Acitretin-induced periungual pyogenic granulomas and review

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Abstract

Periungual pyogenic granulomas are benign vascular tumors that present as painful, round, spontaneously bleeding lesions composed of rapidly proliferating capillaries and excess tissue. The vast majority of pyogenic granulomas are caused by physical trauma or infectious agents and they may resolve spontaneously. Herein, we highlight a very rare case of periungual pyogenic granulomas induced by the regularly prescribed oral retinoid acitretin during treatment for congenital palmoplantar keratoderma. This unique case showed that it is feasible to continue acitretin therapy in the presence of pyogenic granuloma development if proper dose reduction and topical therapies are utilized. The patient's lesions resolved within two weeks of this protocol's initiation and the pyogenic granulomas did not recur over the course of a six-month follow-up observation period. In addition, we performed a systematic review of the literature using PubMed databases for the clinical features and treatments in other reported acitretin-induced pyogenic granuloma cases; we compiled a comprehensive list of other prescription drugs known to cause pyogenic granulomas up-to-date.

Keywords: acitretin, oral retinoids, periungual pyogenic granulomas, palmoplantar keratoderma

Introduction

Pyogenic granulomas (PG) are proliferating vascular nodules that can arise on the skin and may spontaneously bleed because of the presence of a thin overlying epidermis. These lesions are composed of rapidly growing capillaries and vascular tissue and can be caused by physical trauma or infection with the outgrowth of PG representing a vascular and fibrous response. However, it is also known that pyogenic granulomas may be rarely induced as a side effect of oral retinoids, which is significant for physician awareness since PG can visually resemble malignant melanomas [1]. Acitretin is a common oral retinoid prescribed for the treatment of psoriasis, ichthyoses, and palmoplantar keratoderma which functions by exerting anti-inflammatory and anti-proliferative effects to normalize keratinocyte differentiation [2]. The development of PG after the initiation of oral retinoids including acitretin has been sparsely reported in the literature. In most cases the complete discontinuation of retinoid therapy was recommended and summaries offered limited information on alternative treatment options. Herein, we report an unusual case of biopsy-proven acitretin-induced periungual pyogenic granulomas in a man being treated for palmoplantar keratoderma. We show that acitretin therapy may be successfully continued in the setting of the development of PG if dosage modification and topical ointment therapies are implemented as treatment options.

Case Synopsis

A 30-year-old man with a lifelong history of bilateral palmoplantar keratoderma on oral acitretin presented with sudden-onset of painful skin lesions

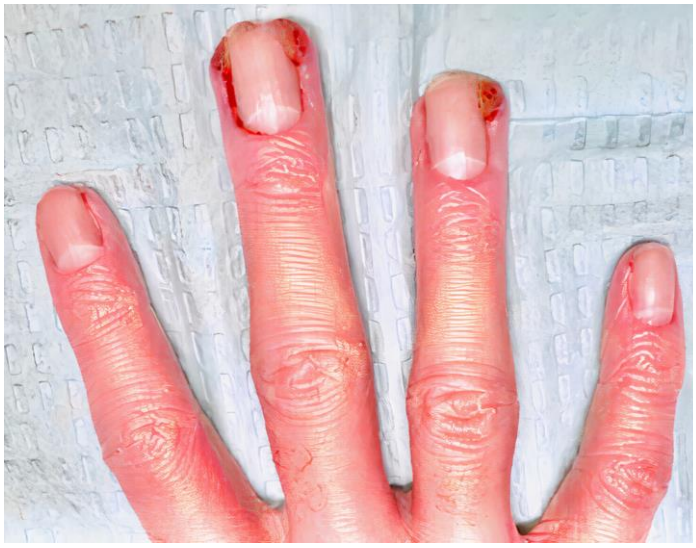

Figure 1. *Close up image of the spontaneously hemorrhaging periungual pyogenic granuloma papules on the lateral nail folds of patient's right middle and ring fingers.*

on the lateral nail folds of his right middle and ring fingers. The patient had been slowly titrated to 50mg of acitretin daily over the course of several months with significant improvement of his keratoderma and had no family history of adverse reactions to oral retinoids. He had not experienced any trauma to the region and did not perform trauma-inducing behaviors such as nail-biting that could have affected his fingers.

