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Acute kidney injury following isotretinoin treatment

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Patient: Female, 17
Final Diagnosis: Acute kidney injury
Symptoms: Flank pain • nausea • vomiting
Medication: Isotretinoin
Clinical Procedure: Acne treatment
Specialty: Nephrology

Objective: Unknown etiology

Background: Isotretinoin is widely used for the treatment of acne that is unresponsive to topical therapy. Despite its efficacy, isotretinoin has various adverse effects, including cheilitis, increased risk of cutaneous *Staphylococcus aureus* infections, and liver function abnormalities.

Case Report: A 17-years-old female was admitted to the hospital with a 5-day history of bilateral flank pain, nausea and vomiting. On physical examination, acne was observed over her face treated with Isotretinoin. Both vital signs and physical examination were normal apart from tenderness over both flanks. Initial laboratory results revealed serum creatinine of 2 mg/dl, blood urea nitrogen 20 mg/dl. Complete blood count, full chemistry panel, complements and urinalysis were all normal. Twenty four hours urine collection showed creatinine clearance test of 33 ml/min and urine protein of 390 mg/day. Chest X-ray and ultra sound of kidneys were normal. Acute kidney injury was suspected and she was treated with intravenous fluids. Despite these measures her kidney function steadily worsened. Her serum creatinine on days 2 and 3 were 2.16 and 2.24 mg/dl, respectively. Wright's staining for eosinophils was positive. Fortunately her serum creatinine started to decrease and was 2 mg/dl and 1.4 mg/dl by day 4 and 5, respectively. A tentative diagnosis of acute interstitial nephritis due to Isotretinoin was made, with the recommendation to avoid this treatment in the future. Two weeks later her serum creatinine and urinary protein returned to normal values.

Conclusions: Flank pain should raise suspicion of Isotretinoin-induced acute kidney injury, suggesting that a careful kidney function test besides testing for liver function is warranted in patients with these symptoms.

Key words: isotretinoin • acne • acute interstitial nephritis • acute kidney injury

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Background

A variety of pharmacological treatments for acne exist, including topical benzoyl peroxide, topical retinoids, topical antibiotics, oral antibiotics, hormonal therapy, isotretinoin and others [1]. Isotretinoin is generally reserved for severe, recalcitrant, nodular acne that is unresponsive to topical therapy. Although effective against severe acne, isotretinoin is associated with various adverse effects, including cheilitis, dry skin and mucous membranes, epistaxis, increased risk of cutaneous *Staphylococcus aureus* infections, myalgia, hyperlipidemia, and liver function abnormalities [2]. There are no published reports on renal side effects of Isotretinoin. We report a case of acute kidney injury (AKI) in a patient treated with this drug.

Case Report

An otherwise previously healthy 17-years-old female with no prior medical history was admitted to the hospital with a 5-day history of bilateral flank pain, nausea and vomiting. She denied other gastrointestinal or urinary symptoms, hematuria, fever or use of cyclooxygenase 2 inhibitors (COXIBs) and nonsteroidal anti-inflammatory drugs (NSAID). Her past medical history is not noteworthy, except for the use of Isotretinoin 2 years previously for acne treatment. Two months prior to admission she was retreated with Isotretinoin owing to acne, and stopped when symptoms developed. On physical examination, acne was observed over her face, mild pallor however, no skin rash was noted. Both vital signs and physical examination were normal apart from tenderness over both flanks. Initial laboratory results revealed the following: Serum creatinine (Scr) was 2 mg/dl, Blood urea nitrogen (BUN) 20 mg/dl,

Complete blood count (CBC), full chemistry panel, rheumatoid factor (RF), An anti-streptolysin O titre (ASOT), Protein electrophoresis (PEP), antinuclear antibody (ANA) and complements were all normal. Blood Gases$_{(v)}$: pH 7.35; Pco_2: 35 mmHg; HCO_3: 18 mEq/L. Anion Gap: 21. Urinalysis: Specific gravity 1.010; pH 6; white blood cells (WBC) 25/ul; Red blood cells (RBC) 10/ul, protein +1. Urine Sediment showed WBC 5–7/hpf; RBC 3–4 hpf/ul; Epithelial cells ++/hpf without evidence of WBC, RBC or granular casts. 24 h urine collection showed creatinine clearance of 33 ml/min and urine protein of 390 mg/day. Chest X-ray (CXR) and ultra sound (U/S) of kidneys were normal. On admission, she was treated with intravenous (IV) fluids, but despite these measures her kidney function steadily worsened. Her Scr on days 2 and 3 were 2.16 and 2.24 mg/dl, respectively. Repeated urine sediment showed 5 WBC casts, 20–30 WBC/hpf, no RBCs or other casts, Wright's staining for eosinophils was positive (Figure 1). A tentative diagnosis of acute interstitial nephritis (AIN) was made on the basis of these clinical and laboratory findings. A rescue therapy with steroids

