tumors has not been defined. Further, the frequency with which it presents as the predominant symptomatic process or with the unusual radiographic pattern described here is unknown. The demonstration of diffusely narrowed airways on chest CT of a patient with dyspnea and/or airflow obstruction should, however, raise the possibility of submucosal metastatic disease as an etiology. This entity should be added to the differential diagnosis of dyspnea in a cancer patient with a nondiagnostic chest radiograph.

**References**


**Tubulointerstitial Nephritis Induced by the Leukotriene Receptor Antagonist Pranlukast**

Scott J. Schurrman, MD; Janice M. Alderman, PharmD; Marc Massamari, PharmD, FCCP; Atlano G. Lacson, MD, and Sharon A. Perlman, MD

A 7-year-old boy with asthma was receiving the leukotriene receptor antagonist pranlukast (Ultair; SmithKline Beecham; Pittsburgh) as part of an open-label clinical trial. The patient’s asthma improved, and he remained asymptomatic; but routine study evaluations 9 to 12 months into therapy showed microhematuria, proteinuria, glucosuria, anemia, and renal insufficiency. Renal biopsy demonstrated...
changes classic for acute allergic tubulointerstitial nephritis (ATIN), with mixed interstitial inflammatory infiltrate including eosinophils. Within 6 months of pranlukast withdrawal, anemia resolved and urinary sediment and renal function normalized. The case demonstrates that hypersensitivity reaction to pranlukast and resultant ATIN is possible, and that periodic urine testing in patients receiving pranlukast should be considered.

(CHEST 1998; 114:1220–1223)

Keywords: drug-induced acute tubulointerstitial nephritis; eosinophils; leukotriene receptor antagonist; renal insufficiency

Abbreviations: ATIN = acute tubulointerstitial nephritis; H/H = hemoglobin and hematocrit ratio

Leukotriene receptor antagonists represent the first novel therapy for the treatment of asthma in more than 25 years.1 Zafirlukast (Accolate; Zeneca Pharmaceuticals; Wilmington, DE) and montelukast (Singular; Merck; Montreal, Canada) have both recently received US Food and Drug Administration approval, while pranlukast (Ultair; SmithKline Beecham; Pittsburgh), which is still in phase III trials in the United States, was approved for use in Japan in 1995. Placebo-controlled clinical trials have demonstrated that these agents improve asthma symptom scores and peak expiratory flow rates, and decrease the need for bronchodilators and corticosteroids.2 Availability in tablet form and once- or twice-daily dosage makes these medications particularly attractive; and they have been remarkably well tolerated, with only minor gastrointestinal complaints slightly more common in treated patients compared to those receiving placebo.3

We report acute tubulointerstitial nephritis (ATIN) in a child participating in an open-label clinical trial of pranlukast. The case demonstrates that while pranlukast modifies the immune response to allergens, hypersensitivity reaction to the drug itself is possible. In addition, this patient’s clinical course suggests that periodic urinalysis testing of patients receiving pranlukast should be strongly considered.

CASE REPORT

A 7-year-old white boy with a 4-year history of moderate persistent asthma was enrolled via the University of South Florida (Tampa) division of Allergy and Immunology in a double-blind, placebo-controlled clinical trial of pranlukast. Prior to study enrollment, therapy for asthma included nebulized albuterol 2 to 4 times daily. Acute exacerbations 1 and 18 months prior to enrollment required 5 days of pulse therapy with oral prednisolone, but he was not receiving other corticosteroid therapy. Whether the patient received pranlukast or placebo is unknown; however, 3 months later he was moved to an open-label trial, receiving pranlukast twice daily. The patient’s asthma improved almost immediately, allowing nebulized albuterol to be delivered only as needed.

As part of study participation, the patient was evaluated monthly, including blood tests and urinalysis. The available results date from 6 months after open-label enrollment, and they include normal urinalysis and a CBC count showing a hemoglobin and hematocrit ratio (H/H) of 13.0/35.2 and a WBC count of 10,000, with a differential count including 8% eosinophils. Mild eosinophilia persisted as the only clinical or laboratory abnormality until testing 3 months later revealed glucosuria (urine glucose, 100 mg/dL) and mild anemia (H/H, 11.1/33.3). Renal function was normal with a serum creatinine of 0.8 mg/dL (0.3 to 1.0).

Over the following 6 weeks multiple laboratory studies were obtained, with urinalyses demonstrating persistent glucosuria and development of microhematuria, nonnephrotic range proteinuria (1+ by dipstick), and granular and hyaline casts. Serum electrolytes and proteins were normal, but serum creatinine increased to 1.0 mg/dL and anemia worsened with an H/H of 9.4/29.3, prompting nephrology referral.