On physical examination, the patient had red raspberry-like papules on the lateral nail folds of several fingers that bled spontaneously (**Figure 1**) and the surface epidermal layers appeared to be necrotizing. The patient's toes were also examined and showed signs of early-stage PG development that were less severe than the fingers. Biopsy of all fingernail PG lesions was performed for diagnosis and debulking purposes; this revealed a negative gram stain and an ulcerated vascular proliferation composed of lobules of capillary-sized vessels and mixed inflammation (**Figure 2**). Based on the results of the clinical examination and biopsy findings, a diagnosis of acitretin-induced periungual pyogenic granulomas was made.

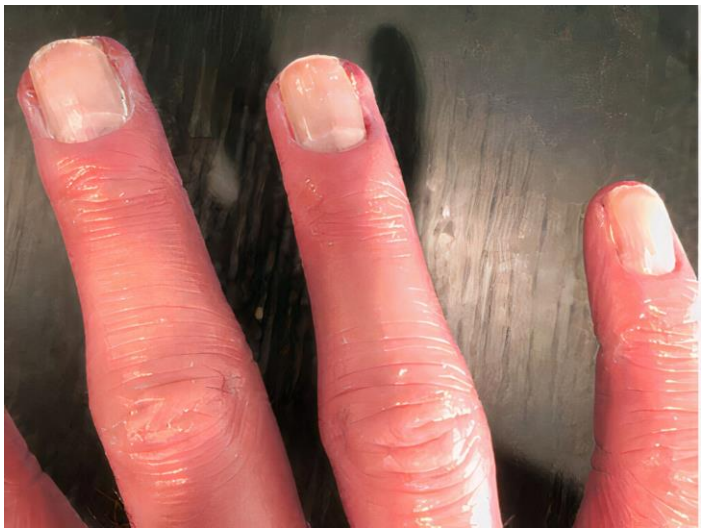

Figure 2. *Improvement of the periungual pyogenic granuloma lesions at follow-up two weeks after treatment.*

The patient was recommended to lower his dose to 35mg daily and undergo shave biopsies with daily applications of topical mupirocin in the morning and topical clobetasol ointment nightly. At follow-up two weeks later, the patient had achieved resolution of all lesions and continued improvement of his palmoplantar keratoderma condition (**Figure 3**). After six months of routine follow-up visits, there were no reported or observed intermediate relapses of newly formed pyogenic granulomas.

Case Discussion

Pyogenic granulomas (PG) are generally benign vascular tumors that typically present as smooth

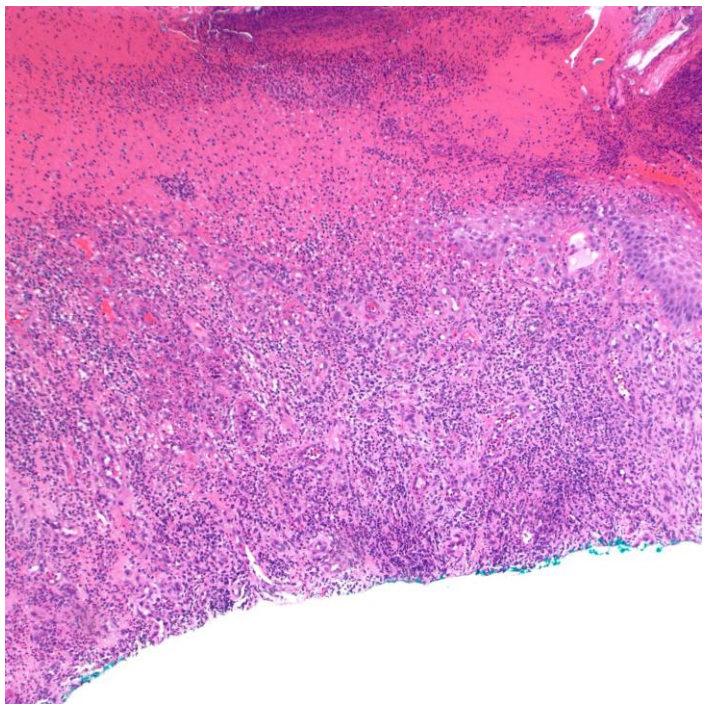

Figure 3. *Periungual pyogenic granuloma histopathology of patient showing lobules of capillary-sized vessels and dense mixed inflammation with surface epidermal necrosis. H&E, 100×.*

papules consisting of excess granulation tissue [3]. These lesions can form spontaneously, as a result of injury or infection, and as a consequence of vascular malformation. Albeit rare, there are several classes of medications that are known to induce PG development as a very uncommon side effect including oral retinoids [4,5]. A systematic review of PubMed databases for drug-induced pyogenic granuloma cases yielded six common classes of medications as potential etiologies of PG (**Table 1**). It is important for physicians to be reminded of the potential rare risk of PG development when prescribing these common medications and a thorough patient history of previous drug-induced pyogenic granulomas should be performed before requesting the prescription. The clinical treatment findings in this study may also be applicable in the situation of pyogenic granuloma development while taking these more common prescriptions in **Table 1**, such that the patient would be able to continue benefitting from the therapy at lower doses without discontinuation. However, future studies are needed to examine this potential outcome across the various classes of medications.

