Erythema nodosum induced by oral isotretinoin in a patient with condylomata acuminata

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Abstract

Erythema nodosum (EN) is a form of septal panniculitis, which is believed to represent a delayed hypersensitivity reaction activated by infectious agents, drugs, granulomatous and autoimmune diseases, pregnancy, and malignancies. There are only four reported cases of EN during oral isotretinoin therapy to our knowledge, all of them occurring in patients with severe acne. Since acne itself can trigger EN, the question as to whether there is indeed a causative relationship between isotretinoin and EN in the reported cases remains to be elucidated. We present herein a 20-year-old woman with multiple vulvar condylomata acuminata who developed EN two weeks after onset of oral isotretinoin therapy. To the best of our knowledge, this is the first report of EN occurring during isotretinoin treatment in a patient without acne and strongly indicates that the pathogenesis of EN can be directly related to the biological actions of isotretinoin. Erythema nodosum should be regarded as a rare side effect of oral isotretinoin therapy, regardless of the underlying disease. Physicians should be aware of this rare side effect.

Keywords: isotretinoin, erythema nodosum, condylomata acuminata

Introduction

Erythema nodosum (EN) is a form of septal panniculitis, which is considered to represent a delayed hypersensitivity reaction activated by infectious agents, drugs, granulomatous and autoimmune diseases, pregnancy and malignancies [1]. Erythema nodosum has a female predilection (ratio 5:1) and more frequently occurs between the second and the fourth decades of life. It is clinically characterized by the presence of red or violaceous, painful, non-ulcerating subcutaneous nodules, typically occurring in crops located on the extensor aspect of the lower limbs and rarely on the trunk or the upper extremities [1, 2]. Nodules are often accompanied by systemic signs and symptoms and usually resolve without scarring after two to eight weeks.

Isotretinoin (13-cis-retinoic acid), is a representative of the first retinoid generation, which was originally approved in 1982 by the US Food and Drug Administration (FDA) for the oral treatment of severe, recalcitrant nodular acne that is unresponsive to conventional therapy. Since then, oral isotretinoin has revolutionized the treatment of acne and is still regarded as the drug of choice for severe forms of this disease [3, 4]. However, owing to its pleiotropic immunomodulatory, anti-neoplastic, and anti-inflammatory actions, isotretinoin has also been successfully used as an off-label therapy for various diseases including among others rosacea, skin neoplasms including cutaneous T-cell lymphomas, hidradenitis suppurativa, granuloma annulare, lupus erythematosus, lichen planus, and condylomata acuminata [5]. Isotretinoin's most important side effects are teratogenesis, hyperlipidemia, hepatotoxicity, mucocutaneous dryness, photosensitivity, and neurologic adverse

reactions (headache, depression, disulfiram-like reactions, pseudotumor cerebri, dizziness, oculogyric crisis, and decreased hearing), [4].

In an attempt to improve the awareness among physicians of EN being a rare side effect of isotretinoin, we present herein the case of a 20-year-old woman with multiple vulvar condylomata acuminata who presented with EN two weeks after onset of oral isotretinoin therapy.

Case Synopsis

A 20-year-old HIV-negative woman presented with a 7-month-history of multiple condylomata acuminata on the vulva, which had relapsed three months after treatment with electrocauterization. She had no history or evidence of autoimmune or neoplastic disorders and systemic infections. Moreover, a meticulously taken medication history revealed the intake of no currently or recently prescribed drugs or over-the counter medications. In particular, the patient, being aware of the side effects and risks associated with oral contraceptives, had never used them, but chose other methods of contraception. On physical examination, she exhibited multiple pink papules (4-8mm in diameter) in the vulva. Both colposcopy and proctoscopy failed to detect any lesions. The results of routine laboratory investigations were unremarkable. Histological examination of biopsy specimens obtained from two different lesions revealed the histological features of condylomata acuminata, whereas in situ hybridization using biotinylated HPV-DNA probes showed the occurrence of HPV types 6/11 in the nuclei of keratinocytes of the upper epidermal layers. Since the patient refused any form of surgical or destructive treatment and because of the extent of the condylomata, we suggested administration of oral isotretinoin. Subsequent to detailed information about the possible side effects of this compound, the patient gave a written consent and oral treatment was initiated with 1mg/kg/day isotretinoin.

