Case Report
Olgu Sunumu

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Isotretinoin induced dysuria: A case report and review of literature about urological effects of isotretinoin

İzotretinoine bağlı dizüri: Olgu sunumu ve isotretinoinin ürolojik yan etkilerinin değerlendirilmesi

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Abstract

Isotretinoin is often used in the treatment of severe acne. However, many adverse reactions were reported, including mucocutaneous, metabolic, neurological and psychiatric, ophthalmologic, hematologic side effects and teratogenicity. The mucocutaneous are the most common side effects and often develop in a dose-dependent manner. I present a case of a 20-year-old male with the unusual non-specific dysuria only and review the literature on the urological effects of isotretinoin.
Keywords: Isotretinoin, dysuria, urology

Öz

İzotretinoin genellikle şiddetli akne tedavisinde kullanılır. İzotretinoin ile bildirilen mukokutanöz, metabolik, nörolojik ve psikiyatrik, oftalmolojik, hematolojik yan etkiler, teratojenite gibi birçok yan etki vardır. Bunlar arasında mukokutanöz yan etkiler en yaygın olanlardır ve sıklıkla doza bağlı bir şekilde gelişirler. Burada 20 yaşında sistemik izotretinoin kullanan bir erkek hastada görülen dizüri sunulmuş olup, izotretinoinin ürolojik etkileri hakkındaki literatür gözden geçirilmiştir.
Anahtar Kelimeler: İzotretinoin, dizüri, üroloji

Introduction

Isotretinoin (13 cis-retinoic acid) is a vitamin A-derived agent, which has been used for many years for the treatment of severe nodulocystic or therapy-resistant moderate acne vulgaris. This has been the most effective treatment of choice in all steps of acne pathogenesis. Isotretinoin has anti-inflammatory effects and suppresses sebum secretion, prevents comedo formation, and reduces *Propionibacterium acnes* colonization[1]. Although the mechanism is not fully understood, it acts through influencing apoptosis, cellular morphogenesis, growth and differentiation[2].

There are many adverse reactions reported with isotretinoin, including mucocutaneous (cheilitis and dry eyes), metabolic (elevated serum lipids), neurological and psychiatric (depression with suicidal thoughts), ophthalmologic (night blindness), hematologic side effects (neutropenia and thrombocytopenia), and teratogenicity. Thus, the mucocutaneous are the most common side effects and often develop in a dose-dependent manner[3,4].

However, few publications reported adverse effects on the urinary system on systemic isotretinoin treatment, such as acute renal injury, tubulointerstitial nephritis, nephrotic

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syndrome, urethritis, and hematuria[5-17]. Thus, this may be an overlooked side effect of systemic isotretinoin.

Therefore, I present an unusual side effect of isotretinoin with only non-specific dysuria and review the literature about urological effects of isotretinoin.

Case Report

A 20-year-old Caucasian male patient was started on 0.5 mg/kg/day of oral isotretinoin treatment for resistant acne vulgaris therapy. After 2 months he presented to our clinic with a complaint of dysuria.

The patient had no relevant sexual history, and no penile discharge was noted. The urologist examined the meatal mucosa with normal findings. Tests for sexually transmitted and other infectious diseases screening were negative. Urinalysis was performed two times, and both were normal. Urine culture showed no bacterial growth. In addition, urinary ultrasonography and computed tomography were unremarkable.

Blood biochemical values were all within the normal range. Furthermore, no side effects of isotretinoin have been observed, except for mild to moderate cheilitis.

The drug was discontinued considering that his complaints were due to the use of isotretinoin. His complaints decreased and disappeared within 2 weeks. After one month, the treatment was administered again with a dose of 0.3 mg/kg/day, the complaint of dysuria developed within 1 week. Therefore, the treatment was terminated immediately. His symptom disappeared and did not report the return of any urological symptoms. Informed consent was obtained.

Discussion

Systemic isotretinoin is used in dermatology practice, often in the treatment of acne, and increasingly in many, cases such as seborrheic dermatitis, rosacea, and chemoprevention of cutaneous malignancies[18]. Although isotretinoin has many side effects, mucocutaneous ones are most common, and they are often dose-dependent that can be controlled with a dose modification and symptomatic treatment[3,4].

However, the pathogenesis of the adverse reactions remains unclear. Keratolytic effects of isotretinoin and apoptosis in sebocytes may lead to alteration of epidermal barrier, dehydration in the degree of stratum corneum, increase of transepidermal water loss and increase skin pH levels: all these may play a key role in mucocutaneous side effects. In addition, dryness of the mucous membranes, mucosal dermatitis, cheilitis, dry skin, peeling, epistaxis, desquamation, photosensitivity, and pruritus are the results of this situation[19,20].

We have limited information about the effects of systemic isotretinoin on the urinary system. Although there are a limited number of reports, acute renal injury, tubulointerstitial nephritis, nephrotic syndrome, hematuria, and urethritis have been reported in the literature[5-17]. Urological side effects reported in the literature are shown in Table 1.

