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Pyogenic granulomas during isotretinoin therapy

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Abstract

Background: A review of scientific literature reveals a sparse documentation of periungual pyogenic granulomas as an adverse effect of isotretinoin therapy.

Main observations: Periungual pyogenic granulomas appeared in four patients receiving isotretinoin therapy for severe acne. Oral and topical antibiotic treatments were ineffective and all cases spontaneously resolved once isotretinoin is discontinued.

Conclusion: This report demonstrates the idiosyncratic nature of this side effect. We suggest that, although infection is possible due to the transformed nature of the normally protective skin barrier, oral and topical antibiotic treatments appear ineffective. Pyogenic granulomas spontaneously resolve once isotretinoin is discontinued.

Introduction

Isotretinoin is an effective treatment for severe acne. It is known to be associated with numerous cutaneous adverse effects including chelitis, facial dermatitis, xerosis, pruritus, conjunctivitis, and dry nasal mucosa.[1] Pyogenic granulomas (PG) around the nail sulci have been reported as a rare side effect of isotretinoin treatment.[2,3,4] We report on four patients who displayed this infrequent manifestation while taking isotretinoin and discuss the possible pathogenic mechanism.

Case Reports

CASE 1

A 17-year-old male had severe facial acne. He had no other significant medical problems, no pre-existing nail problems, and was taking no other medications. He began isotretinion therapy at a dose of 40 mg daily (0.57 mg/kg/day) for the first month and his dose was later increased to 80 mg daily (1.14 mg/kg/day). He was responsive to treatment and his acne improved. After 3 months, he developed erosive, painful, excess periungual tissue around the fourth finger on the left hand (Fig. 1). There was marked erythema and edema. At this time his cumulative dose was approximately 45 mg/kg. The complication self-resolved by the fifth month while he was still on isotretinoin therapy.

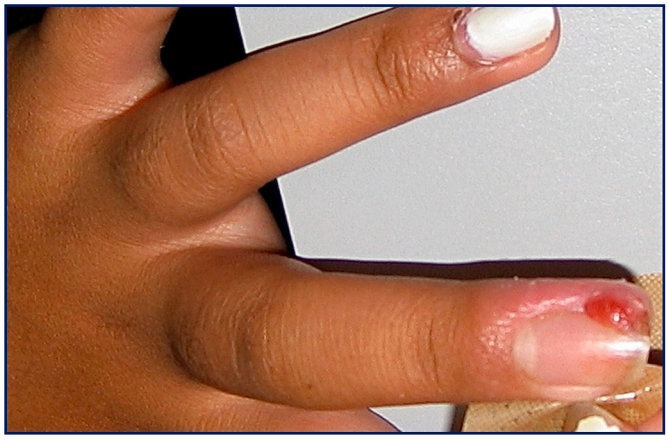

Figure 1

Excess periungual granulation tissue and paronychia located on the left hand, fourth digit of patient #1.

CASE 2

A 16-year-old male had severe acne primarily on his face. He had no other significant medical problems, no pre-existing nail problems, and was taking no other medications. He began isotretinoin therapy at a dose of 40 daily (0.58 mg/kg/day) for the first month, which was increased to 80 mg daily in the second month (1.16 mg/kg/day). He was responsive to treatment and his acne improved. Between 5-6 months of therapy, several fingers became erythematous and edematous. The PGs were tender and had serous discharge but no pus. Based on clinical picture, oral cephalexin and topical ciclopirox olamine were attempted separately, and failed. The isotretinoin dose was decreased to 40 mg daily but the lesion continued to worsen. At a cumulative dose of 140 mg/kg isotretinoin was discontinued. One month later the lesions had improved. Two months later the lesions had resolved.

CASE 3

A healthy 16-year-old male had severe facial acne. He had pre-existing mild eczema for which he intermittently used a mild cortisone cream. He had no prior nail problems. The patient began isotretinoin at a daily dose of 30 mg (0.43 mg/kg/day) for the first month, and was later increased to 60 mg daily (0.86 mg/kg/day). He was responsive to treatment and his acne improved. During the fourth month he complained of excess, erosive periungual tissue on his right great toe that was encroaching upon the nail. There was overgrowth of the lateral nail folds and edema. Initially it was thought to be an ingrown toenail. There was no pus. He was instructed to soak the toe in water and apply topical fusidic acid. The lesion was unresponsive to treatment. Almost two months after isotretinoin was discontinued, some periungual PG persisted. He was told to return in 6 weeks if the lesions were unresolved. He did not follow up; therefore it was assumed that the granulation tissue did resolve after being off isotretinoin therapy for three and a half months.

CASE 4

A 13-year-old female had severe facial acne. She had no other significant medical problems and no pre-existing nail problems. She was not on any other medication. She began isotretinoin at a dose of 30 mg daily (0.44 mg/kg/day) for the first month, and increased to 60 mg daily (0.88 mg/kg/day). Between 2-3 months of treatment, she noticed a lesion on her left third finger (Fig. 2). The PG and paronychia was unresponsive to two topical treatments of silver nitrate and three treatments of cephalexin. Isotretinoin was discontinued at a cumulative dose of 60 mg/kg because of depression secondary to the medication. The lesion began to regress shortly after discontinuation of isotretinoin. Six months later, the lesion had resolved.