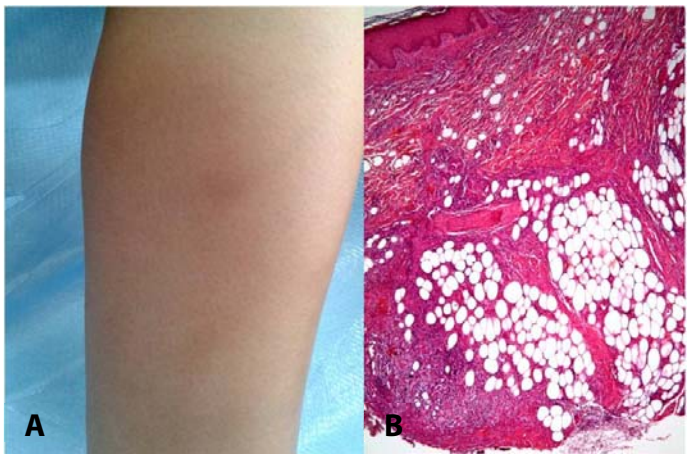

Figure 1. ***A)*** *Clinical aspect of erythema nodosum on the right tibia of the patient.* ***B)*** *Histology of skin biopsy showing predominantly septal panniculitis, with dense inflammatory infiltration consisting of neutrophils, lymphocytes, plasma cells, and histiocytes. H&E, 25×.*

Ten days after onset of treatment a distinct decrease in the size of condylomata acuminata could be observed. After two weeks of continuous oral isotretinoin therapy, the patient developed livid red, very tender and painful nodules (1-3cm in diameter) on the extensor surface of both tibiae (**Figure 1A)**. Histologically the lesions showed features of predominantly septal panniculitis, characterized by fibrous cords with mixed inflammation consisting of neutrophils, lymphocytes, plasma cells, histiocytes, and rare multinucleated cells, spilling over to fat lobules. The dermis showed also periadnexal and perivascular inflammation (**Figure 1B)**.

In view of the clinical morphology of the lesions and the corresponding histological findings, the diagnosis of erythema nodosum was established. Full blood count revealed a moderate leukocytosis and increase of erythrocyte sedimentation rate, whereas biochemical parameters and urinalysis were unremarkable. Throat swab culture, stool examination for bacteria, fungi, and parasites, and chest radiograph were negative. Additionally, the results of immunological and serological investigations were either negative or within normal limits.

Discontinuation of oral isotretinoin administration led to a rapid improvement and to a complete spontaneous remission of erythema nodosum within two weeks. The patient refused an attempt to reinitiate oral isotretinoin administration and at her request condylomata acuminata were treated with electrocauterization. She has presently completed a 21-month follow-up without any evidence of EN relapse.

Case Discussion

Through binding to, and activation of retinoic acid receptors (RAR), isotretinoin is capable of controlling the transcription of specific target genes and of exerting a wide range of biological effects including regulation of cellular proliferation and differentiation, induction of apoptosis, and potent immunomodulatory, anti-inflammatory, and anti-neoplastic action [6]. An inverse relationship has been found between the concentrations of retinoids and of HPV-DNA within infected epithelial cells, indicating that isotretinoin may inhibit the DNA replication and assembly of HPV either directly or via its ability to affect epithelial differentiation [7]. These findings served as the theoretical background for the use of oral isotretinoin in the treatment of HPV infections with promising results [8, 9].

To the best of our knowledge there are only four reported cases of EN that occurred during oral isotretinoin therapy [10-12]. Interestingly, all of them were seen in patients with severe acne. Kelett et al. (1985) reported two patients with acne fulminans that developed EN during isotretinoin treatment [10], whereas a similar case was reported by Tan et al. (1997), [11]. In both reports, isotretinoin therapy was not discontinued and EN was treated either with prednisolone that led to distinct improvement within 1 month [10] or dapsone that led to remission within 2 weeks [11]. The authors of both reports considered the EN to be related to acne fulminans and not to isotretinoin. Kellett et al. (1985) supported this view by the finding of circulating immune complexes in their patients, presumably as part of an Arthus reaction triggered by *Propionibacterium acnes*. Krug-Milon also described a patient with widespread acne who developed EN during isotretinoin treatment. In this case isotretinoin was discontinued and EN cleared within two months [12].

Since severe forms of acne can trigger EN even in patients who are not treated with oral isotretinoin, it has been suggested that there is a causative relationship between acne and EN [13]. In our patient, the possibility that this compound was not the causative factor of EN cannot be definitely ruled out but seems very unlikely since EN occurred soon after initiation of isotretinoin administration and rapidly improved after its discontinuation. Moreover, a thorough clinical and laboratory investigation excluded any other possible triggering factors for EN.

It is well known that the binding affinity of all-*trans*-retinoic acid (atRA) to nuclear retinoid receptors is much higher than that of isotretinoin. Thus, steric isomerization to atRA is of paramount importance for the biologic actions and therapeutic effects of isotretinoin (14). Since EN reportedly occurs also in patients treated with atRA (15-17), physicians should be aware of the fact that EN is side effect that both retinoids have in common, regardless of the underlying disease for which they are administered.

Conclusion

To the best of our knowledge, this is the first report of EN occurring during oral isotretinoin treatment in a patient not suffering from acne. Moreover, it strongly indicates that the pathogenetic mechanisms of EN are most probably directly related to the biological actions of isotretinoin. In conclusion, EN should be regarded as a rare side effect of oral isotretinoin therapy, regardless of the underlying disease. Physicians should be aware of this rare adverse reaction.

Potential conflicts of interest

The authors declare no conflicts of interests.

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