Dysuria is a symptom of pain, burning, stinging, or itching of the urethra or urethral meatus when urinating. This usually happens due to bladder muscle contraction and peristalsis of the urethra, causing the urine to come in contact with the inflamed mucosal lining leading to stimulation of pain receptors. In addition, this may be caused by urinary tract infections, sexually transmitted diseases (genital herpes,

Table 1. Urological side effects of isotretinoin reported in the literature

Study	Age, sex	Symptoms	Isotretinoin dosage per day	Isotretinoin duration	Findings	Diagnosis	Management
Kellock et al.[5]	30, M	Dysuria, hematuria	100 mg/d	2 weeks	Dermatitis on meatus	Urethritis	Dosage reduction
Kellock et al.[5]	25, M	Pain, urethral discharge	60 mg/d	3 months	Fissure and dermatitis on meatus	Urethritis	Resolved spontaneously
Kellock et al.[5]	20, M	Dysuria, urethral discharge	60 mg/d	6 weeks	Urethral discharge	Urethritis	Termination of drug
Edwards and Sonnex[6]	23, M	Pain, urethral discharge	NM	NM	Dermatitis on meatus and urethral discharge	Urethritis	Oral tetracycline
Edwards and Sonnex[6]	35, M	Urethral discharge	NM	1 week	Urethral discharge	Urethritis	Oral tetracycline
Pavese et al.[7]	34, M	NM	40 mg/d	2 months	Creatinine elevation Urinalysis: Protein+ Erythrocytes+	Acute renal failure	Termination of drug
van Oers et al.[8]	19, M	Facial, pretbial, ankle edema	40 mg/d	4 months	Urinalysis: Protein+ Proven renal biopsy	Nephrotic syndrome + Minimal change disease	Termination of drug and systemic steroid
Sarifakioglu et al.[9]	16, M	Dysuria, hematuria	0.5 mg/kg/d	1 month	Urinalysis: Erythrocytes+	Terminal hematuria	Termination of drug

Armaly et al.[10]	17, F	Flank pain, nausea, and vomiting	NM	2 months	Creatinine elevation Urinanalysis: Erythrocytes+ Protein+	Acute interstitial nephritis	Termination of drug
Alli and Yorulmaz[11]	23, M	Dysuria, pruritus	40 mg/d	4 months	Dermatitis on meatus Urinalysis: Erythrocytes+ Epithelial cells++	Retinoid dermatitis on urethral meatus	Dosage reduction + symptomatic treatment (petrolatum)
Kaya Aksoy et al.[12]	16, M	Palpitation	40 mg/d	3 months	Creatinine elevation Urinalysis: glucose+++ Protein+ Leukocytes+ Proven renal biopsy	Eosinophilic tubulointerstitial nephritis	Termination of drug + systemic steroid
Yesilkaya et al.[13]	15 patients (16-32 years)	Hematuria	0.5-1 mg/kg	Scalp	Urinalysis: Erythrocytes+	Hematuria	NM
Ballout and Maatouk[14]	28, M	Pain, dysuria, urethral discharge	60 mg/d	1 month	Dermatitis on meatus	Urethritis	Dosage reduction
Sivaraj et al.[15]	18, M	No symptom	1 mg/kg/d	5 months	Dermatitis on meatus and external urethra	Urethritis	Symptomatic treatment, resolved after termination
Paredes-Bhushan et al.[16]	17, M	Urine stream issues	60 mg/d	5 weeks	Dermatitis on meatus	Urethritis	Symptomatic treatment (topical steroid)
Presented case	20, M	Dysuria	40 mg/d	2 months	Not remarkable	Non-specific dysuria	Termination of treatment

NM: Not mentioned, M: Male, F: Female, d: Day

chlamydia, and gonorrhea), stones in the urinary tract, irritation of the urethra due to sexual activity, side effects from some medications, and tumors in the urinary tract. All these problems can cause inflammation or irritation of the urinary tract or genital area, leading to dysuria[21].

In our presented case, urinary tract infections were ruled out with urinalysis and urinary culture. Although the patient had no sexual history, sexually transmitted diseases were ruled out with serological tests and microbiological investigations. Urinary ultrasonography, and computed tomography for stones and any tumors in the urinary tract were performed and they were also unremarkable. After all these factors were excluded, it was thought that systemic isotretinoin might have mucosal side effects in this patient. Cessation of treatment led to a gradual decrease in symptoms, and the re-administration of the medication resumed the complaints.

Complaints of dysuria have been rarely reported in the literature; however, these patients showed signs of mucosal irritation (erythema of meatus) or hematuria. Sarifakioglu et al.[9] reported a 16-year-old boy with dysuria and terminal hematuria after one month of treatment with isotretinoin. Alli and Yorulmaz[11] also reported a 23-year-old male with dysuria and meatitis during isotretinoin treatment, his symptoms resolved after dosage reduction. Although urethritis is often symptomatic, Sivaraj et al.[15] reported a case of asymptomatic external urethritis presenting as an erythematous lesion at the tip of the urethra. Unlike these reported cases, there was no extra complaint in our case and skin and mucous membranes was unremarkable. All these side effects can be thought to be due to the xerotic mucosal effect of isotretionin within the urethral mucosa.

The side effects on the urological system of systemic isotretinoin have been reported with an increasing number, and this may be an overlooked side effect of systemic isotretinoin. It may be managed accordingly by dose reduction or termination of the treatment. Being aware of this adverse effect and questioning these side effects will increase our knowledge on this issue.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

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