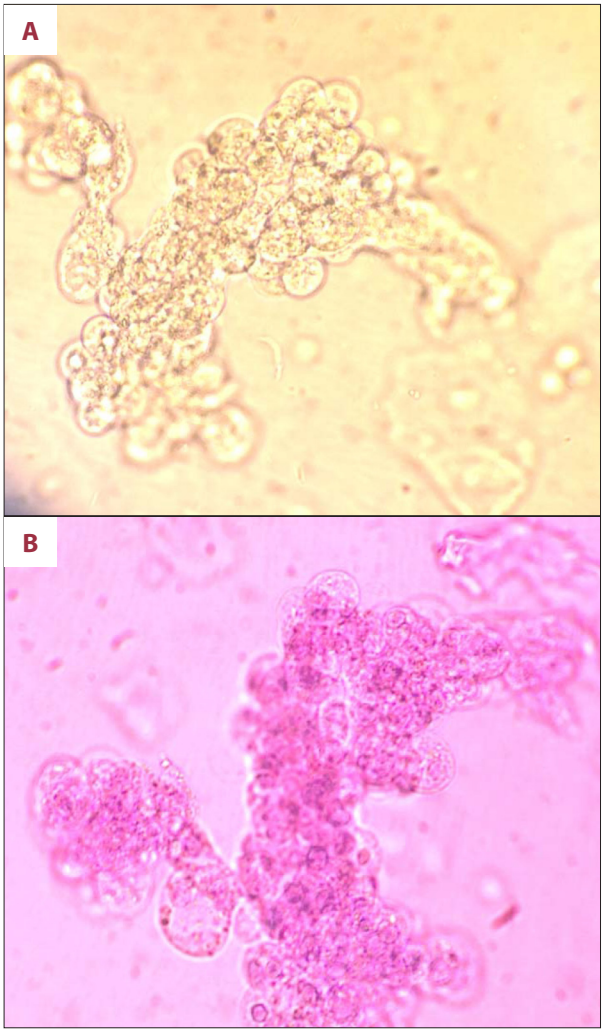

Figure 1. White blood cell casts (**A**) in the urine of Isotretinoin treated patient. (**B**) Wright's staining for eosinophils.

was suggested because of the continued deterioration of her kidney function tests. Fortunately her Scr started to decrease and was 2 mg/dl and 1.4 mg/dl by day 4 and 5, respectively, therefore steroid therapy was not applied. The patient was diagnosed with AKI, probably due to AIN caused by isotrentinoin. Recommendation to avoid this treatment in the future was issued. Two weeks later her Scr and urinary protein returned to normal values (Scr=0.7 mg/dl).

Discussion

A 17 year old previously healthy female was admitted with AKI, accompanied with flank pain, nausea and vomiting, 2 months after re-exposure to anti-acne treatment with Isotretinoin. A tentative diagnosis of AIN was made on the basis of these presenting clinical and laboratory findings especially the appearance of white blood cell casts in the urine (eosinophils). AIN is

an immunologically-induced hypersensitivity reaction to an antigen that is classically a drug or an infectious agent [3–6]. The unifying presentation in AIN includes an abrupt onset of renal injury, accompanied by no or few clinical signs, such as oliguria, flank tenderness, anorexia, malaise, nausea, vomiting, and urine sediment contains RBCs, WBCs (eosinophiluria) and occasional WBC, renal tubular cell and granular casts [3–6]. AIN is a self-limited disease and full recovery within a few weeks is the rule in patients when the offending agent was withdrawn early [3,4,6,7]. Our patient clinical manifestations and disease course meet all the criteria of AKI induced by Isotretinoin due to AIN. Therefore, the patient was diagnosed with AKI, probably due to AIN caused by isotrentinoin. Defensive AIN requires renal biopsy, which was not performed in the current case. Isotretinoin has never been included in the list of drugs that can cause AIN [3–6]. Actually, retinoids exhibit antiproliferative, antiinflammatory, and immune-modulatory effects [8]. In line with these effects, retinoids were shown to reduce both glomerular and tubular damage and inflammation in experimental models of glomerulonephritis and renal interstitial disease [9].

Most recently, Sarifakioglu et al. [10], described a case report of 16-year-old boy who developed terminal hematuria after 1 month of treatment with isotretinoin for acne vulgaris. However, terminal hematuria occurs at the end of the urine stream and may have a prostatic, bladder, or trigonal cause, rather than renal origin. These authors concluded that the hematuria is probably due to the xerotic mucosal side effects of the drug, in the same fashion isotretinoin is known to affect the nasal mucosa, causing nasal bleeding.

Conclusions

Our findings suggest that a careful kidney function test in addition to liver abnormalities testing is warranted in patients treated with Isotretinoin.

To the best of our knowledge, this is the first case report of AIN resulting from the use of Isotretinoin.

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