


Acute Interstitial Nephritis: A Rare and Unusual Side Effect of Omalizumab

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Abstract

Acute interstitial nephritis (AIN) is a relatively common cause of acute kidney injury with etiologies that include drug therapy, infections, and systemic diseases. Of these etiologies, drug therapy accounts for ~70% of AIN cases. Although any drug can cause AIN, there are no reported cases of AIN caused by omalizumab, a humanized monoclonal antibody that binds to and inhibits circulating immunoglobulin E. In this article, we share the first reported case of AIN following administration of omalizumab for the treatment of moderate to severe persistent asthma.

Keywords

nephrology, acute interstitial nephritis, drug-induced interstitial nephritis, omalizumab, acute renal failure

Introduction

Omalizumab is a humanized monoclonal antibody that binds to and inhibits circulating immunoglobulin (Ig) E and is Food and Drug Administration approved for use in treating moderate to severe persistent asthma that is poorly controlled with inhaled corticosteroids.^{1–3} Major adverse effects reported include anaphylaxis, cardiovascular affects, and vasculitis symptoms consistent with eosinophilic granulomatosis with polyangiitis (EGPA).⁴ In 2018, omalizumab was to be evaluated as a potential treatment of drug-induced acute interstitial nephritis (DI-AIN), a common cause of acute kidney injury (AKI), but was withdrawn due to a lack of participants.⁵ Instead of omalizumab therapy for treating DI-AIN, however, we present a rare case of AIN as a side effect of omalizumab therapy.

Case Presentation

A 71-year-old obese Filipino female with moderate to severe asthma, uncontrolled type 2 diabetes, hypertension, heart failure with preserved ejection fraction, and chronic kidney disease (CKD) stage 4 presented to the emergency department for progressively worsening shortness of breath and productive cough for 1 week with increased severity in the past 2 days. The patient was in her normal state of health up until 3 weeks prior to presentation when she received her first omalizumab injection for refractory asthma. Omalizumab was the only new medication added to her home medication regimen (Table 1). After the injection, she developed mild

generalized weakness and fatigue but otherwise felt well. After receiving the second injection of omalizumab 2 weeks later, she experienced worsening of the generalized weakness, fatigue, and developed shortness of breath with a productive cough. This prompted her to go to the emergency department.

On presentation in the emergency department, the patient was in no acute distress, afebrile, and nonhypoxic with an oxygen saturation of 96% on room air. Pulmonary examination revealed decreased breath sounds, diffuse bilateral wheezing, and rales at the bilateral lung bases. The patient also had 2+ bilateral pitting edema with the rest of the physical examination unremarkable. While in the emergency department, she was treated for heart failure exacerbation with intravenous (IV) furosemide, kidney failure, and acute asthma exacerbation. She then became increasingly lethargic with obtained laboratory values significant for an elevated potassium of 8.1 mEq/L (8.1 mmol/L; Table 2), blood urea nitrogen of 139 mg/dL (49.62 mmol/L), creatinine of 8.08 mg/dL (714.27 μ mol/L) from a baseline creatinine of 2.09 mg/dL (184.76 μ mol/L), and urine microalbumin/creatinine

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Table 1. Home Medications.

Albuterol PRN	Linagliptin 5 mg
Fluticasone/salmeterol 500/50 µg BID	Losartan 50 mg
Montelukast 10 mg	Metoprolol tartrate 50 mg BID
Ipratropium/albuterol Q6H PRN	Amlodipine 2.5 mg
Insulin detemir	Furosemide 40 mg
Insulin aspart	Atorvastatin 40 mg
Gabapentin 100 mg TID	

Abbreviations: PRN, as needed; Q6H, every 6 hours; TID, 3 times a day; BID, twice a day.

Table 2. Significant Laboratory Results.

Parameter	Value	Reference
Potassium	8.1 mEq/L	3.5-5.1 mEq/L
Cr	8.08 mg/dL	0.6-1.1 mg/dL
eGFR	5 mL/min	>60 mL/min = normal
Urine Mic Alb/Cr ratio	2524 µg/mg	0-30 µg/mg
Eosinophil count	1.2×10^3 µL	Adults: $0-0.9 \times 10^3$ µL
Serum IgA	408 mg/dL	81-463 mg/dL
Serum IgE	4 758 000 U/L	<114 000 U/L
Serum IgG	1701 mg/dL	694-1618 mg/dL
Complement, C3	128 mg/dL	83-193 mg/dL
Complement, C4	35 mg/dL	15-57 mg/dL
Complement total (CH50)	>60 U/mL	31-60 U/mL
ANA screen	Positive	Negative
ANA AB titer	1:640	<1:40 negative 1:40-1:80 low antibody level >1:80 elevated antibody level
Myeloperoxidase AB	<1.0	<1.0 no antibody detected
Proteinase-3 AB	<1.0	<1.0 no antibody detected

