ONLINE FIRST

Double Trouble

Therapeutic Challenges in Patients With Both Juvenile Dermatomyositis and Psoriasis

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Background: Juvenile dermatomyositis (JDM) and psoriasis are inflammatory disorders that share interferon-α induced responses and dysregulation of cytokines, including tumor necrosis factor alpha. Although 13% of patients with JDM have a family history of psoriasis there is little information concerning children with JDM and psoriasis.

Observations: We identified 3 children with both JDM and psoriasis. In 2 cases, psoriatic lesions occurred after the child's JDM symptoms had diminished following effective immunosuppressive therapy (high-dose intermittent intravenous methylprednisolone, methotrexate, and low dose oral corticosteroids). Patient 2, initially diagnosed as having psoriasis, was treated with prednisone and methotrexate but then developed classic JDM, which worsened following use of tumor necrosis factor alpha inhibitor and reduction of prednisone and methotrexate dosage. For each child, their history of JDM complicated the choice of therapy for psoriasis.

Conclusions: Two therapies commonly used to treat psoriasis—phototherapy and tumor necrosis factor-alpha antagonists—must be used with caution in patients with both JDM and psoriasis owing to their potential to exacerbate clinical manifestations of JDM. We discuss the implications affecting treatment of children with these dual diagnoses and consider the pathophysiology linking these 2 conditions.


Juvenile dermatomyositis (JDM) is a vasculopathy associated with proximal muscle weakness and characteristic skin manifestations, including heliotrope sign over the eyelids, often with microvascular dilation, and Gottron's papules over extensor joint surfaces. Although JDM is the most common inflammatory myopathy of childhood, it is classified as a rare disease, with an incidence of 3.2 children per million in the United States. Photosensitivity, particularly to UV-B light, as well as a response to possible microbial antigens and other factors in the environment have all been implicated as potential triggers for development of idiopathic inflammatory myopathy in the setting of a genetically susceptible host. Although the etiology of JDM remains unknown, it is clear that disease pathophysiology involves the exuberant induction of interferon alpha (IFN-α)–induced genes increased serum IFN-α activity early in the disease course, accompanied by localization of both IFN-α–induced proteins and mature plasmacytoid dendritic cells in the diagnostic muscle and skin biopsy specimens of children with untreated JDM. In addition, the inflammatory cytokine, tumor necrosis alpha (TNF-α) contributes to the inflammatory process.

See Practice Gaps at end of article

Psoriasis in childhood often occurs in the setting of a positive familial history and is an inflammatory disorder that primarily affects the skin. It is a disease of keratinocyte hyperproliferation typically characterized by well-defined erythematous papules and plaques with silvery scale. The true incidence of childhood psoriasis is unknown; however, psoriasis prevalence is estimated at 2.2% in the United States, and 31.5% of patients experience disease onset before age 16 years. As in JDM, despite many hypotheses, no specific etiology has been identified, and, similar to JDM, IFN-α has been implicated in psoriasis disease pathophysiology in association with activation of plasmacytoid dendritic cells. Review of over 304 cases of children with definite or probable JDM at our center has shown that approximately 13% of patients with JDM also have a family history of psoriasis by self-report, but review of the literature re-
Table. Clinical Laboratory Information at Time of Juvenile Dermatomyositis (JDM) and Psoriasis Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>White</td>
<td>White/Native American</td>
<td>White</td>
</tr>
<tr>
<td>At JDM diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUD, mo</td>
<td>5</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>JDM onset age, y</td>
<td>8</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>JDM heliotrope sign</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>and Gottron’s papules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CMAS score</td>
<td>NA</td>
<td>46/52</td>
<td>38/52</td>
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<tr>
<td>Elevated muscle enzymes</td>
<td>2/4</td>
<td>2/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Muscle biopsy findings</td>
<td>+</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>MRI</td>
<td>+</td>
<td>–</td>
<td>+, Minimal</td>
</tr>
<tr>
<td>FHx of AI in first-degree relative</td>
<td>Psoriasis</td>
<td>None</td>
<td>HThy</td>
</tr>
<tr>
<td>Characteristic NFC changes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Medications prescribed</td>
<td>Oral prednisone, IV methylprednisolone, methotrexate, mycophenolate mofetil</td>
<td>Oral prednisone, IV methylprednisolone, methotrexate</td>
<td></td>
</tr>
<tr>
<td>At psoriasis diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at psoriasis onset, y</td>
<td>18</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Skin biopsy specimen positive for psoriasis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Medications prescribed</td>
<td>Methotrexate</td>
<td>Topical: fluorocaine acetonide, clotrimazole propionate, fluocinonide, hydrocortisone</td>
<td>Topical: mometasone furoate ointment, alclometasone dipropionate, fluorocinonide solution</td>
</tr>
</tbody>
</table>

