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Case Report

Isotretinoin in Refractory Confluent and Reticulated Papillomatosis (CARP): A Case Series

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Abstract

Importance: Confluent and Reticulated Papillomatosis (CARP) is an uncommon condition that affects young adults and adolescents. Current treatment options have variable results and efficacy, without sustained improvement in some patients.

Objective: To determine whether oral isotretinoin can be an effective treatment for CARP.

Design: Case series of patients with CARP treated with isotretinoin since October 2015.

Setting: Single center outpatient dermatology clinic at an academic medical center.

Participants: Patients seen at our clinic with diagnosis of CARP treated with oral isotretinoin, resulted in 3 patients to review in our study.

Keywords: Keloid; Topical Steroids; Corticosteroids; Hypertrophic Scar; Fibrosis; Wound

Key Points:

Question: What is response to treatment of CARP with systemic isotretinoin?

Findings: In this case series of three patients with CARP, they achieved improvement in symptoms after 2-6 months of oral isotretinoin.

Meaning: Consider the use of systemic isotretinoin in the treatment of CARP for patients with concurrent acne.

Introduction

Confluent and Reticulated Papillomatosis (CARP) is an uncommon dermatosis that occurs during the adolescent and young adult years. The key clinical feature is an asymptomatic rash of hyperpigmented macules and papules which coalesce to form centrally confluent and peripherally reticulated patches and plaques.1 Patients are frequently mis-diagnosed with a common cutaneous fungal infection (tinea versicolor) and ineffectively treated with topical and oral antifungal therapies. In patients correctly diagnosed with CARP, the most common treatment approached is with oral tetracyclines. Other oral antibiotics have also been reported to be effective [2]. Unfortunately, the oral antibiotics can have variable results in some patients highlighting the need for other more definitive treatment options [3,4]. We report three cases of CARP seen at our pediatric dermatology clinic that were unresponsive or refractory to treatment with oral antibiotics and resolved with systemic isotretinoin therapy.

Case Report

Case 1

An obese 15-year-old female presented to clinic with velvety hyperpigmented papules and plaques located in the intramammary region, abdomen, neck, and back. The rash had been present for approximately four years and had been treated unsuccessfully with ketoconazole cream and shampoo. The patient also had moderate-severe acne. She was initially treated with oral

doxycycline 100 mg twice daily, ketoconazole shampoo, and topical lactic acid cream. Her rash did not improve with several weeks of treatment after which the patient stopped taking her doxycycline. She was subsequently initiated on isotretinoin at 40 mg daily. The patient had improvement reported after her second month of isotretinoin, at 80 mg daily. Complete resolution of the plaques was reported at the three-month visit during which time the patient had just completed a month at 120 mg daily (Fig. 1). The patient continued on isotretinoin for twelve months for a cumulative dose of 228 mg/kg and completed her treatment course just prior to submission of this case series.

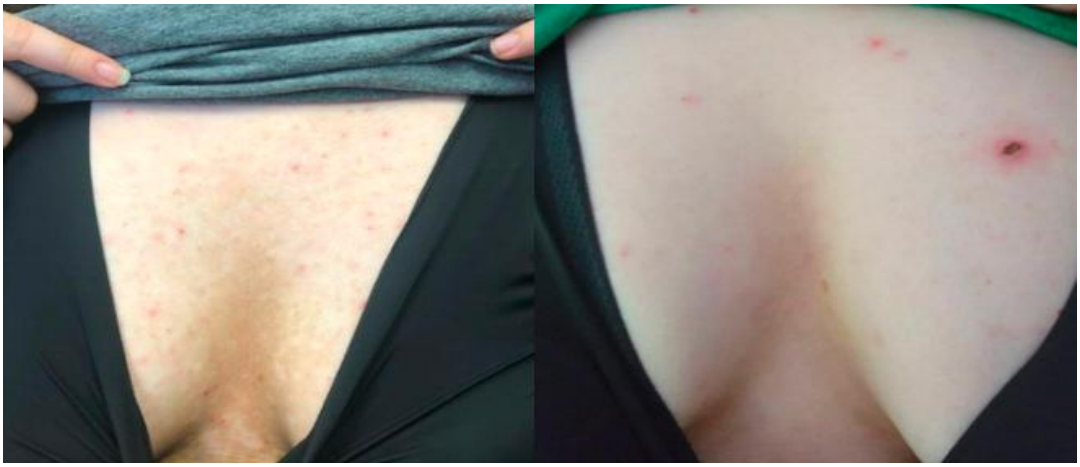

Figure 1: Intra-mammary region in patient with CARP before and after three months of isotretinoin.