Abbreviations: eGFR, estimated glomerular filtration rate; Mic, micro; Alb, albumin; Cr, creatinine; Ig, immunoglobulin; ANA, antinuclear antibody.

ratio of 2524 mg/g. Electrocardiogram demonstrated peaked T waves, and chest X-ray (CXR) revealed mild diffuse bilateral pulmonary infiltrates consistent with pulmonary edema. The patient did not demonstrate any signs or symptoms of infection. Computed tomography scan of the brain was obtained and was unremarkable. The patient's altered mental status was attributed to AKI after excluding other causes of metabolic encephalopathy. She then underwent emergent dialysis with a temporary internal jugular dialysis catheter and was admitted to the intensive care unit for further management. After 2 sessions of hemodialysis, the patient's symptoms and CXR findings significantly improved with her potassium, blood urea nitrogen, and creatinine levels decreased to 4.8 mEq/L (4.8 mmol/L), 90 mg/dL (32.13 mmol/L), and 5.66 mg/dL (500.34 µmol/L), respectively. By

this time, the patient was hemodynamically stable and downgraded to the medical floor. In the setting of asthma with pulmonary infiltrates on CXR, eosinophilia (1.2×10^3 µL), and sudden-onset acute kidney failure requiring hemodialysis, there were concerns for possible AIN secondary to omalizumab therapy versus EGPA (formerly known as Churg-Strauss syndrome). The patient was started on high-dose methylprednisolone for 3 days while workup for autoimmune disorders was obtained. Her antinuclear antibodies screening was positive with a titer of 1:640. Antineutrophil cytoplasmic antibodies (ANCA) for myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA) were both negative. A kidney biopsy was then obtained, which demonstrated moderate diffuse glomerulosclerosis, focal segmental glomerulosclerosis, and moderate arterio- and arteriolosclerosis. There was no evidence of lupus nephritis or ANCA-associated necrotizing/crescentic glomerulonephritis. Focal eosinophils were noted near the corticomedullary junction, consistent with a drug-induced interstitial nephritis (Figure 1). The patient's hospital course remained uncomplicated and she was discharged on day 7 with oral steroids and outpatient hemodialysis 3 times per week with instructions to avoid omalizumab.

The patient had a baseline creatinine of 2.09 mg/dL (184.76 µmol/L) and estimated glomerular filtration rate of 23 mL/min 1 month prior to admission. After 3 days of methylprednisolone 1 g IV with an 8-week taper of oral prednisone 40 mg outpatient, her urine micro-albumin/creatinine ratio decreased from 2524 µg/mg on admission to 889 µg/mg (Table 1). Eight weeks after being discharged, the patient recovered from her AKI and no longer required hemodialysis.

Discussion

Omalizumab was approved by the Food and Drug Administration in 2003 for the treatment of moderate to severe persistent asthma in patients 12 years and older with elevated IgE level whose symptoms were not adequately controlled with inhaled corticosteroids. Omalizumab is also approved for treating chronic idiopathic urticaria in patients 12 years and older who continue to be symptomatic despite H1 antihistamine treatment. Our patient continued to have asthma exacerbations requiring multiple emergency room visits despite being on high-dose inhaled glucocorticoids, antileukotriene agents, and long-acting muscarinic antagonists (Table 1). She was a good candidate for a trial of omalizumab given the difficulty in managing her asthma symptoms with traditional therapy and elevated IgE levels (1 289 000 U/L at the time of agreeing to omalizumab therapy). The black box warning for omalizumab is anaphylaxis with other serious warnings that include malignancy and eosinophilic conditions with symptoms consistent with EGPA. Other side effects that have been noted include a higher risk of cardiovascular events such as transient ischemia attacks and ischemic strokes.⁵ In 2018, there was interest in evaluating

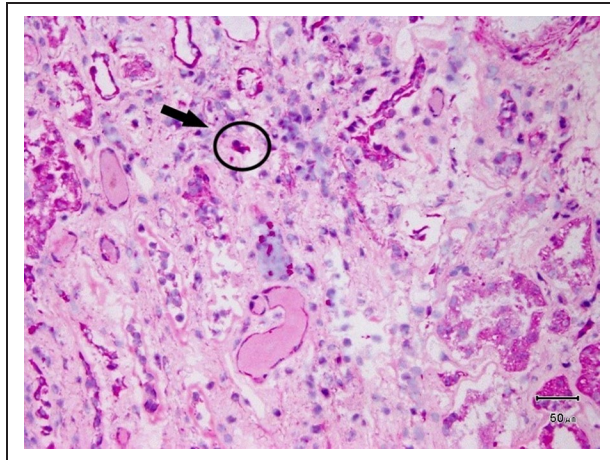


Figure 1. Renal biopsy: eosinophils (arrow) at the corticomedullary junction consistent with acute interstitial nephritis.

omalizumab as a potential treatment for AIN with the goal of shortening the duration of prednisone use in treating DI-AIN; however, due to a lack of participants, the study was withdrawn.⁶ Currently, there are no studies or reports of omalizumab causing AIN.