Abbreviations: AI, autoimmune disease; CMAS, Childhood Myositis Assessment Scale; DUD, duration of untreated disease; FHx, family history; HThy, hyperthyroidism; IV, intravenous; MRI, magnetic resonance imaging; NA, not available at date of diagnosis; ND, not done; NFC, nail fold capillary changes; +, positive; –, negative.

*Patient 2 was diagnosed as having psoriasis before JDM and was receiving therapy for psoriasis when JDM was diagnosed; a muscle biopsy was not performed prior to referral to Children’s Memorial Hospital (Chicago, Illinois), where findings from a skin biopsy specimen were compatible with diagnoses of both JDM and psoriasis (Figure).

The following 3 case histories were obtained by retrospective medical chart review of children with inflammatory myopathy attending the Juvenile Myositis Clinic, examined by 1 investigator (L.M.P.) at Children’s Memorial Hospital (CMH), Chicago, Illinois, using a standardized database format at the time of diagnosis.

The diagnosis of JDM was made using the criteria of Bohan and Peter in 1975.29 One of the 3 patients (case 1) met at least 3 criteria (plus the cutaneous eruption) of the following major criteria to make a “definite” diagnosis of JDM: (1) symmetric, proximal muscle weakness; (2) positive findings from a muscle biopsy specimen for inflammation; (3) elevated serum skeletal muscle enzyme levels (ie, creatine kinase, aldolase, aspartate aminotransferase, lactate dehydrogenase); (4) positive results from electromyography; and (5) pathognomonic dermatologic features of dermatomyositis (including heliotropic sign, peri-orbital edema, and Gottron’s papules) (Table). In addition, all children had characteristic nail fold capillary changes on microscopy with loss of end row loops and capillary dilation.30,31 Decreased muscle strength and endurance was assessed by the Childhood Myositis Assessment Scale (CMAS)32 in cases 2 and 3 (it was not available when the diagnosis was made in case 1). Two patients (cases 2 and 3) met at least 2 (plus the “characteristic” heliotrope sign and Gottron’s papules) of the diagnostic criteria sufficiently to make a “probable” diagnosis of JDM.

**REPORT OF CASES**

**CASE 1**

An 8-year-old, previously healthy, untreated white girl with a family history of psoriasis and vitiligo presented with symmetrical, proximal muscle weakness and a heliotrope sign. Laboratory data, magnetic resonance imaging (MRI), and MRI-directed biopsy pathology were consistent with JDM. She was treated with intravenous methylprednisolone, 30.0 mg/kg, with a 1-g maximum dosage on several occasions until her muscle enzyme levels normalized, in conjunction with oral prednisone, 0.5 mg/kg/d, and did well, eventually discontinuing all steroid therapy after 2 years of treatment. She remained free of symptoms for 9 years. At age 18 years, she developed a new cutaneous eruption of thick, scaly, erythematous plaques on her legs and elbows. Otherwise, she had no JDM symptoms, evidence of activation on laboratory testing, or arthritis. Findings from a skin biopsy specimen confirmed these new skin lesions as psoriasis, and a trial of methotrexate by mouth was initiated. All of her other indicators of immune activation returned to normal limits. She improved with methotrexate and topical corticosteroids but continues to have significant plaque psoriasis.