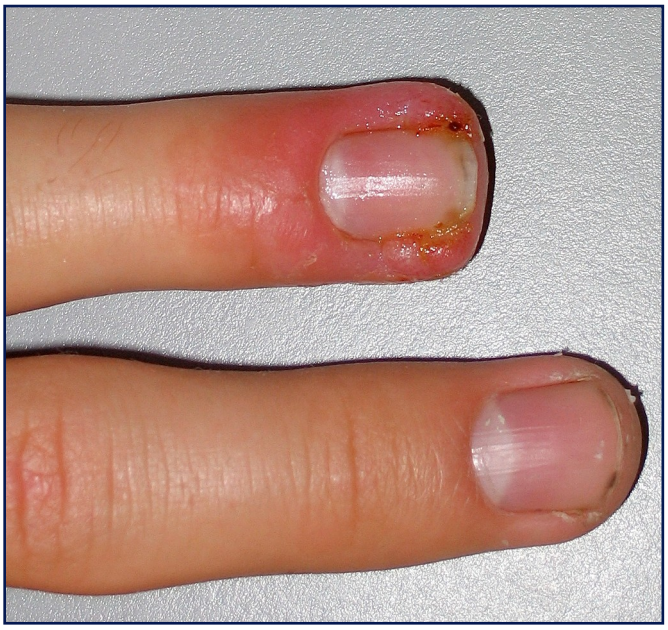

Figure 2

Excess periungual granulation tissue and paronychia located on left hand, third digit of patient #4.

Discussion

Pyogenic granulomas are commonly acquired benign vascular tumors. They frequently involve the periungual tissues. PGs can occur secondarily to acute or chronic trauma, infection, drugs and the hormonal changes of pregnancy.[6] Though systemic retinoids are known to cause PGs, they are uncommonly reported as a side effect of isotretinoin. The cases reported here were collected over 3 years. During this time, the investigating clinician had approximately 50 patients on isotretinoin therapy. In pre-existing literature, the largest series was reported in 1988. It mentioned four cases of paronychia caused by the overgrowth of the distal and lateral nail folds, with associated excess granulation tissues.[2] Multiple fingers were involved in all patients. Rechallenge with isotretinoin led to a secondary flare up in one patient, suggesting causality.[2]

The mechanism by which isotretinoin causes pyogenic granulomas is not known. All patients exhibited associated paronychia; therefore, it was hypothesized that infection may be the cause based on clinical presentation. Swabs were not taken prior to antibiotic therapy, as the diagnosis of infection was a clinical one. The community prevalence of resistant skin bacteria is very low and it was expected that routine antibiotic therapy would suffice for presumed infection. However, three of the patients failed one or more anti bacterial treatments. Blumental[3] also reported non-responsiveness to topical antibiotic ointment. These findings suggest that infection is not the primary problem. It is now believed that the primary problem is the pyogenic granuloma, and infection may or may not co-exist secondarily due to the transformed nature of the normally protective skin barrier. This is supported by the knowledge that isotretinoin is

known to cause exuberant granulation tissue or pyogenic granuloma-like lesions at the sites of acne between the third and twelfth week of therapy.[5,7,8] Therefore, it is reasonable to suggest that isotretinoin may cause excess granulation tissue or pyogenic granulomas at other locations on the body. Furthermore, exuberant periungual granulation tissue of both fingers and toes is a documented side effect of other retinoid therapies. Campbell *et al*[9] reported on six patients who developed this complication while receiving etretinate therapy for psoriasis. These lesions appeared to be idiosyncratic and unrelated to daily dose and total cumulative dose. Similar comments can be made pertaining to our patients who first presented anywhere between 2-6 months of treatment. In general, retinoids are known to decrease the attachments between keratinocytes and cause nail brittleness that allows for fragment penetration between the nail bed and adjacent tissue.[10] Retinoids also promote the early stages of wound healing, cause the accumulation of mononuclear cells in the dermis, and stimulate collagen synthesis. Some or all of these factors combined may increase an individual's susceptibility to the growth of excess periungual granulation tissue.[9]

A 2-3 week course of topical steroid under occlusion and topical antibiotic is one first-line treatment for periungual pyogenic granulomas suggested in the literature.[6] Topical antibiotic helps prevent any secondary infection. In cases where topical treatment was insufficient, surgical curettage was preformed under local anaesthetic.[6]

Conclusions

Knowledge of this uncommon side effect is important for clinicians managing patients on isotretinoin. It appears that discontinuing isotretinoin therapy is not necessary for lesion resolution, as Case 1 spontaneously resolved prior to discontinuation. Therefore patients should carefully weigh the benefits and disadvantages of discontinuing therapy for this problem. Consideration should be given to topical steroids with possible addition of antibiotics as a therapy option.

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