History revealed no fevers, rashes, fatigue, or other abnormalities. Physical exam was normal, including BP of 102/60. Additional laboratory testing included random urine protein/creatinine, 0.40 mg/mg (normal, < 0.2; nephrotic range, > 2.0); CBC count with H/H, 9.8/28.7; reticulocyte count, 0.8% and normal peripheral blood smear. Hypersensitivity reaction to pranlukast was suspected, and the drug was discontinued. Evaluation 1 month later showed persistence of urinary abnormalities and serum creatinine increased to 1.4 mg/dL, prompting a diagnostic kidney biopsy.

The biopsy findings on light microscopy included moderate to severe interstitial inflammatory infiltrate with lymphocytes, plasma cells, neutrophils, and eosinophils (Fig 1). Renal tubules showed various stages of degeneration and regeneration with widespread exocytosis of neutrophils and lymphocytes (Fig 2). Focal tubular atrophy was also noted. Glomeruli were normal and immunofluorescence negative. Given findings classic for drug-induced ATIN, the family was offered corticosteroid therapy but chose monitoring off therapy. Over the next 6 months, hematuria, proteinuria, and glucosuria resolved, serum creatinine decreased to a baseline of 0.8 mg/dL, and the H/H improved to 13.0/38.5.

DISCUSSION

Binding of the single leukotriene receptor present in human bronchial smooth muscle by the cysteinyl-leukotrienes (LTC4, LTD4, and LTE4) contributes to the immediate and long-term bronchoconstriction, microvascular permeability, mucus secretion, and eosinophil influx that mediates the airway obstruction present in patients with asthma.1 Experimental evidence in animals and humans indicates that pranlukast significantly reduces these responses, and clinical trials have demonstrated that pranlukast reduces the symptoms of asthma and use of β2-agonists in patients with bronchoconstriction induced by allergens, exercise, cold air, and aspirin.2

ATIN is an acute or sub-acute disease characterized pathologically by an inflammatory infiltrate of the renal tubules and interstitium, but sparing of glomeruli and vessels.4 The disease can occasionally be caused by viral or other infections, or be associated with a systemic autoimmune process like lupus erythematosus; however, the vast majority of cases result from drug exposure and hypersensitivity.
Figure 1. Moderate to severe interstitial inflammation with focal tubular atrophy (arrow) and glomerular sparing. (Periodic acid-methenamine silver; original ×100.)

Sensitivity. In fact, our patient’s renal biopsy findings, intense interstitial infiltration by lymphocytes, plasma cells, neutrophils, and eosinophils with tubular degeneration/regeneration are classic for drug-induced ATIN.4,5 Absence of symptoms suggestive of infection or histologic evidence of immune-complex-mediated disease further implicate pranlukast, this patient’s only medication, as the cause of his renal disease.

The normal renal interstitium contains both the antigen-presenting macrophages and T lymphocytes necessary...
for initiation of an immune response to foreign antigens.3 Thus, following glomerular filtration or tubular secretion of an offending drug, activation of the cellular immune response results in recruitment of inflammatory cells, including eosinophils, and release of proinflammatory cytokines.4 From a mechanistic standpoint, the observation of pranlukast-associated ATIN may be particularly important given a recent report noting patients with asthma who developed pulmonary infiltrates, eosinophilia, and cardiomyopathy while receiving zafirlukast.5 Biopsy specimens of lung and heart revealed an inflammatory infiltrate with eosinophils. Based on the rarity of drug-induced vasculitis, the authors speculate that allergic reaction was less likely than a primary eosinophilic infiltrative disorder unmasked by steroid withdrawal. However, ATIN in our patient indicates that despite the potential for significant modification of the inflammatory response, hypersensitivity reactions can occur in the setting of leukotriene receptor blockade. Of note, while no patients with this cardiopulmonary syndrome had renal disease,6 a small percentage of both zafirlukast and montelukast, like pranlukast, is excreted intact in urine.

Other lessons from this case include the mode of presentation. Experience over the last 2 decades shows that the classic presentation of fever, rash, and marked eosinophilia actually occurs in a minority of patients with drug-induced ATIN.4,5 Instead, many patients present with findings similar to those seen in this boy: subtle urinary abnormalities and nonoliguric renal dysfunction after months of drug exposure. Mild microscopic anemia, likely the result of ongoing inflammation, is also commonly reported.4 Since patients with ATIN from a particular drug generally present in a similar manner, the experience in this boy suggests that patients receiving pranlukast should have periodic urine testing, and that microhematuria, proteinuria, or glucosuria should prompt additional evaluation for ATIN. Although the vast majority of patients with ATIN eventually recover completely following drug discontinuation, irreversible nephron loss can occur.7 In fact, patchy tubular atrophy in our patient indicates that such a process had begun, and leads us to speculate that chronic changes would have been more global had diagnosis been made only after development of symptomatic renal disease.

REFERENCES