplicate real-time PCR reactions were averaged for each gene in each complementary DNA sample. For each sample assayed, the mean Ct value for the gene of interest was subtracted from the mean Ct value of 18S rRNA to obtain the ΔCt value. The ΔΔCt value was calculated by subtracting the mean ΔCt calibrator values from the ΔCt sample values. The relative quantification was then calculated by $2^{-ΔΔCt}$. The mRNA quantity for the calibrator is expressed as the $1 \times$ sample, and all other quantities are expressed as a number of fold differences relative to the calibrator. The mean ΔCt of the normal adherent sample without IFN-β was used as the calibrator for the adherent samples, and likewise the mean ΔCt of the normal nonadherent sample without IFN-β was used as the calibrator for the nonadherent samples. The standard deviation values for ΔΔCt were added to, or subtracted from, the ΔΔCt to generate the upper and lower standard deviation boundaries. To generate error bars, these ΔΔCt values were then transformed $(2^{-ΔΔCt/s})$, where s is the standard deviation of the ΔΔCt value.
RESULTS

MxA STAINING IS ENHANCED DURING INTERFERON BETA TREATMENT

Cutaneous type I IFN signaling was evaluated by immunofluorescence staining using a monoclonal antibody against MxA, an IFN-α– or IFN-β–inducible intracellular protein that is well established as a specific marker for IFN-α or IFN-β production and signaling.7,10,20,21 Biopsy specimens obtained from our patient at day 2 and day 19 following interferon beta treatment (Figure 2B) were examined for the presence of MxA using confocal laser scanning microscopy. At 2 days after interferon beta treatment, just before the patient’s first admission, the epidermal staining pattern for MxA was strongly positive (Figure 3B). In contrast, MxA staining was markedly diminished (comparable to normal skin [A]) 19 days following the discontinuation of interferon beta and the beginning of clinical treatment (C). Discoid lupus erythematosus (positive control). The MxA staining is specific, as staining of discoid lupus erythematosus with fluorescent secondary antibody with (E) and without (F) isotype control is negative. All samples are counterstained with the nuclear stain Draq5 (red).

INTERFERON BETA–INDUCED GENE EXPRESSION IS ENHANCED IN DERMATOMYOSITIS CELLS VS NORMAL NONADHERENT (LYMPHOID) CELLS

As a surrogate approach to confirm that our patient was indeed reacting to interferon beta, we examined the effect of in vitro interferon beta exposure on PBMCs isolated from the patient’s blood and compared it with that of healthy controls. Blood samples were obtained from our patient while receiving treatment (prednisone and methotrexate) and 32 days following readmission (33 days after interferon beta administration [Figure 2B]). The iso-

Figure 3. Skin biopsy specimens showing Myxovirus-resistance protein A (MxA) immunofluorescence staining. A-C, Epidermal MxA staining (green) is strongly positive 2 days after interferon beta treatment in our patient with dermatomyositis (B), while MxA staining is markedly diminished (comparable to normal skin [A]) 19 days following the discontinuation of interferon beta and the beginning of clinical treatment (C). D, Discoid lupus erythematosus (positive control). The MxA staining is specific, as staining of discoid lupus erythematosus with fluorescent secondary antibody with (E) and without (F) isotype control is negative. All samples are counterstained with the nuclear stain Draq5 (red).
lated PBMCs were rested overnight and were then incubated for 24 hours in the presence or absence of interferon beta (100 IU/mL). The cells were then fractionated into nonadherent (lymphoid) and adherent (dendritic) cell populations before RNA extraction for gene expression analysis.

Type 1 IFN signaling was assessed by examining the levels of 2 signature IFN-induced genes, MxA and ISG15, both of which have been shown to be upregulated in dermatomyositis and in SLE.3,6,23-25 Relative fold expressions of MxA and ISG15 were determined using real-time PCR (Figure 4). Whereas the mean (SD) interferon beta–induced MxA expression in normal PBMCs was 121 (24) fold, lymphoid cells obtained from our patient with dermatomyositis induced MxA to 354 (42) fold (an increase of 2.9 times). Similar hypersensitivity to IFN-β was seen in dermatomyositis lymphoid cells for ISG15 (mean [SD], 539 [198] fold increase vs 2001 [221] fold increase in lymphoid cells from our patient) (an increase of 3.7 times). This differential gene expression was observed only in nonadherent (lymphoid) cell populations.