Although periugual pyogenic granuloma development on acitretin has been rarely documented, similar medications including isotretinoin are more well-known to induce PG-like lesions as a potentially severe side effect [3]. However, the mechanism of isotretinoin-induced PG-like lesions is poorly understood and this phenomenon may also be underreported in the literature [3,5]. It is believed that pyogenic granuloma reactions on certain oral retinoids including acitretin may have been more commonly observed by physicians in the past especially in trauma-impacted areas such as the shin, which may have led to an underreporting of this phenomenon in the literature.

The most widely accepted mechanism underlying PG development during retinoid treatment is that systemic acitretin therapy can result in similar outcomes as hypervitaminosis A by inducing onycholysis and desquamation of the lateral nail folds followed by a localized foreign body vascularization reaction [3,6,7]. Retinoids also decrease inter-keratinocyte attachment and can induce nail brittleness, increasing the susceptibility of tissue penetration through the nail folds which contributes to the formation of excess granulation tissue in PG [5]. There is no clear predominance of specific age or gender cohorts being more vulnerable to the development of PG in oral retinoid patients [4].

Despite the common usage of acitretin for several distinct skin disorders, very few cases of acitretin-induced pyogenic granulomas have been documented in the literature with the majority of cases being associated with non-periungual regions

Table 1. *Drug-induced etiologies of pyogenic granulomas reported in the literature.*

Class of drugs	Specific drugs capable of inducing pyogenic granulomas	Reference
Cancer therapeutics	**Chemotherapy:** 5-fluorouracil, capecitabine, docetaxel, mitoxantrone, paclitaxel, panitumumab, imatinib **EGFR inhibitors:** cetuximab, gefitinib **Cancer antibody treatments:** rituximab, anti-CD20 **BRAF inhibitors, mTOR inhibitors**	[6] [13] [14] [15] [19]
Antiretrovirals	Indinavir, lamivudine	[6] [19]
Retinoids–oral and topical	**Oral:** isotretinoin, etretinate, acitretin **Topical:** retinoic acid, tretinoin, tazarotene	[6] [19]
Immunosuppressants	Cyclosporine	[6] [19]
Hormones	Erythropoietin, levothyroxine, hormonal contraceptives	[14] [16] [17]
Anticonvulsants	Carbamazepine	[18]

[7,8]. A systematic review of the literature for cases of acitretin-induced PG using PubMed databases resulted in only six peer-reviewed studies. The following table includes the clinical features and treatment methods employed in the patients featured in those studies (**Table 2**). It is important for physicians to familiarize themselves with the range of specific clinical features and descriptions of acitretin-induced pyogenic granulomas reported in the sparse literature since these PG lesions are capable of mimicking Kaposi sarcoma, angiosarcoma, and other primary and metastatic cutaneous tumors, in which case a biopsy and microscopic examination should be used for diagnosis [1,18,20]. Consequently, the clinical features in **Table 2** should serve as a diagnostic supplement and reminder for the potential rare development of pyogenic granulomas on acitretin. Physicians should cautiously diagnose new lesions in patients taking acitretin after careful scrutiny to avoid misdiagnosing between PG and potential tumors.

As evidenced from **Table 2**, typical treatment of PG includes retinoid discontinuation, excision via biopsy or electrodessication, and the use of cryotherapy or ablative lasers. However, this unique case illustrates that acitretin therapy may be continued in the setting of the development of pyogenic granulomas if proper dose reduction and topical ointment therapies are employed. Accordingly, the patient in this case demonstrated rapid and marked improvement of his PG lesions after only two weeks at follow-up using this protocol.

