A Novel Case of Recalcitrant Juvenile Pityriasis Rubra Pilaris with Response to Bexarotene

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Abstract

Pityriasis rubra pilaris (PRP) is generally treated with single or combination regimens of topical agents, systemic retinoids, methotrexate, biologics, various other immunosuppressant agents, and light therapy; however, cases of PRP that are not amenable to these therapies can be challenging to control. We present the case of a male with biopsy-proven juvenile PRP followed for ten years, with failure to respond to all traditional treatment regimens. Significant improvement in the patient’s cutaneous and rheumatological symptoms occurred when the patient was treated with bexarotene (Targretin®). To our knowledge, this represents the first reported successful treatment of PRP with bexarotene. Thus, treatment with bexarotene may represent a beneficial option for cases of PRP recalcitrant to traditional treatment modalities.

Keywords: Bexarotene; Pityriasis rubra pilaris; Targretin

Abbreviations: PRP: Pityriasis Rubra Pilaris

What’s already known about this topic?

- First-line systemic treatments of pityriasis rubra pilaris (PRP) include retinoids and methotrexate, with various biologics and other immunosuppressants used as second-line regimens. Phototherapy may be used as monotherapy or in combination with these agents.

What does this study add?

- For cases of PRP recalcitrant to traditional therapies, bexarotene (Targretin®) should be considered.

Report of a Case

A 6-year-old Caucasian male presented to our psoriasis clinic with bilateral scaling and fissuring of the palms and soles and a persistent rash involving the elbows, knees, and scalp present for over a year. Prior topical therapies had little effect. The patient reported a strong family history of pityriasis rubra pilaris (PRP) with both his father and grandfather having a history of the disorder. On exam, there was a moderate degree of scaling on the scalp and ears. Follicular erythematous hyperkeratotic papules were noted on the elbows and knees bilaterally. Most prominent was confluent inflammatory hyperkeratosis of the palms and soles bilaterally with fissuring.

Biopsies were performed on lesions of the patient’s right posterior axilla and right knee, confirming a diagnosis of PRP (Figure 1). Over the ensuing years, the patient developed multiple erythrodermic episodes covering major portions of his body surface area.

For many years, the patient had been treated with a multitude of systemic treatments, including isotretinoin, acitretin, methotrexate, cyclosporine, prednisone, etanercept, adalimumab, and efalizumab. All regimens provided only mild relief of cutaneous symptoms. The patient also developed joint pain and stiffness, especially of the fingers, wrists, knees, and ankles. Additionally, the patient was seen by a growth specialist and was shown to have a bone age of seven years when he was eleven years old. The psychological effect of the patient’s unremitting disorder led to development of depression, insomnia, and ultimately, a threatened suicide attempt. After approximately seven years of these multiple failed treatment regimens, the patient was started on bexarotene (Targretin®).

At follow-up after two years of continuous bexarotene treatment, the now 16-year-old patient’s cutaneous condition had improved dramatically. The severity and frequency of erythrodermic flares and joint complaints had decreased. Relative to previous exams, a decrease in hyperkeratosis and scaling of the patient’s scalp were noted. Erythematous plaques with scaling and islets of sparing were noted on the patient’s trunk, back, and upper and lower extremities (Figure 2). There was also a significantly reduced hyperkeratosis of the hands (Figure 3a and Figure 3b) and feet bilaterally, leading to significant improvement in his quality of life relating to daily activities. In addition to these improvements of his PRP signs and symptoms, the patient had...
Pityriasis rubra pilaris (PRP) is a rare inflammatory papulosquamous disorder of unclear etiology [1,2]. PRP occurs in three distinct peaks, during the first decade, second decade, or in adulthood (40-60 years) [1,3]. Most commonly, PRP develops as an acquired disorder [1,3]; however, it has been estimated that, as in our case, 6.5% of PRP cases are due to familial inheritance [1]. The inheritance pattern is generally autosomal dominant with variable expressivity, though an autosomal recessive pattern has also been reported [3].

Various hypotheses explaining the pathophysiology of PRP have been proposed. PRP has been reported in association with various malignancies, immunologic abnormalities, infections, and trauma [1-4]. When associated with such inciting events, PRP may develop because of an abnormal immune response elicited against an antigenic trigger [3,4]. Because of the efficacy of retinoids in treating PRP, vitamin A and retinol binding protein deficiencies have been postulated to play a role in PRP [1,4]. These proposed mechanisms have yet to be validated.