**CASE 2**

A 7-year-old, Native American/white girl with a family history of psoriasis was diagnosed as having the cutaneous
manifestations of psoriasis. She was treated with topical agents, including fluocinolone acetonide, clobetasol propionate, fluocinonide, and hydrocortisone, with improvement. She then developed proximal small joint arthritis, which was partially responsive to oral prednisone and subcutaneous methotrexate. Ten months after the onset of her psoriasis cutaneous manifestations, she presented with peri-orbital edema, cutaneous erythema, and vascular changes typical of JDM, proximal muscle weakness, early fatigue, and elevated muscle enzyme levels consistent with a diagnosis of JDM. She was started on treatment with etanercept, but the oral steroid and methotrexate were tapered followed by worsening of her skin and muscle symptoms. She was referred to CMH for further evaluation. At CMH, findings from a skin biopsy specimen then confirmed that the predominant pattern was that of psoriasis, but there was also a concomitant increase in mucin, typical of cutaneous dermatomyositis (Figure). A muscle biopsy was not performed. Etanercept therapy was discontinued; she was given intermittent high-dose intravenous methylprednisolone, 30 mg/kg; low-dose (0.5–mg/kg/d) oral prednisone, and subcutaneous methotrexate, 25 mg/M2; followed by mycophenolate mofetil, 20 mg/kg, divided every 12 hours, and cyclosporine to obtain a therapeutic blood level of 80 to 100 mg/mL with improvement in her symptoms.

CASE 3

A 2-year-old, previously healthy, untreated white girl had an extensive family history of hypothyroidism, as well as systemic lupus erythematosus. She presented with Gottron’s papules on the hands, dilated eyelid capillaries, palatal erythema, and nail fold capillary end row loops, which were both dilated and markedly decreased in number. A diagnosis of JDM was made when these cutaneous manifestations had been present for more than 6 months. The MRI images of the proximal muscles documented minimal involvement, and the CMAS was abnormal for her age. The child was given high-dose, intermittent methylprednisone supplemented with low-dose oral prednisone on the days she did not receive the intermittent methylprednisone, and subcutaneous weekly methotrexate, 25 mg/m2, with gradual tapering of the steroids, once her cutaneous symptoms improved. During this taper, the child developed numerous red, scaly papules and plaques on her scalp, face, chest, back, and legs. Findings from a biopsy of a lesion was diagnostic for psoriasis. She has responded to topical therapies, including mometasone ointment, alclometasone dipropionate ointment, and fluocinonide solution, and the psoriatic lesions have cleared. Currently, all medications have been discontinued and she is symptom free.

COMMENT

Despite the rarity of reports of patients with both dermatomyositis and psoriasis,27,28 we present the cases of 3 children with this dual diagnosis. It is significant that the type 1 interferon pathways are shared by both psoriasis and JDM and with a spectrum of autoimmune diseases.24,31 It is not known if the young age of the children in this report is an added risk factor, in addition to a strong family history that was positive for autoimmune disease, which facilitated the expression of both JDM and psoriasis.

There is ample evidence that TNF-α and interferon α/β (IFN-α/β) may play an important role in the pathogenesis of JDM.5,6,17-20 Patients with JDM have an increased frequency of the A polymorphism at the TNF-α-308 promoter region compared with controls.27 This polymorphism is associated with increased production of TNF-α by peripheral blood mononuclear cells in both the unstimulated and stimulated state, as well as resistance to therapy with resultant disease chronicity.27 Findings from muscle biopsy specimens from adult patients with dermatomyositis showed increased levels of TNF-α and its receptors,18 and TNF-α is produced by the muscle fibers themselves in children with JDM.20 One speculation is that viral or microbial antigen(s) may stimulate an IFN-α/β–induced response, spreading to increase IFN-γ activity, which may be augmented by the local production of TNF-α.20 Though environmental and histocompatibility features seem be associated with JDM susceptibility, the TNF-α-308A polymorphism seems to be associated with disease severity and chronicity.27

The pathogenesis of psoriasis involves many of the same inflammatory pathways as JDM. In psoriasis, the IFN-γ, TNF-α, and IFN-α/β signaling pathways were shown to be activated in the lesions of patients with psoriasis.26,34 In addition, psoriatic lesions contained plasmacytoid dendritic cells expressing high levels of IFN-α.35 These dendritic cells may also induce cytokines interleukin (IL)-23 and IL-20, which can activate T cells and keratinocytes, respectively. An imbalance of these cytokines is believed to disrupt the regulation of keratinocyte proliferation, leading to the hyperproliferation seen in psoriatic lesions.25

As suggested by the shared cytokine pathways in both JDM and psoriasis, there is a great deal of overlap between the treatment options available for these conditions. The topical steroids, systemic methotrexate, and cyclosporine used as successful treatment options for psoriasis36 can also be used effectively in patients with JDM,37 but currently, the usual dosage of these medications differ for JDM and psoriasis. The occurrence of both illnesses with similar path-
ways raises the distinct possibility of developing a single effective regimen for both clinical problems in the future. However, at the moment, there are 2 effective therapeutic approaches, discussed herein, that must be viewed with special consideration when treating patients with both psoriasis and JDM.