Conclusion

The spontaneous development of pyogenic granulomas related to oral retinoids has been rarely documented in the literature and only limited treatment options for this infrequent side effect have been promulgated. This report presents a healthy 30-year-old man who developed periungual pyogenic granulomas after the initiation of the oral retinoid acitretin and was successfully treated with dosage modification and the application of topical ointments. Physician and patient lesion monitoring will help select the proper dose regimen that produces the desired clinical outcome while concurrently minimizing potential side effects.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 2. *Clinical characteristics and treatment methods of reported patient cases of acitretin-induced pyogenic granulomas.*

Number of Patients Treated	Clinical Features of Individual Patients	Treatment for Individual Patients	Source
5	**Patient 1:** 53-year-old woman treated for psoriasis with 35mg daily acitretin. PG development in lateral nail folds of IRF and IVRF digits. **Patient 2:** 62-year-old man treated for psoriasis with 50mg daily acitretin. PG development in lateral nail folds of IRF and ILF digits. **Patient 3:** 54-year-old-man treated for psoriasis with 35mg daily acitretin. PG development in lateral nail folds of IRT and ILT digits. **Patient 4:** 45-year-old woman treated for nail psoriasis with low-dose 20mg daily acitretin. PG development in lateral nail folds of ILF, IRF, and IIRF digits. **Patient 5:** 67-year-old woman treated for Hallopeau's acrodermatitis with 35mg daily acitretin. PG development in nail bed of IRF and ILF digits.	**Patient 1:** Discontinuation of acitretin and the application of topical steroids. **Patient 2:** Discontinuation of acitretin and the application of topical steroids. **Patient 3:** Discontinuation of acitretin and the application of topical steroids. **Patient 4:** Discontinuation of acitretin and the application of topical steroids. **Patient 5:** Discontinuation of acitretin and the application of topical steroids.	Reference [6] **Study Type:** Retrospective, observational study of all PG cases seen by department in last five years
1	**Patient 1:** 70-year-old man being treated for palmoplantar psoriasis with 25mg daily actiretin. Patient presented with rapidly growing, erythematous, bleeding and raised lesions on the dorsum of the toenail on both first toes. The physical examination demonstrated spontaneously bleeding vascular tissue with friable lateral nail folds on both first toenails. Tumors were noted to spontaneously reoccur even after electrodessication.	**Patient 1:** The complete resolution of patient's acitetin-induced PG was achieved only after the complete discontinuation of the acitretin therapy.	Reference [7] **Study Type:** Case Study
1	**Patient 1:** 22-year-old man being treated for total body epidermolytic hyperkeratosis (EHK) with 50mg daily acitretin. The patient presented with bulbous, erythematous growths in the web space of 4-5 toes.	**Patient 1:** The lesions were removed with saucerization and electrodessication of the web areas.	Reference [9] **Study Type:** Case Study
1	**Patient 1:** 40-year-old man being treated for a medical history of psoriasis with 35mg daily acitretin. The patient presented with painful red spots on the lateral nail folds of his left middle finger that under dermoscopic imaging revealed a red, homogeneous area with white rail lines intersecting the PG.	**Patient 1:** Treatment not disclosed.	Reference [10] **Study Type:** Case Study
2	**Patient 1:** Developed periungual pyogenic granulomas after taking 50mg daily acitretin for moderate to severe psoriasis. **Patient 2:** Developed periungual pyogenic granulomas after taking 50mg daily acitretin for moderate to severe psoriasis.	**Patient 1:** Treatment not disclosed. **Patient 2:** Treatment not disclosed.	Reference [11] **Study Type:** Double-blind, placebo-controlled trial of acitretin in patients with psoriasis
1	**Patient 1:** 92-year-old woman being treated for plaque psoriasis with 10mg daily acitretin.	**Patient 1:** The PG lesions only resolved upon complete	Reference [12]

	The patient presented with friable, painful, rapidly growing red nodules on her right second toe. The patient also independently presented with another PG lesion showing erosion, granulation tissue, and associated edema on her left heel after initial treatment. Histopathology of both lesions showed ulceration and lobular capillary arrangement with mixed tissue inflammation.	discontinuation of the acitretin therapy.	**Study Type:** Case Study
1	**Patient 1:** 30-year-old man being treated for congenital palmoplantar keratoderma with 50mg daily acitretin. The patient developed periungual PG on lateral nail folds of right middle and ring fingers. The papules bled spontaneously and showed surface epidermal necrosis. Histopathology showed ulcerated vascular proliferations of lobule vessels and evident inflammation.	**Patient 1:** The patient was able to spontaneously recover from the PG outbursts via precise dosage reduction and the application of topical mupirocin and clobetasol, which showed that it is plausible to maintain acitretin therapy in the presence of PG development.	Our Case **Study Type:** Case Study

EHK, epidermolytic hyperkeratosis; IIRF, second right finger; ILF, first left finger; ILT, first left toe; IRF, first right finger; IRT, first right toe; IVRF, fourth right finger; PG, pyogenic granuloma(s).