Drug-induced acute interstitial nephritis is a common cause of AKI and is estimated to be the cause in approximately 20% of patients with unexplained AKI.⁷ Many drugs are known to cause AIN with the most common being antibiotics, NSAIDs (nonsteroidal anti-inflammatory drugs), and proton pump inhibitors.⁷ Other drugs that demonstrate an increase in nephrotoxicity with a predominance for AIN are immune checkpoint-inhibitors (CPIs) used in cancer therapy.⁷ Immune CPIs are monoclonal antibodies that activate quiescent T-cells and stops a cancer cell's ability to turn off activated T-cells that would allow for unchecked tumor cell proliferation.⁸ AIN caused by CPIs is slower to develop compared with known drugs that cause AIN and may be missed in the outpatient setting.⁹ Although not used in cancer therapy, omalizumab is also a monoclonal antibody like CPIs and may have similar effects on the kidneys.

The definitive treatment for DI-AIN is stopping the offending agent with no current consensus on the use of steroid therapy.¹⁰ Small case series along with anecdotal reports have suggested that the use of corticosteroids in treating DI-AIN may be beneficial in some patients.¹⁰ However, there are no randomized controlled trials to determine the efficacy of steroids in treating DI-AIN, leaving the decision to be based on clinical judgement. In this patient, because of her acute asthma exacerbation and early concerns for EGPA, methylprednisolone 1 g IV was started early. She received 3 days of methylprednisolone 1 g IV with an 8-week oral prednisone 40 mg taper. Her proteinuria significantly decreased from 2524 µg/mg on admission to 889 µg/mg 15 days post discharge.

In conclusion, this patient had stage III CKD in the setting of uncontrolled diabetes; however, the acute changes in her

kidney function and worsening of proteinuria were attributed to omalizumab. The kidney biopsy confirmed the acute changes of CKD with AIN. The patient has recovered from AKI with corticosteroids. DI-AIN can be caused by any drug, including novel drugs that have been considered for potential treatment of DI-AIN. Our case highlights the first report of AIN as a side-effect of omalizumab therapy and the importance of continued surveillance of possible rare side effects from current medications on the market.

Authors' Note

An abstract of this work was presented at the 2020 Western Medical Research Conference in Carmel, California, from January 23 to 25, 2020.

Declaration of Conflicting Interests

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Ethics Approval

Kern Medical Institutional Review Board granted ethical approval to report this case, Study #19034.

Informed Consent

Written informed consent was obtained from the patient for their anonymized information to be shared in this case report for presentation/publication.

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References

- Godse K, Mehta A, Patil S, Gautam M, Nadkarni N. Omalizumab—a review. *Indian J Dermatol*. 2015;60:381-384. doi:10.4103/0019-5154.160490
- Incorvaia C, Mauro M, Russello M, Formigoni C, Riario-Sforza GG, Ridolo E. Omalizumab, an anti-immunoglobulin E antibody: state of the art. *Drug Des Devel Ther*. 2014;8:197-207. doi:10.2147/dddt.s49409
- US Food and Drug Administration. Omalizumab (marketed as Xolair) information. Accessed July 17, 2020. <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/omalizumab-marketed-xolair-information>
- Xolair [package insert]. Francisco, CA: Genentech, Inc; 2019. Accessed July 17, 2020. https://www.gene.com/download/pdf/xolair_prescribing.pdf
- US Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. Accessed July 17,

2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-asthma-drug-xolair-omalizumab-including>
6. Mayo Clinic. Xolair (omalizumab) for treatment of drug-induced acute tubulointerstitial nephritis (AIN). Accessed July 17, 2020. <https://clinicaltrials.gov/ct2/show/NCT01893658>
 7. Moledina DG, Perazella MA. Drug-induced acute interstitial nephritis. *Clin J Am Soc Nephrol.* 2017;12:2046-2049. doi:10.2215/CJN.07630717
 8. Perazella MA, Shiralil AC. Nephrotoxicity of cancer immunotherapies: past, present and future. *J Am Soc Nephrol.* 2018;29:2039-2052. doi:10.1681/ASN.2018050488
 9. Perazella MA, Spranges B. AKI in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol.* 2019;14:1077-1079. doi:10.2215/CJN.02340219
 10. Krishnan N, Perazella MA. Drug-induced acute interstitial nephritis: pathology, pathogenesis, and treatment. *Iran J Kidney Dis.* 2015;9:3-13.