The finding of an enhanced type I IFN signaling pattern in our patient with dermatomyositis was notable. Therefore, we decided next to investigate whether this could be explained by changes in type I IFN receptor expression or whether this reflected increased endogenous IFN-α or IFN-β production.

IFNAR1 GENE EXPRESSION IS CONSTITUTIVELY ENHANCED IN NONADHERENT (LYMPHOID) DERMATOMYOSITIS CELLS VS CONTROL CELLS

The type 1 IFN receptor is a heterodimer consisting of IFNAR1 α chains and IFNAR2 β chains.26 Because the IFNAR1 chain is required for signal transduction by all type I IFNs,26,27 we examined the relative expression of IFNAR1 using real-time PCR (Figure 5). Constitutively elevated IFNAR1 levels in the nonadherent (lymphoid) PBMC population isolated from the patient with dermatomyositis (mean [SD], 4.5 [0.6] fold increase) were observed, which remained elevated (4.7 [0.5] fold increase) following interferon beta stimulation. In contrast, lymphoid cells from control subjects demonstrated modestly increased IFNAR1 levels (mean [SD], 1.9 [0.4] fold increase) on stimulation.

Figure 4. Interferon beta–induced gene expression (MxA and ISG15) in dermatomyositis vs normal nonadherent (lymphoid) cells using real-time polymerase chain reaction. Interferon beta induced a mean (SD) 354 (42)–fold increase in MxA in lymphoid cells from our patient compared with a 121 (24)–fold increase in normal lymphoid cells (an increase of 2.9 times). Similar hypersensitivity is seen for ISG15 (mean [SD], 539 [198]–fold increase in normal lymphoid cells vs 2001 [221]–fold increase in lymphoid cells from our patient) (an increase of 3.7 times). This differential gene expression was observed only in nonadherent (lymphoid) cell populations.

Figure 5. Relative expression of IFNAR1 determined using real-time polymerase chain reaction. Constitutively high IFNAR1 levels (mean [SD], 4.5 [0.6]–fold increase) are seen in nonadherent (lymphoid) cells isolated from the patient with dermatomyositis. This level was sustained (mean [SD], 4.7 [0.5]–fold increase) following interferon beta stimulation. In contrast, lymphoid cells from control subjects demonstrate modestly increased IFNAR1 levels (mean [SD], 1.9 [0.4]–fold increase) on stimulation.
Dermatomyositis

Relative expression of IFN-α or IFN-β was determined using real-time PCR (Figure 6). Adherent (dendritic) cells isolated from our patient with dermatomyositis exhibited higher baseline mRNA levels of IFN-α and IFN-β (mean [SD], 6.7 [0.4] and 6.4 [0.1] fold increases, respectively) compared with those of controls. The levels of IFN-α or IFN-β expression were not modulated by the addition of interferon beta in vitro, suggesting that a positive feedback mechanism may not be responsible for this observation.

**BASELINE IFN-α OR IFN-β GENE EXPRESSION IS CONSTITUTIVELY ELEVATED IN ADHERENT (DENDRITIC) DERMATOMYOSITIS CELLS VS CONTROL CELLS**

Advances in the development and use of therapeutic biological agents have led to new understanding of disease pathomechanisms. Biological agents such as anti–tumor necrosis factor have induced perturbations in immunomodulatory pathways, resulting in induction or exacerbation of autoimmune diseases such as psoriasis and lupuslike syndrome. In these studies, disease development was attributed to the overexpression of type I IFNs. Type I IFN–induced autoimmune disease is well documented.

The pathogenesis of dermatomyositis has been linked to type I IFNs as demonstrated by recent studies. Dermatomyositis lesional skin and muscle have been shown to contain large numbers of type I IFN–producing plasmacytoid dendritic cells and to express the type I IFN marker gene MxA and elevated levels of the IFN-inducible protein 10–CXCL10. Together, these signals are thought to recruit lymphocytes bearing the IFN-inducible protein 10–CXCL10 ligand CXCR3.