There are well-described characteristic clinical findings of PRP that aid in its diagnosis. Follicular hyperkeratosis with an erythematous background and islands of skin sparing are key features of PRP [1-6]. Follicular keratotic papules have a characteristic “nutmeg grater” roughened surface [1,3] and commonly develop on the trunk, extremities, and dorsa of the fingers. Coalescence of papules may occur, leading to plaques with overlying scale. PRP generally begins on the face and scalp of adults while the lower body is typically involved initially in children [2]. When palms and soles become involved, an orange-red waxy keratoderma is present, oftentimes with associated fissuring. Scaling of the scalp and nail changes are also common in PRP. Rheumatologic associations have been reported with PRP, with seronegative arthritis and dermatomyositis being the most commonly associated disorders [6]. Patients with PRP, especially children, may also experience psychosocial issues because of the stigmatizing nature of their disorder as was seen in our patient.

Histopathology is helpful in confirming a diagnosis of PRP, especially when differentiating from psoriasis. Nonfollicular lesions may demonstrate alternating orthokeratosis and parakeratosis in vertical and horizontal directions (e.g., “checkerboard pattern”), hypergranulosis, thick suprapapillary plates, narrow dermal papillae, broad rete ridges, and sparse lymphocytic perivascular infiltrate [1,4,5]. Follicular lesions also show dilated hair follicles with follicular plugging by cornified cells and irregular acanthosis [1,5]. Parakeratosis may be present on both sides of the plugged follicle, a situation referred to as “shoulder parakeratosis” [2].

PRP has been categorized into six categories by the age of occurrence and clinical presentation, which are summarized in (Table 1). The most common form of PRP, occurring in approximately 55% of affected individuals and presenting with classic clinical findings, is classical adult (type I) PRP. Atypical adult (type II) PRP follows a chronic course and is characterized by ichthyosiform scale of the legs, areas of dermatitis, keratoderma of the palms and soles with lamellated scaling, and areas of alopecia [1,2,4]. Classical juvenile (type III) PRP presents very similarly to type I PRP and generally affects children of five to ten years of age [1,2]. Juvenile circumscribed (type IV) PRP is the most common form of PRP in the juvenile population and presents as discrete areas of follicular hyperkeratosis with keratotic plugging, most often occurring on the knees and elbows [1,2]. Atypical juvenile (type V) PRP is marked by follicular hyperkeratosis and keratotic plugging, most often occurring on the knees and elbows [1,2]. HIV-associated (type VI) PRP can be the initial manifestation of an HIV infection with associated acne conglobata and hidradenitis suppurativa [2]. Inherited forms of PRP are most commonly reported as types II and V PRP; both are atypical in presentation and the only forms of PRP that generally follow a chronic course. Our patient likely falls into the PRP type V classification.

Because of the uncommon nature of PRP and its unknown etiology and spontaneously remitting nature, treatment is largely empiric, with efficacy often difficult to assess. Methotrexate, TNF-α inhibitors, azathiaprine, cyclosporine, systemic corticosteroids, stanozolol (a testosterone-derived anabolic steroid), systemic and additive UV therapy, and various topical applications have shown varying degrees of efficacy in treating PRP, with varying degrees of efficacy in treating PRP.
of efficacy [1,2]. Retinoids, derivatives of vitamin A, affect growth and differentiation of epithelial tissues [2,7] and significantly decrease the hyperkeratosis [2]. Thus, oral retinoids, especially isotretinoin and etretinate, have become the mainstay of PRP treatment.

Retinoids enact their effects by binding to two subfamilies of receptors: retinoid acid receptors (RARs) and retinoid X receptors (RXRs) [7]. There are three subtypes in each subfamily, specifically RARa, RARb, RARg, and RXRa, RXRb, and RXRg [8]. Each retinoid shows specific affinity and activation for the retinoid receptor subtypes, representing receptor-ligand specificity [8]. These receptors homodimerize and bind DNA to affect the function of genes downstream of retinoid acid response elements (RAREs) [7]. Additionally, RXRs have the unique capacity to heterodimerize with other classes of nuclear receptors, including RARs, vitamin D receptor (VDR), thyroid receptor (TR), and peroxisome proliferation activating receptors (PPARs) [8,9]. Therefore, retinoids that bind RXRs, also known as “retinoids,” can affect a variety of cellular pathways.

