Acne fulminans induced by a low dose isotretinoin: case report and review of the literature

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Abstract
Acne fulminans is a rare complication of classic acne. Less than 200 cases have been reported. It usually affects adolescent males with pre-existing acne vulgaris. It is characterized by an acute eruption of numerous and large inflammatory nodules, plaques, erosions, and ulcers covered by hemorrhagic crusts. The disorder may occur spontaneously or may be triggered by isotretinoin. We report a young boy who developed acne fulminans after isotretinoin therapy at a dose of 0.1mg/kg/day. A systematic literature review gathering previously reported cases on PubMed revealed that one similar case has been reported. Regarding therapeutic strategies, there are no randomized clinical trials to identify the best treatment for acne fulminans. Recommendations are based on case series and case reports. We share this case to raise awareness of the induction of acne fulminans by a very low dose of isotretinoin.

Keywords: acne fulminans, isotretinoin, treatment

Introduction
Acne fulminans (AF), a complication of classic acne, is a rare variant with less than 200 cases reported in the literature [1]. It occurs in adolescents aged 13 to 22 with male predominance, and is more common in the Caucasian race [1,2]. It is characterized by an acute eruption of large, inflammatory nodules and friable plaques with erosions and ulcers, most commonly on the trunk. It may occur spontaneously or may be triggered by isotretinoin therapy [1]. Herein, we present a young boy who developed acne fulminans after a very low dose of isotretinoin.
A proposed classification of acne fulminans divides the condition into four variants: Acne fulminans with/without systemic symptoms and isotretinoin-induced AF with/without systemic symptoms [1]. Fever, malaise, arthralgia, bone pain, erythema nodosum, and painful splenomegaly were reported as systemic symptoms associated with AF [3]. Radiographs may reveal osteolytic lesions of the bone [3]. Etiologies of AF include isotretinoin, antibiotics, and anabolic steroids [3], (Table 1).

Precipitation of AF with a very low dose of isotretinoin has been described in one case [4]. Unlike our patient, the other patient was diagnosed with acne conglobata and had a history of anabolic steroid injection. Acne fulminans was induced by a low dose of isotretinoin despite the addition of corticosteroids from the start. Systemic symptoms were noted. Regarding management, he was treated with intravenous then oral corticosteroids with the continuation of isotretinoin. Tables 2 and 3 compare reported treatments and the treatment of our patient.

It has been proposed that genetic, hormonal, immunological, and inflammatory conditions play a role in pathogenesis [1]. A high level of testosterone may represent a risk factor for AF [3]. In addition, the presence of a target population composed of boys under 18 years supports the presence of a genetic predisposition influenced by hormonal factors [5].

The association of AF with pustulosis, hyperostosis, pyogenic arthritis, and pyoderma gangrenosum is recognized as an auto-inflammatory syndrome. The latter is characterized by pro-inflammatory IL1 released by the activation of inflammasome, signaling a role of cytokines in pathophysiology [1].

Regarding isotretinoin, it appears that the drug stimulates the inflammatory process in the skin during the early stages of the treatment. Researchers have detected a high level of metabolic activity of neutrophils in patients receiving this treatment. In addition, the release of cytokines from apoptotic sebocytes leads to the consolidation of the inflammatory state [6,7].
On the other hand, the term pseudo acne fulminans, known also as acne fulminans sine fulminans, has been mentioned in the literature [8]. Fourteen cases of acne with presentation comparable to AF but without systemic symptoms have been reported [9]. A common characteristic of these cases was the presence of macrocomedones before the initiation of isotretinoin and the development of inflammatory lesions [10]. A hypersensitivity reaction to propionibacterium acnes during the treatment with isotretinoin has been proposed to explain the mechanism of pseudo AF [10].

Regarding therapeutic strategies, there are no randomized clinical trials studying the best treatment for AF. Recommendations are based on case series and case reports. [1,4,5,8,9,11–75]

Oral corticosteroid is suggested at a dose of 0.5mg/kg/day to 1mg/kg/day over a period of four weeks (two weeks in case of absence of systemic symptoms) before the addition of isotretinoin at doses of 0.1mg/kg/day. Then, both drugs are given together for four weeks. As tolerated, the dose of corticosteroids can be gradually tapered with increasing doses of isotretinoin for a period of 8 weeks [1].

The treatment with tetracyclines alone or the addition of antibiotics to corticosteroids is not usually first-line therapy for AF [1]. Antibiotic pretreatment to prepare patients before the initiation of isotretinoin remains an unproven strategy.

There are a few cases reported in the literature on the effects of biologic agents like adalimumab, etanercept, and infliximab in the treatment of AF [50,58,69]. Improvement of AF with biological treatment leads to speculation about whether or not AF may represent an atypical presentation of hidradenitis suppurativa. Poli et al. reported the induction of AF by isotretinoin in four cases that later revealed hidradenitis suppurativa [76]. Similar to biologics, dapsone has been given successfully in limited number of cases [18].

We decided to group all the cases of AF reported on PubMed in English. We note that not all details have been mentioned. There were 54 case reports and 15 case series for a total of 188 patients. There were 171 males and 17 females [4,5,8,9,11-75].

There is only one previous case precipitated by isotretinoin at the low dose of 0.1mg/kg (the dose per weight was not mentioned in all cases), [4]. Systemic symptoms were present in 106 patients and absent in 34. Forty-two cases were precipitated by isotretinoin (Table 1).

Concerning management, the combination of oral corticosteroids with the continuation of isotretinoin was given in 55 cases (Table 2). On the other hand, 42 patients were treated by oral corticosteroids and oral antibiotics (Table 2). Poor documentation in some cases and limited follow-up in others do not

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<th>Table 1. Reported triggers for acne fulminans.</th>
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<td>Isotretinoin</td>
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<td>Number of patients</td>
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*Interferon alpha, ulcerative colitis, measles, adrenal insufficiency.

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<th>Table 2. Drugs administered for the management of acne fulminans.</th>
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<td>Oral steroids</td>
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*Dapsone, adalimumab, anakinra, cyclosporine, methotrexate, diaminodiphenylsulfonate, infliximab, topical retinoids, topical steroids, benzoyl peroxide, benzoyl peroxide and aspirin, NSAIDS.
allow adequate comparison of the treatment strategies.

**Conclusion**

Our patient developed AF related to isotretinoin therapy at a dose of 10mg per day without associated systemic symptoms. We report this case to increase awareness of AF induction by a very low dose of isotretinoin.

**Potential conflicts of interest**

The authors declare no conflicts of interest.

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