In this article, we describe a patient having MS treated with interferon beta-1a (30 µg [6M IU]) intramuscularly once a week who developed classic and severe dermatomyositis. The history of this patient did not reveal any predisposition to immune-mediated dysfunction other than his original MS diagnosis, and the patient did not report any additional confounding immunologic disorders. The interval between the onset of interferon beta therapy and the occurrence of dermatomyositis was 5 years. This is in keeping with the variable onset of autoimmune diseases described in the literature (ranging from weeks to years) in patients receiving type I interferon therapy. For example, a case report described the onset of SLE in a patient with MS 3 years after initiating interferon beta treatment. The reason for the delayed onset of signs and symptoms is unclear. Because SLE and dermatomyositis are complex diseases thought to have environmental and genetic triggers, the combined exposure to interferon beta together with genetic susceptibility may trigger disease in certain predisposed patients.

The clinical exacerbation, which correlated with elevated creatine kinase and liver enzyme levels in our patient, peaked within 48 hours following each interferon beta injection (Figure 2B). The pharmacokinetics of interferon beta-1a from findings in healthy subjects demonstrate that serum levels peak 3 to 15 hours after a single intramuscular dose and then decline at a rate consistent with a 10-hour elimination half-life. More biologically relevant marker of interferon beta activity is the measurement of MxA mRNA levels after interferon beta injection. Investigators examining MxA gene expression levels in PBMCs of 62 patients having MS treated with intramuscular injections of interferon beta-1a (30 µg/wk) reported the lowest levels of MxA on the day of the injection (day 1), followed by a subsequent peak at 12 hours (day 2), and then a gradual decline during the following 3 days. Based on this information, our observations regarding clinical exacerbation on 2 separate occasions occurring approximately within 48 hours after interferon beta injections (Figure 2B) are in keeping with the pharmacokinetics and reported biological activity of...
the drug, further supporting a causal role for interferon beta in our patient’s disease.

Elevated levels of MxA (Figure 3) in the skin of our patient having dermatomyositis obtained within 48 hours after interferon beta injection may be attributed directly to the interferon beta therapy. However, given that dermatomyositis skin and muscle have previously demonstrated increased levels of MxA, one could argue that the cutaneous increase in MxA may also reflect disease activity, irrespective of interferon beta treatment, and that decreased MxA expression (Figure 3) may reflect clinical improvement secondary to therapy with intravenous immunoglobulin and systemic corticosteroids for our patient’s dermatomyositis symptoms (Figure 2B).

A recent article by Baechler et al describes a potential IFN signature in PBMCs of patients with dermatomyositis that seems to correlate with disease activity. To determine if PBMCs from our patient also expressed genes in common with this signature, we examined the effects of interferon beta on MxA, ISG15, IFNAR1, IFN-α, and IFN-β expression levels. We demonstrated hypersensitivity to interferon beta in dermatomyositis nonadherent (lymphoid) cells (approximately 3- to 4-fold increase in MxA and ISG15 mRNA expression over normal) (Figure 4), which seemed to correlate with constitutively increased expression of IFNAR1 (approximately 5-fold increase over normal) (Figure 5). We also found constitutively increased gene expression of IFN-α and IFN-β in the adherent (dendritic) cells (approximately 6- to 7-fold increase over normal) (Figure 6). Despite clinical improvement and while the patient was being treated with intravenous immunoglobulin, methotrexate, and corticosteroids (Figure 2B), the increased baseline was maintained. Our observation of increased levels of IFN-responsive genes in lymphoid cells is in agreement with recent evidence demonstrating increased responsiveness of psoriatic T cells to IFN-α. However, in the case of psoriatic T cells, this increased signaling was identified at the level of signal transducers and activators of transcription (STAT) activation. This finding is notable given that psoriasis has been reported to be induced or aggravated by interferon alfa. Interferon pathway activation in patients with dermatomyositis has been previously demonstrated and recent studies showing PBMC IFN signature has led to speculation that patients with dermatomyositis may be primed to respond through increased levels of functional IFN receptor or increased downstream (JAK-STAT) signaling pathways and that signaling may be promoted by the enhanced release of endogenous IFN-α or IFN-β. In our patient, we observed increased basal expression of IFN-α or IFN-β in adherent PBMCs, as well as increased basal expression of the type 1 IFN receptor gene IFNAR1 in nonadherent PBMCs. Whether these changes are unique to our patient, intrinsic to dermatomyositis, or a result of previous interferon therapy is unclear. Furthermore, given the observation of plasmacytoid dendritic cells in skin and muscle of patients with SLE and dermatomyositis, our adherent PBMC population with elevated baseline IFN-α and IFN-β levels may represent this population of plasmacytoid dendritic cells. These cells may have the potential for producing high levels of endogenous type 1 IFNs. Taken together, our results provide further support for the potential mechanism of IFN-response genes associated with the development of hypersensitivity to type 1 IFNs. Our clinical observation of dermatomyositis exacerbation and induction following interferon beta treatment, together with the results from our in vitro studies, suggests that the symptoms seen in our patient are associated with interferon beta treatment and subsequent signaling.