Case 2

An obese 12-year-old female was referred to our clinic from an outside practice for centrally confluent hyperpigmented plaques located on the neck, torso, and antecubital fossa with peripheral reticulation. The rash had been present for six months. Prior workup had included a biopsy which confirmed a diagnosis of CARP. The patient had tried oral minocycline 100 mg daily which had some initial improvement but did not completely resolve the eruption. Initially, her dose of oral minocycline increased to 100 mg twice daily. She returned to clinic two years later reporting that the condition had never been fully resolved, with interim thickening and darkening. The patient restarted on oral minocycline again at 100 mg twice daily and her symptoms resolved. The patient returned to clinic two years later, at the age of 15 now with acne and worsening CARP (Fig. 2). At this time, she started systemic isotretinoin at 40 mg daily. Improvement was noted at her one-month visit after initiation of isotretinoin (Fig. 3). The patient remained on isotretinoin for a total of six months with gradual increase to an average of 140 mg daily and completed her course with a cumulative dose of 272 mg/kg. She reported significant improvement and lightning of her rash on her neck and back. She has not returned since completing her isotretinoin course four years ago.

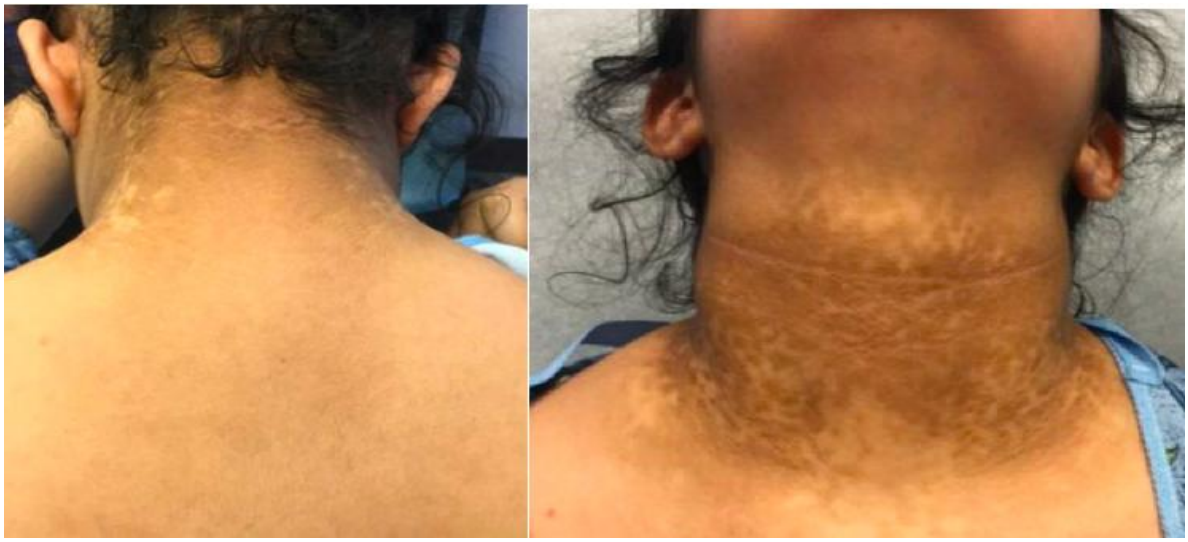

Figure 2: Anterior and posterior neck of patient with CARP following two months of minocycline treatment prior to isotretinoin initiation.

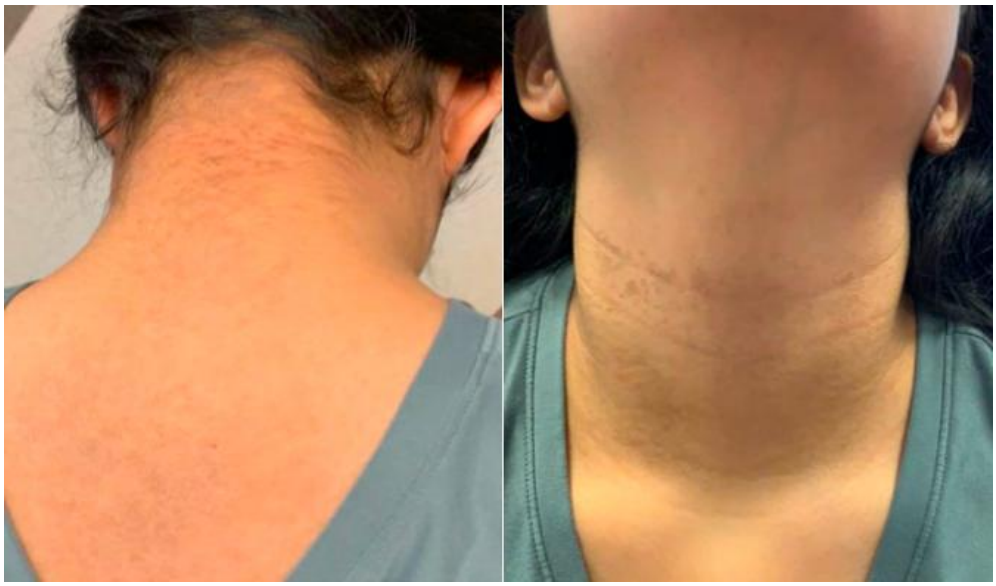

Figure 3: Anterior and posterior neck of patient in Fig. 2 following three months of treatment with isotretinoin.