Phototherapy is the therapeutic use of UV radiation and is currently an integral treatment option for adult patients with moderate to severe psoriasis, and narrow-band UV-B is well tolerated and effective in the pediatric population as well. A study of 68 pediatric patients with psoriasis showed a response—defined as a greater than 75% improvement in the cutaneous psoriasis—in over 90% of the patients. In another study of 20 children with psoriasis, 80% of patients sustained at least a 50% reduction in their Psoriatic Area Severity Index (PASI) score.

Although phototherapy is generally reserved for older children and adolescents with widespread disease who have failed topical treatments, approximately 8% of children with psoriasis require phototherapy or systemic therapies.

In contrast, children with JDM are advised to practice strict photoprotective behaviors owing to the sunlight's ability to aggravate the cutaneous features of JDM. Patients can experience worsening of their cutaneous inflammation and provocation of new skin lesions with sunlight exposure, particularly to UV-B light. Therefore, they are advised to avoid direct sunlight as well as artificial forms of UV light.

UV-B phototherapy is thus contraindicated in children with dual diagnoses of psoriasis and JDM. Though it is emerging as a useful and well-tolerated treatment for childhood psoriasis, the potentially detrimental effects it may have for those with JDM raise considerable concerns for patients with both diseases.

TNF-α is a proinflammatory cytokine associated with the pathophysiology of many inflammatory conditions, including psoriasis and JDM. Targeting this marker of inflammation, TNF-α antagonists have been used for management of a range of autoimmune diseases. Currently, 3 TNF-α antagonists are available for use in the pediatric population: infliximab, etanercept, and adalimumab.

Infliximab and etanercept have been reported (case reports) as successful therapies for children and adolescents with severe psoriasis. In psoriasis, TNF-α antagonists are used with the observation that elevated levels of serum and lesional TNF-α decrease following clinically effective psoriasis treatment. This suggests that the inflammatory effect of this cytokine is an important key to the progression of the disease, although it is well recognized that in some cases of psoriasis, inhibition of TNF-α is associated with florid disease flares, and in other instances, the development of a spectrum of autoimmune diseases.

Although JDM is an inflammatory process also involving TNF-α, the safety and efficacy of TNF-α antagonists in these patients is questionable. Some case reports have described favorable clinical improvement in adult patients with dermatomyositis who have been treated with TNF-α antagonists; however, there are also patients who showed exacerbation of disease with these agents. In a study of adult patients with refractory myopathies, 2 of 5 patients with polymyositis and 1 of 4 patients with dermatomyositis experienced disease flare with worsening muscle fatigue and increased creatine kinase levels after treatment with infliximab. In addition, in the same study, 2 of 3 patients enrolled in a myositis study who had initial improvement in disease symptoms actually had disease flares when infliximab was used as an extended treatment. In a case series of 5 adult patients with dermatomyositis treated with etanercept, all patients experienced worsening of their disease with muscle weakness and elevation of creatine kinase and lactate dehydrogenase levels.

The mechanism of increased inflammation in some conditions treated with TNF-α antagonists is not established. A cross-regulatory suppression of TNF-α on the production of IFN-α has been proposed, which allows some IFN-α-associated autoimmune disorders to emerge or flare when patients are treated with TNF-α antagonists. Although the mechanism of interaction is not well defined, inhibitors of TNF-α may be useful to control symptoms of psoriasis, once evidence of IFN-α activity has abated. This may be possible because serum IFN-α activity seems to be elevated for a relatively short time when there is active inflammation, but the levels of TNF-α seem to be elevated over time. The use of TNF-α antagonists, such as etanercept, is increasing in frequency in the population of pediatric patients with psoriasis. Clinical studies show efficacy and a relatively safe profile in children with moderate to severe psoriasis. However, owing to the potential for promoting a JDM flare, these TNF-α antagonists should be used with caution in patients with both psoriasis and JDM. Discussion of these therapies emphasizes the complications that may arise when treating patients with both psoriasis and JDM. It is clear that some modalities used to treat one disease may exacerbate the symptoms of the other.

Clinicians who encounter and treat patients with both JDM and psoriasis should be aware of the potential risks associated with the use of UV-B therapy and TNF-α antagonists in these unique cases.

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