There are different expression patterns of retinoid receptors throughout the body. In the skin, there are five times as many RXRs as there are RARs [8]. Here, RXRa is the predominant subtype, with RARg also highly expressed [8]. Thus, gene expression resulting from RXRa-RARg heterodimerization is thought to be a major way in which retinoids enact their effects in the skin [8]. Additionally, VDR is also highly expressed in the skin, making RXR-VDR heterodimerization and its effects another important product of retinoid treatment [8].

Bexarotene is a novel synthetic oral retinoid that has been used predominantly for cutaneous T-cell lymphoma and non-small cell lung cancer therapy. Bexarotene differs from older synthetic retinoids, such as isotretinoin and etretinate, which only activate the RAR pathway [7]. Bexarotene is capable of suppressing cell growth through interactions with a multitude of growth-regulatory pathways, activating RXRs as compared to RARs [8]. Therefore, gene expression resulting from RXRa-RARg heterodimerization is thought to be a major way in which bexarotene enacts its effects in the skin [8]. Additionally, VDR is also highly expressed in the skin, making RXR-VDR heterodimerization and its effects another important product of bexarotene treatment [8].

Bexarotene treatment carries a significant potential of developing hyperglyceridemia, hypercholesterolemia, and hypothyroidism [13]. These events can be managed with careful dosing of bexarotene and concomitant treatment with lipid-lowering agents for hypertriglyceridemia and hypercholesterolemia and thyroxine for hypothyroidism [13]. Leukopenia has also been reported more frequently with bexarotene treatment than with other retinoids [14].

Our patient presented with severe, recalcitrant atypical juvenile (type V) PRP of ten years’ duration with associated arthritis. Though no other combinations of various systemic and topical regimens resulted in significant clinical improvement, our patient showed significant improvement in cutaneous, rheumatological, and psychological aspects of the disease after treatment with bexarotene. To our knowledge, no other cases of any form of PRP, with or without associated arthritis, have been treated to date with bexarotene. Considering the aforementioned discussion of its mechanisms of action, it can be concluded that, when compared to older retinoids, bexarotene’s more potent antineoplastic, anti-keratinizing, and anti-inflammatory characteristics make it a more effective option for the treatment of severe cutaneous proliferative and inflammatory rheumatologic symptoms of PRP, as in our patient. This case is presented to highlight that bexarotene has the potential to provide a beneficial therapeutic option for cases of PRP that are chronic in duration, recalcitrant to other systemic medications, or associated with rheumatologic abnormalities.

References

Table 1: Modified Griffiths classification of PRP (adapted from Klein et al. [2] and Chan et al. [3]).

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of onset</th>
<th>Incidence (%)</th>
<th>Clinical manifestations</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (classical adult)</td>
<td>Adult</td>
<td>55</td>
<td>Confluent red-orange plaques with islands of sparing in generalized distribution. Follicular keratotic papules. Waxy palmoplantar keratoderma.</td>
<td>Spontaneous resolution in 80% of cases with 3 years</td>
</tr>
<tr>
<td>II (atypical juvenile)</td>
<td>Adult</td>
<td>5</td>
<td>Ichthyosiform scale in generalized distribution with areas of dermatitis and alopecia. Palmoplantkeratoderma with lamellated scaling.</td>
<td>Chronic course</td>
</tr>
<tr>
<td>III (classical juvenile)</td>
<td>5-10 years</td>
<td>10</td>
<td>Similar to type I.</td>
<td>Most resolve within 1 year</td>
</tr>
<tr>
<td>IV (circumscribed juvenile)</td>
<td>3-10 years</td>
<td>25</td>
<td>Follicular hyperkeratosis, mainly of the knees and elbows. Only type to be localized.</td>
<td>Unclear</td>
</tr>
<tr>
<td>V (atypical juvenile)</td>
<td>0-4 years</td>
<td>5</td>
<td>Follicular hyperkeratosis in generalized distribution.</td>
<td>Chronic course</td>
</tr>
<tr>
<td>VI (HIV-associated)</td>
<td>Variable</td>
<td>Unclear</td>
<td>Similar to type I. Associated with acne conglobata and hidradenitis suppuritiva.</td>
<td>Variable</td>
</tr>
</tbody>
</table>

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