Case 3

A non-obese 16-year-old female presented with a hyperpigmented macular rash with reticulation and fine scale present on the neck, axilla, and chest. The condition had been present for over five years prior to being seen in our clinic. The patient had previously been diagnosed with tinea versicolor and was treated with ketoconazole cream and shampoo without improvement. The patient was initially treated with minocycline 100 mg twice daily and a glycolic acid wash. The patient's eruption resolved after six weeks of minocycline. However, the hyperpigmented macules recurred several years later at which point she was prescribed doxycycline 100 mg twice daily for concurrent CARP and acne. The patient discontinued doxycycline after two weeks due to side effects and then was started on isotretinoin at 40 mg daily with monthly increase in daily dosage. On her two-month visit after initiating therapy, she was noted to have resolution of her CARP on physical examination at which time she had been taking 80 mg daily. She completed a six-month treatment course for acne reaching a cumulative dose of 252 mg/kg. She has not returned since completing her course two years ago.

Discussion

The pathogenesis of CARP remains uncertain, however composite aggregate data over recent years combined with the effectiveness of certain medications help clinicians hypothesize the underlying pathophysiologic changes that may contribute to this disease process. It has been described as a disorder of abnormal keratinization, with histopathology commonly showing hyperkeratosis. Systematic reviews have shown patients are more likely to be obese and have comorbidities related to insulin resistance such as acanthosis nigricans, polycystic ovarian syndrome, type 2 diabetes mellitus, and precocious puberty, consistent with phenotypes that have been commonly described in individual case studies of patients [4,5]. A more recent study evaluated laboratory values associated with glucose dysmetabolism and found that patients with CARP have notably high serum insulin levels, suggested as an earlier marker of metabolic dysfunction [6]. The strong association described between CARP and concurrent endocrine disorders demonstrates that insulin resistance has a potential role in the etiology of the disease. Elevated insulin levels have been shown to have mitogenic and anti-apoptotic activities on keratinocytes [7,8]. Retinoic acids have long been described in the literature with use for conditions such as ichthyoses, pityriasis rubra pilaris, psoriasis, and Darier's disease [9]. Research suggests retinoic acids bind specific retinoid nuclear receptors leading to the activation or repression of genes responsible for cell differentiation, growth, and apoptosis [10]. The effect of this pathway on keratinocyte differentiation is the proposed mechanism of isotretinoin's efficacy on hyperkeratotic diseases like CARP.

The recent systematic review by Xiao, et al., supports that the most common medications prescribed in current practice remain tetracycline antibiotics, albeit describing high rates of recurrence after initial successful treatment [4]. These antibiotics have the benefit of anti-inflammatory properties in addition to the antibacterial properties that are conventionally attributed to them. Tetracycline medications affect the immune system by inhibiting various molecules that are part of the inflammatory response, notably pro-inflammatory cytokines [11]. Given that many patients experience inconsistent or unsustained results on

tetracycline, retinoic acid can be considered as an alternative option for treatment. Four prior case studies demonstrate patients with successful clearance of their CARP within two to five months using various isotretinoin dosing regimens [12-15].

In our three patients, we observed disease course that was refractory to initial treatment with minocycline or doxycycline. As all of these patients concurrently had acne, it was decided to treat them with isotretinoin at doses typically used for acne vulgaris at our institution. All three patients experienced resolution of their CARP within several months in addition to improvement of their acne. Given these results, we propose that isotretinoin be considered as a treatment for CARP in patients with refractory disease and concurrent acne.

Limitations

Limitations to our observation include lack of long-term outcomes and unknown recurrence rates given the small number of patients, short-term follow-up and sparse literature regarding isotretinoin and CARP.

Conclusion

This case series demonstrates the short-term effectiveness and rapid response of CARP to systemic retinoids and highlights the need for future studies given the lack of treatment options for refractory disease. Providers should strongly consider isotretinoin in patients with recalcitrant CARP.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Contributions

All authors have contributed equally to this work and have reviewed and approved the final manuscript for publication.

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Consent for Publication

Informed consent for publication was obtained from the patient involved in this case report, as documented in the manuscript.

Informed Consent Statement

Informed consent was obtained from the participant involved in this study.

Ethical Statement

Not applicable

Data Availability Statement

Not applicable.

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