To our knowledge, ours is the first case report of dermatomyositis exacerbated or induced by interferon beta therapy and extends the spectrum of autoimmune disorders induced by interferon beta therapy. Our findings implicate interferon beta in the pathogenesis of dermatomyositis but, in keeping with the central role for type 1 IFNs in the disease process, cannot be generalized to all patients with dermatomyositis. However, our findings support other evidence on IFN signatures associated with dermatomyositis and may serve as a springboard for future investigations that delineate further the gene profiles of dermatomyositis and other autoimmune diseases. In the meantime, clinicians should be alert to possible induction of dermatomyositis in their patients receiving interferon-based therapies or with the use of immunomodulators known to induce type 1 IFN signaling.

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Correspondence: Ally-Khan Somani, MD, PhD, Dermatology and Plastic Surgery Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (somania@ccf.org).

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REFERENCES


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19. Applied Biosystems PE.


25. Bennett L, Palucka AK, Arce E, et al. Interferon and granulopoiesis signatures in


receptor into mouse cells: cloning and expression of its cDNA. Cell. 1990;50

(2):225-234.

27. Novick D, Cohen B, Rubinstein M. The human interferon α/β receptor: charac-


28. de Gannes GC, Ghoreishi M, Pope J, et al. Psoriasis and pustular dermatitis trig-

gered by TNF-α inhibitors in patients with rheumatologic conditions. Arch Dermatol.


29. Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of

TNF and IFN-α in autoimmune diseases. Proc Natl Acad Sci U S A. 2005;102

(9):3372-3377.

30. Wells J, Kossard S, McGrath M. Abdominal wall ulceration and mucinosis sec-


46(3):202-204.

31. Pachman LM. Juvenile dermatomyositis: immunogenetics, pathophysiology, and

32. O'Connor KA, Abbott KA, Sabin B, Kuroda M, Pachman LM. MxA gene expres-

sion in juvenile dermatomyositis peripheral blood mononuclear cells: associa-

33. De Paeppe B, De Keyser KK, Martin JJ, De Bleeker JL. Alpha-chemokine recep-
tors CXCR1-3 and their ligands in idiopathic inflammatory myopathies. Acta


patients with multiple sclerosis is affected by treatment regimen and neutralis-

36. Wenzel J, Scheler M, Bieber T, Tüting T. Evidence for a role of type I interferons


37. Eriksson KW, Lovato P, Skov L, et al. Increased sensitivity to interferon-α in pso-


38. Gota C, Calabrese L. Induction of clinical autoimmune disease by therapeutic


responsiveness to human IFN-β1a. J Interferon Cytokine Res. 2002;22(4):

491-501.

40. Liu YJ. IPC: professional type 1 interferon–producing cells and plasmacytoid den-


and activation of plasmacytoid dendritic cells following imiquimod treatment.


42. Wenzel J, Uerlich M, Haller O, Bieber T, Tüting T. Enhanced type I interferon

signaling and recruitment of chemokine receptor CXCR3–expressing lympho-

cytes into the skin following treatment with the TLR7-agonist imiquimod. J Cut-